Official Protocol Title:	A Single-Blind, Randomized, Phase 2A, Dose Ranging Study (Part 1) of ACE-011 Therapy Followed by a Phase 2B/3, Double-Blind, Randomized, Placebo-Controlled Study (Part 2) of ACE-011 for Chemotherapy Induced Anemia (CIA) in Subjects With Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated With First-Line Platinum-Based Chemotherapeutic Regimens
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A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE RANGING STUDY (PART 1) OF ACE-011 THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF ACE-011 FOR CHEMOTHERAPY INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

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Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator and Title **Site Number:_____** **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.	

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PROTOCOL SUMMARY

Study Title

A single-blind, randomized, phase 2a, dose ranging study (**Part 1**) of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of ACE-011 for chemotherapy induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia in Subjects with Metastatic NSCLC.

Objectives

The primary objectives are:

- **Part 1**: To determine an effective dose of ACE-011 showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate within 4 months following initiation ACE-011/placebo treatment.

The secondary objectives are:

Part 1 and **Part 2**:

- To estimate the effect of ACE-011 treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in advanced NSCLC subjects with CIA.
- To evaluate the safety and tolerability of ACE-011 treatment for advanced NSCLC subjects with CIA.
- To determine the pharmacokinetics (PK) of ACE-011 in subjects with advanced NSCLC receiving platinum-based chemotherapy.
- To estimate the duration of hematopoietic response associated with ACE-011.
- To evaluate the effect of ACE-011 treatment on the quality of life (QoL) of NSCLC subjects with CIA.

Part 2:

- To evaluate hematopoietic response

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of each ACE-011 treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between ACE-011 exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).

- To evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population.
- Circulating tumor cell enumeration and molecular studies.
- To assess renal function biomarkers.

Study Design

This is a single-blind, randomized, phase 2a, dose ranging study (**Part 1**) of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of ACE-011 for CIA subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose finding segment in which up to approximately 90 subjects will be randomized to one of three ACE-011 dose treatment arms. The primary objective is to determine an effective dose of ACE-011 showing a hematopoietic response in the treatment of CIA in advanced NSCLC subjects. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05. A Data Monitoring Committee (DMC), composed of both internal Celgene and external independent reviewers, will conduct periodic data reviews during the review of Part 1 data, to define the recommended ACE-011 dose to be used in Part 2 of the study.

Part 2 is the Phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive ACE-011, at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During **Part 2** (first and second stage) overall survival will assessed. The total sample size of 750 subjects will allow observation of at least 536 deaths and thus, at least 80% power to exclude more than 15% hazard increase in the ACE-011 arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:ACE-011) of 0.87, assuming the ACE-011 arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:ACE-011) of 1.11.

Study Population

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening, Treatment Period, Post Treatment Follow-Up Period, and Survival Follow-Up Period. Study treatment is defined as ACE-011 in Part 1 and ACE-011/placebo in Part 2.

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days of randomization, as outlined in the Table of Events, Section 5. **Historical tumor assessment data from six weeks prior to initiation of platinum-based chemotherapy through randomization to the study will be collected.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from initial diagnosis of NSCLC and red blood cell (RBC) transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the screening period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Subjects will also be provided the opportunity to participate in an optional full PK assessment.

Treatment Period (up to 6-9 months):

The treatment period is approximately six months (four doses of study treatment given on Day 1, every 42 days), two additional ACE-011/placebo doses may be given only in **Part 2**, at the discretion of the Investigator.

In **Part 1** (the dose ranging portion of the study), subjects who meet all eligibility criteria will be randomized to receive one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

Each dose level will be administered every 42 days for up to four doses.

The effective dose of ACE-011 is defined as follows:

> An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks during the first two doses of ACE-011 (Dose 1/Day 1 through and including Dose 2/Day 43 [prior to Dose 3]), in approximately 70% of subjects, in at least one or more treatment arms (in the absence of RBC transfusions and/or ESAs.

Evaluation of response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the optimal dose for Part 2.

In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

In **Part 2**, a total of 750 subjects will be randomized to receive either ACE-011 or placebo, at a ratio of 1:1:

- 375 subjects will receive ACE-011 (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of ACE-011 or placebo will be administered every 42 days for four doses. Up to two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive ACE-011 (at the dose determined from Part 1) or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is > 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, ACE-011 should be administered ≥ 7 days from the date of the RBC transfusion.

In **Part 1**, full PK blood samples will be collected to evaluate the full PK profile of ACE-011 from approximately 30 subjects at select centers in approximately 10 subjects for each ACE-011 dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose.

In **Part 2**, sparse PK blood samples will be collected.

The following events are considered sufficient reasons for discontinuing a subject from the Treatment Period:

- AE(s)
  - Medically significant hypertension which 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)
  - Creatinine clearance < 40 ml/min
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria
- Lack of ACE-011 therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of ACE-011 or ACE-011/placebo.
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- ACE-011 or ACE-011/placebo Dose Modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥ 3.0 g/dL following a two level dose reduction due to a Hgb increase ≥ 3.0 g/dL
  - In **Part 2**: > 3 dose reductions and/or delays
- Disease progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

Post Treatment Follow-Up Period (monthly for up to 6 months)

Subjects who enter the Post Treatment Follow-Up Period will be followed monthly for up to 6 months from their last dose of ACE-011 or ACE-011/placebo. All subjects will continue to be followed for TTP and PFS up to one year from their first dose of ACE-011 or ACE-011/placebo or until progression of their NSCLC, whichever comes first.

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

- Completed study, per protocol (subject has completed six to nine month Treatment Period plus up to six month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- AE(s)
- Disease Progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

Survival Follow-up Period (monthly for up to 24 months after first dose of ACE-011 or ACE-011/placebo)

In both **Part 1** and **Part 2**, survival data will be collected monthly via telephone contact for up to 24 months following the subject's first dose of ACE-011 (Part 1) or ACE-011/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit.

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Overview of Efficacy Assessments

- Serum hematology, absolute reticulocyte counts
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Tumor Assessments
- Documentation of concomitant RBC transfusions

Overview of Safety Assessments

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac and thromboembolic events
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- AE(s)
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy testing

- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone).
- QoL Assessment (FACIT Fatigue Scale [Version 4]) and Lung Cancer Symptom Scale (LCSS) questionnaire.
- Documentation of concomitant medications / procedures.

Overview of Exploratory Assessments

- Bone or other protein/biomarkers
- Circulating tumor cell enumeration and molecular studies
- DXA scan
- Renal function biomarkers

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 18
2. STUDY OBJECTIVES 34
2.1. Primary Objective 34
2.2. Secondary Objectives 34
2.3. Exploratory Objectives 34
3. STUDY ENDPOINTS 35
3.1. Primary Endpoint(s) 35
3.2. Secondary Endpoint(s) 35
3.3. Exploratory Endpoint(s) 36
4. OVERALL STUDY DESIGN 37
4.1. Study Design 37
4.1.1. ACE-011 Dose Modification, Reduction and Escalation Rules 40
4.2. Study Design Rationale 42
4.2.1. Fixed Dose 43
4.2.2. Dosing Schedule 43
4.2.3. Starting Dose Levels in Part 1 43
4.2.4. Evaluation of Dosing Schema via Modeling/Simulation 44
4.3. Study Duration 45
5. TABLE OF EVENTS 46
6. PROCEDURES 53
7. STUDY POPULATION 61
7.1. Number of Subjects 61
7.2. Inclusion Criteria 62
7.3. Exclusion Criteria 63
8. DESCRIPTION OF STUDY TREATMENTS 65
8.1. Description of Investigational Product(s) 65
8.2. Treatment Administration and Schedule 65
8.2.1. Selection of Dose for the Study 66
8.2.2. Selection and Timing of Dosing for Each Subject 66

8.2.3. Discontinuation 67
8.3. Method of Treatment Assignment 69
8.4. Packaging and Labeling 69
8.5. Investigational Product Accountability And Disposal 69
8.6. Investigational Product Compliance 69
9. CONCOMITANT MEDICATIONS AND PROCEDURES 70
9.1. Permitted Concomitant Medications and Procedures 70
9.2. Prohibited Concomitant Medications and Procedures 71
9.3. Required Concomitant Medications and Procedures 71
10. STATISTICAL ANALYSES 72
10.1. Overview 72
10.2. Study Population Definitions 72
10.3. Sample Size and Power Considerations 72
10.4. Background and Demographic Characteristics 73
10.5. Subject Disposition 73
10.6. Efficacy Analysis 73
10.7. Safety Analysis 74
10.8. Interim Analysis 74
10.9. Other Topics 75
10.10. Data Monitoring Committee (DMC) 75
11. ADVERSE EVENTS 76
11.1. Monitoring, Recording and Reporting of Adverse Events 76
11.2. Evaluation of Adverse Events 76
11.2.1. Seriousness 76
11.2.2. Severity 77
11.2.3. Causality 78
11.2.4. Duration 78
11.2.5. Action Taken 79
11.2.6. Outcome 79
11.3. Abnormal Laboratory Values 79
11.4. Pregnancy 79
11.4.1. Females of Childbearing Potential: 79
11.4.2. Male Subjects 80

11.5. Immediate Reporting of Serious Adverse Events 80
11.5.1. Safety Queries 80
11.6. Expedited Reporting of Adverse Events 80
12. DISCONTINUATIONS 82
13. EMERGENCY PROCEDURES 83
13.1. Emergency Contact 83
13.2. Emergency Identification of Investigational Products 83
14. REGULATORY CONSIDERATIONS 84
14.1. Good Clinical Practice 84
14.2. Investigator Responsibilities 84
14.3. Subject Information and Informed Consent 84
14.4. Confidentiality 85
14.5. Protocol Amendments 85
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 85
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 86
14.8. Closure of the Study 86
15. DATA HANDLING AND RECORDKEEPING 87
15.1. Data/Documents 87
15.2. Data Management 87
15.3. Record Retention 87
16. QUALITY CONTROL AND QUALITY ASSURANCE 89
16.1. Study Monitoring and Source Data Verification 89
16.2. Audits and Inspections 89
17. PUBLICATIONS 90
18. REFERENCES 91
19. APPENDICES 94
Appendix A: Response Evaluation Criteria in Solid Tumors 94
Appendix B: ECOG Performance Status Scale 96
Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 97
Appendix D: New York Heart Association - Classification of Heart Failure 98

LIST OF TABLES

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation 26
Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall 29
Table 3: Summary of SAEs Reported 30
Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days 30
Table 5: ACE-011 and ACE-011/Placebo Dose Reduction Levels 41
Table 6: ACE-011 Dose Escalation Levels (Part 1 Only) 42
Table 7: ACE-011 NSCLC Schedule of Assessments 46
Table 8: Schedule of Pharmacokinetic Assessments 52
Table 9: ECOG Performance Status Scale 96
Table 10: Classification of Heart Failure 98

LIST OF FIGURES

Figure 1: Study Design 39
Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population 45

1. INTRODUCTION

This is a single-blind, randomized, phase 2a, dose ranging study of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of ACE-011 for chemotherapy induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects will be randomized to one of three ACE-011 dose treatment arms. A Data Monitoring Committee (DMC), composed of both internal Celgene and external independent reviewers, will review data from Part 1 to define the recommended ACE-011 dose to be used in Part 2 which is the phase 2b/3, randomized, double-blind, placebo-controlled segment of the study. **Part 2** will be performed in two stages. In the first stage approximately 180 subjects will be randomized to receive ACE-011, at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

ACE-011 (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The 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, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

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

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 the terminal differentiation step in erythropoiesis to allow additional rounds of erythroid cell replication before cells enter the terminal differentiation phase. The result is a substantial increase in mature erythrocytes released into circulation. Since this proposed mechanism is different to that of known agents, ACE-011 may provide a different clinical profile in the treatment of CIA.

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

Non-Small Cell Lung Cancer Current Therapy Status

Lung cancer is the leading cause of cancer death in the world, accounting for 32% of cancer deaths in males and 25% in females, affecting approximately 171,000 people annually in the US (Parker, 1997; Sandler, 2006) and more than 200,000 people in Europe (Rossi, 2006). Of these patients, approximately 85% have NSCLC, including squamous carcinoma, adenocarcinoma and

large cell carcinoma (Rossi, 2006; Sandler, 2006). These histologies are typically classified together because the approaches to diagnosis, staging and prognosis, and treatment are similar.

Patients are often diagnosed with an advanced stage of disease. Studies of advanced NSCLC patients treated with platinum-based chemotherapy report a one year survival rate that ranges from 30 to 43 percent and a median survival that ranges from seven to ten months (Dang, 2008). The 5-year survival rate of patients with NSCLC varies by stage, from 60 to 70% for patients with stage I disease to < 1% for patients with stage IV disease (Hong, 2008). Patients having stage IIIb/IV NSCLC are not considered to be candidates for curative resection surgery or radiation, and radiation therapy is primarily used as palliative treatment in advanced stages of NSCLC.

The role of chemotherapy is now well established as the recommended treatment of advanced NSCLC (Non-small Cell Lung Cancer Collaborative, Group 1995). The current globally accepted standard of treatment for NSCLC is platinum-based combination therapy. In advanced-stage (stage IIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine (Gemzar®), vinorelbine, taxanes (paclitaxel or docetaxel) or pemetrexed are reference regimens. When compared head-to-head in phase III studies, these doublets have shown comparable efficacy, in regards to overall survival (Schiller, 2002) with differences in toxicity profiles (Schiller, 2002). When administered in a 3-week schedule, cisplatin plus gemcitabine, or cisplatin plus pemetrexed are effective and are widely used regimens for first-line treatment of NSCLC. A recent phase III study in NSCLC compared cisplatin plus gemcitabine with cisplatin plus pemetrexed (Scagliotti, 2008). Both had similar efficacy, with cisplatin plus pemetrexed having better tolerability and more convenient administration than cisplatin/gemcitabine. This study was also the first prospective phase III study in NSCLC to show a survival difference based on histologic type (non-squamous benefited from pemetrexed plus cisplatin). Drug-related grade (G) 3 or 4 anemia was at the rate of 6% for cisplatin/pemetrexed versus 10% for cisplatin/gemcitabine. The incidence of RBC transfusion was 16.1% versus 27.3% and administration of erythropoietic agents 10.4% versus 18.1% respectively. There was no significant difference between treatment arms in the incidence of or reason for deaths (7%).

Treatment of Chemotherapy-Induced Anemia

Chemotherapy-induced anemia is an area of unmet medical need. Erythropoiesis-stimulating agents (ESAs) can successfully mitigate transfusion need in a proportion of these patients, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002).

The current treatment options for CIA include blood transfusion and ESAs. However, the blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients in chemotherapy has therefore been

rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. In the pivotal Aranesp study for CIA in NSCLC, 27 % of patients were transfused with Packed Red Blood Cells (PRBC's) at 4 months vs. 52% in the placebo arm. In a subsequent recent Phase III study of Alimta®/CDDP vs. Gemcitabine/CDDP where all first-line NSCLC patients with anemia or not were enrolled, 16.1% vs 27.3% of patients respectively were transfused with PRBC's during that study. (Scagliotti, 2008)

Chemotherapy-induced anemia is a significant problem for patients with cancer, causing fatigue and reducing quality-of-life (QoL). Treatment with ACE-011 resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two Phase 1 studies in healthy volunteers, as well as in a Phase 2a study for multiple myeloma (MM).

The ability for ACE-011 to rapidly increase and sustain Hgb levels in anemic subjects, while showing a safety benefit as well as no decrement in Overall Survival (as part of this study design endpoints), suggests that ACE-011 may then serve as an alternative therapeutic agent for the treatment of CIA.

Activin Biology

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

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

The activin signaling pathway has been shown to induce terminal erythroid differentiation in some preclinical models. Inhibition of activin may lead to increases in proliferation of the erythroid lineage. Based on its pharmacologic effects, ACE-011 is being developed for the

treatment of anemia associated with a variety of disorders, such as in chronic renal failure and CIA.

In a retrospective study (Seder, 2009) activin immunoreactivity was found in 78% of lung adenocarcinomas surveyed (n=164). Expression ranged from moderate in the majority of individuals to high in approximately 19.7% of samples evaluated. Gene expression analysis was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples. An average of three-fold more activin transcript was detected in diseased tissue relative to normal samples and particularly high levels of overexpression were associated with worse overall survival in stage I patients with NSCLC.

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

ACE-011

ACE-011 (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of ACE-011. However, in order to reduce the potential immunogenicity of the human molecule, ACE-011, and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of ACE-011 with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below.

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 (IP) 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 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 HCT levels from 43% to 38% three days following treatment. RAP-011 administered three days prior to paclitaxel injection was sufficient to keep the HCT levels above 42% at three days and up to two weeks following paclitaxel administration. Therefore, prophylactic treatment with RAP-011 was able to prevent paclitaxel-induced anemia in mice.

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

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

The data demonstrate that RAP-011 treatment acts to inhibit MDA-MB-231 metastasis to bone and may also play a role in inhibiting tumor growth in soft tissue. Furthermore, in the presence of tumor cells, RAP-011 is able to prevent lytic disease through an anabolic mechanism of bone formation. Lastly, inhibition of tumor growth and metastasis with RAP-011 leads to a greater than 25% survival benefit in this model.

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model of myeloma in which the extra-cellular domain of the murine activin type II receptor, fused to a murine IgG-Fc fragment, (RAP-011) was shown to prevent the development of osteolytic bone disease in a preventative setting. Additionally, RAP-011, an antagonist of activin, was shown to reverse ovariectomy-induced bone loss *in vivo*.

The effect of this antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in isolated 5T2MM murine myeloma cells from the bone marrow of disease bearing animals.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

This study showed that, in the preclinical murine model for myeloma, RAP-011 stimulates bone formation by increasing osteoblast perimeter and number, mineralisation and bone formation rate but had no effect on osteoclast activity. RAP-011 also prevented the development of osteolytic bone disease.

In addition, the RAP-011 was highly effective in restoring bone mineral density (BMD) when administered therapeutically in a murine model of postmenopausal osteoporosis. RAP-011 has also been shown to increase trabecular bone density in normal mice.

The efficacy of RAP-011 was also examined in two orthotopic metastatic models of breast cancer using luciferase-tagged human MCF-7 and MDA-MB-231 breast cancer cells (estrogen receptor positive and negative, respectively). Mice were pretreated for 2 weeks with RAP-011 (10 mg/kg, biweekly, SC) prior to the intra-cardiac implantation of tumor cells into female nude mice. Treatment with RAP-011 was continued for an additional 7 weeks following tumor implantation at which time mice were sacrificed and assessed for tumor burden. RAP-011 either modestly decreased the tumor burden (in the case of mice bearing MCF-7 tumors) or delayed tumor growth by approximately 3 weeks (MDA-MB-231 model) as measured by bio-luminescence. In addition, in the MCF-7 model, a 60% reduction in tumor weight was observed in the RAP-011 treated mice.

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

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 and phase 1b multiple doses of 0.1 to 2 mg/kg (monthly, SC). Weekly (rat and IV monkey studies) or every 2 week (SC monkey studies) dosing in animals was designed to provide continuous, but fluctuating serum concentrations of ACE-011, which would be mimicked by a one-month dosing interval in humans.

Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in

ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-ACE-011 antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats. However, high plasma concentrations of ACE-011 in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (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, the NOAEL from the 6 month monkey study is < 10 mg/kg. A 9-month monkey study to evaluate the effects of lower concentrations of ACE-011 has been completed (refer to Potential Risks for Human Use).

Summary of Clinical Experience

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

ACE-011 was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal 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 (PK) of ACE-011 was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (CL) ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half life in serum ($t_{1/2,z}$) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, ACE-011 was completely absorbed, and the mean $t_{1/2,z}$ was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs was mild in severity and were judged to be unrelated to ACE-011. No deaths, serious AEs (SAEs), or AEs leading to discontinuation were reported. Changes in RBCs, Hgb, 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, postmenopausal female volunteers in single dose levels up to 0.1 mg/kg SC and 3.0 mg/kg IV, the highest dose levels tested in this study.

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

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 SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of 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 levels, up to 20 g/dL and HCT levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting 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 Hgb, 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

Other than the serious case of Hgb increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the subjects in the 1.0 mg/kg group with elevated Hgb levels underwent phlebotomies and all Hgb

elevations were resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups.

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

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

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

The PK of ACE-011 were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of ACE-011 following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ((apparent) volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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

Study A011-04 is 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).

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, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. ACE-011 was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg ACE-011, 8 subjects received 0.3 mg/kg ACE-011, and 8 subjects received 0.5 mg/kg ACE-011. Twenty six (86.7%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

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

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

Fourteen out of 24 subjects (58%) who received study treatment (ACE-011) did receive 3 doses or more (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level).

Safety: Overall, 22 (91.7%) subjects receiving ACE-011 and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving ACE-011, AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (ie, those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving ACE-011 and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving ACE-011 and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (ACE-011 or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg ACE-011 dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg ACE-011 dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg ACE-011 group and 3 (37.5%) subjects in the 0.5 mg/kg ACE-011 group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to ACE-011, and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to ACE-011. One subject in the 0.5 mg/kg ACE-011 dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to ACE-011.

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups and Table 3 is a summary of SAEs reported.

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

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

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

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug (ACE-011 or placebo).

Table 3: Summary of SAEs Reported

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

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

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

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hgb values were observed within 28 days after administration of the first dose of ACE-011/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose ACE-011/Placebo				
	mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

Taken together, these data, suggest a beneficial pharmacodynamic effect of ACE-011 on erythropoiesis in a patient population with cancer CIA.

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 subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~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 postimplantation 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 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, and TSH and 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

- **Part 1**: To determine an effective dose of ACE-011 showing a hematopoietic response in the treatment of CIA in advanced NSCLC subjects.
- **Part 2**: To assess transfusion rate within 4 months following initiation ACE-011 treatment.

2.2. Secondary Objectives

Part 1 and **Part 2**:

- To estimate the effect of ACE-011 treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in advanced NSCLC subjects with CIA.
- To evaluate the safety and tolerability of ACE-011 treatment for advanced NSCLC subjects with CIA.
- To determine the PK of ACE-011 in subjects with advanced NSCLC receiving platinum-based chemotherapy.
- To estimate the duration of hematopoietic response associated with ACE-011.
- To evaluate the effect of ACE-011 treatment on the quality of life (QoL) of NSCLC subjects with CIA.

Part 2:

- To evaluate hematopoietic response

2.3. Exploratory Objectives

Part 1 and **Part 2**:

- To estimate the effect of each ACE-011 treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between ACE-011 exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population.
- To assess circulating tumor cells and molecular studies
- To assess renal function biomarkers

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Part 1: Dose Finding

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of ACE-011, a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions and/or ESAs. In order to determine the optimal dose of ACE-011 to be used in Part 2, evaluation of hematopoietic response will be determined from ACE-011 Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).
- In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

Hematopoietic response will be determined by laboratory analysis.

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following ACE-011/placebo treatment

3.2. Secondary Endpoint(s)

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- TTP
- PFS (including at 6 and 12 months)
- OS (at 12 months and up to 24 months)
- ORR
- ACE-011 concentration in serum
- Non-compartmental PK parameters for ACE-011 (**Part 1** only)
- QoL assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire (Hollen, 1995)

3.3. Exploratory Endpoint(s)

- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or ACE-011 mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Change in time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- A population PK model for ACE-011
- A population pharmacodynamic model describing Hgb response as a function of time, ACE-011 exposure, and subject characteristics
- Expression/overexpression of Activin A and other protein/biomarkers related to ACE-011 mechanism of action in blood and tissue in a NSCLC population
- Change in circulating tumor cells and molecular studies
- Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other serum biomarkers

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a single-blind, randomized, phase 2a, dose ranging study of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of ACE-011 for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects will be randomized to one of three ACE-011 dose treatment arms. A DMC, will conduct periodic data reviews, including the review of Part 1 data, to define the recommended ACE-011 dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 1 is planned to be conducted primarily at selected US sites. The study will then be extended to additional global sites for the conduct of Part 2.

Study treatment is defined as ACE-011 in Part 1 and ACE-011/placebo in Part 2.

Three starting ACE-011 dose levels, 15.0, 30.0, and 45.0 mg, were selected for Part 1 of the study. Up to approximately 90 subjects will be randomized to one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following DMC review, analysis of safety data and assessment of dose effects of Hgb levels, a decision will be made to start concurrent randomization to:

- ACE-011 45.0 mg SC

Each dose level will be administered every 42 days for four doses.

The DMC will continue to monitor safety of the ACE-011 45.0 mg dose level.

In **Part 2**, a total of 750 subjects will be randomized to receive either ACE-011 (at the dose determined in Part 1) or placebo, at a ratio of 1:1:

- 375 subjects will receive ACE-011 (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of ACE-011 or placebo will be administered every 42 days for four doses; two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive ACE-011, at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

The Treatment Period for Part 1 is up to approximately six months and for Part 2 up to nine months. Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6

months from their last dose of ACE-011 or ACE-011/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of ACE-011 or ACE-011/placebo or until progression of their NSCLC, whichever comes first.

Survival data will be collected monthly for up to 24 months following the subject's first dose of ACE-011 in Part 1 or ACE-011/placebo in Part 2.

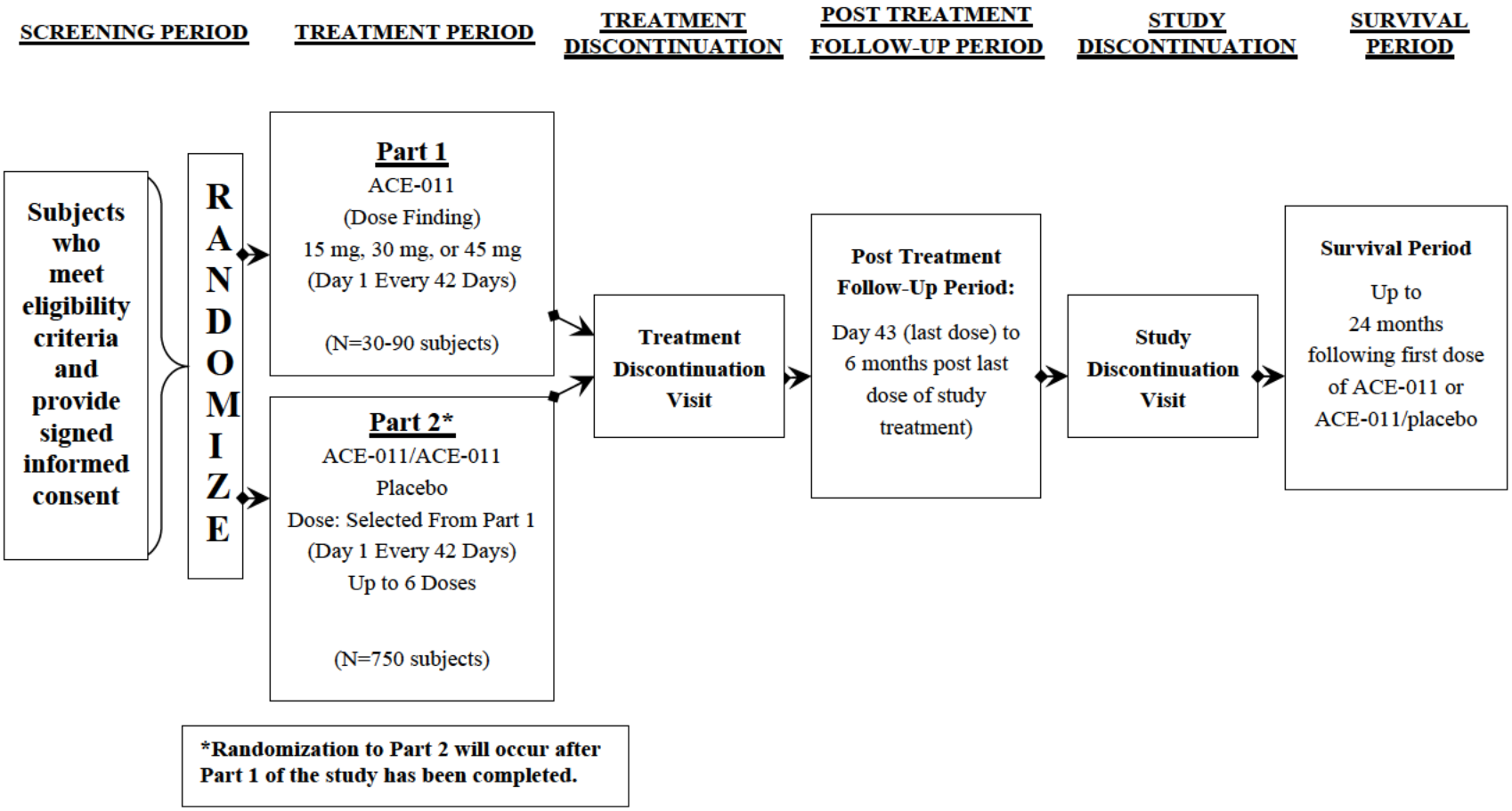
At the time of randomization, all subjects must be receiving a first-line platinum-containing chemotherapy regimen, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles of this first-line platinum-based regimen to be eligible for the study. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Maintenance chemotherapy with a pemetrexed-containing regimen will only be allowed following completion of the subject's platinum-based chemotherapy, with a best response of at least stable disease.

Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

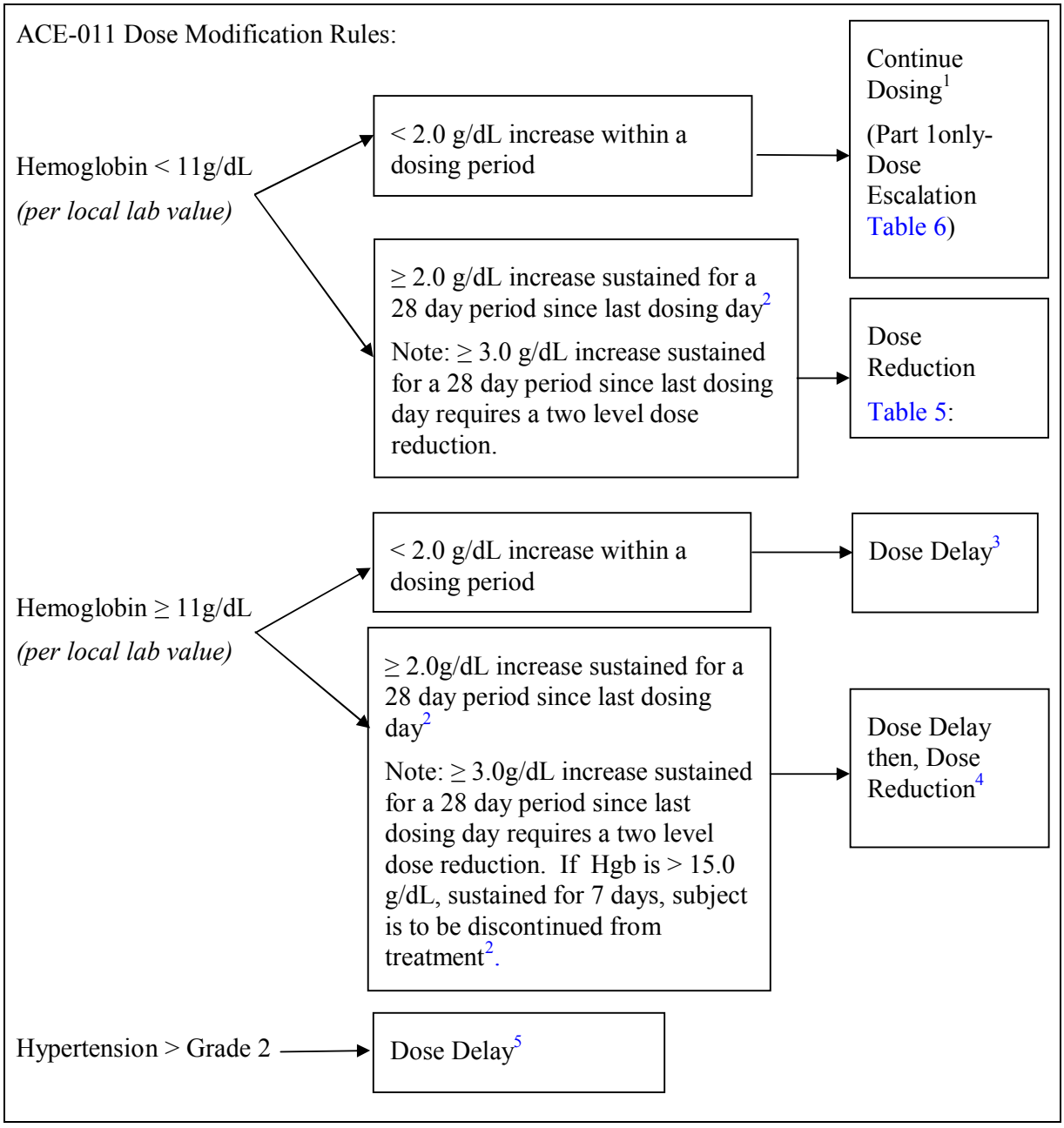
- In **Part 1**, subjects will be randomized to one of three ACE-011 dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
- In **Part 2** subjects will be randomized to receive either ACE-011 or placebo and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
  3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
  4. ECOG Performance Status 0-1 vs. 2

Figure 1: Study Design



4.1.1. ACE-011 Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for ACE-011 or ACE-011/placebo for the subject's **second** dose of study treatment and beyond.



[1]Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** ACE-011 dosing level if the transfusion was given greater than 7 days from the previous dose of ACE-011 (or ACE-011/placebo) AND the Hgb level is < 11 g/dL AND hypertension is ≤ Grade 2 on the day of dosing. ACE-011 (or ACE-011/placebo) should not be administered within 7 days post RBC transfusion.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of ACE-011, the subsequent dose of ACE-011 will be **increased** one dose level (Refer to ACE-011 Dose Escalation Levels-Table 6).

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed by the local lab for the dosing day, 7, 14 , 22 (after first dose of study treatment) and 28 days after dosing, and reviewed in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent ACE-011 or ACE-011/placebo dose reduction of two dose levels (Refer to ACE-011and ACE-011/Placebo Dose Reduction Levels (Table 5). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]ACE-011 should be **delayed** until Hgb is < 11g/dL and hypertension ≤ Grade 2. The follow-up dosing can commence at 7 days or later after the originally planned ACE-011/placebo dose that was **delayed**. Subsequent ACE-011/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** ACE-011/placebo dose is defined as a dose not administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > Grade 2, and/or ACE-011 related toxicity).

[4]ACE-011 should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of ACE-011 will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]ACE-011 should be held until hypertension resolves to ≤ Grade 2 (current active minor version NCI CTCAE v4.0) and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: ACE-011 and ACE-011/Placebo Dose Reduction Levels

When required, per dose modification rules above, ACE-011 dose(s) in **Part 1** and ACE-011/placebo dose(s) in **Part 2** should be reduced as follows:

Dose Schedule ACE-011 or ACE-011/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days-45.0 mg	38.0 mg	33.0 mg	28.0 mg
Every 42 days-30.0 mg	26.0 mg	22.0 mg	18.0 mg
Every 42 days-15.0 mg	13.0 mg	11.0 mg	9.0 mg

*Note: Any Hgb increase of ≥3.0 g/dL will require a subsequent ACE-011 or ACE-011/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL following a two level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for four doses. An additional two doses (total of 6 doses) may be given only during **Part 2** at the discretion of the Investigator.

Blood pressure and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of ACE-011 and ACE-011/placebo.

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. A dose level may not be increased following a dose reduction.

Dose reduction steps and the subsequent administration of the reduced dose(s) of ACE-011 or ACE-011/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. In Part 2, subjects in the placebo group who are designated by their treating physician to undergo dose reduction will continue to receive placebo.

Placebo will be administered at the same volume as the corresponding ACE-011 or ACE-011/placebo dose reduction.

ACE-011 Dose Escalation Levels:

The following dose escalation rules apply for ACE-011 dose(s) in **Part 1** only. Dose escalations are not allowed in **Part 2**:

- Less than 1.0 g/dL increase in Hgb in response to prior ACE-011 dose
- Hgb level must be < 11.0 g/dL and hypertension ≤ Grade 2
- Dose escalation to begin at next every 42 day scheduled dosing visit
- ACE-011 should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of ACE-011 at the subsequent visit per the escalation table below.

Table 6: ACE-011 Dose Escalation Levels (Part 1 Only)

Dose Schedule ACE-011	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45.0 mg	50.0 mg	55.0 mg	61.0 mg
Every 42 days-30.0 mg	33.0 mg	36.0 mg	40.0 mg
Every 42 days-15.0 mg	17.0 mg	20.0 mg	23.0 mg

Blood pressure and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of ACE-011 and ACE-011/placebo.

Dose increase steps and the subsequent administration of the increased dose(s) of ACE-011 will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject.

4.2. Study Design Rationale

The A011-01, A011-02 and A011-04 studies have shown that dosing with ACE-011 resulted in a significant 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.

Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

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.

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 by taking into consideration the rapid and prolonged Hgb response to ACE-011 as well as the dosing schedule for the platinum-based chemotherapies. The Hgb-increasing effect of ACE-011 was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks. In addition, as platinum-based chemotherapy is often administered once every 3 weeks, a once every 6 weeks dosing schedule allows administration of ACE-011 at the same visit for the chemotherapy, which is convenient to both subjects and study sites.

4.2.3. Starting Dose Levels in Part 1

Three starting dose levels, 15.0, 30.0, and 45.0 mg, were chosen for Part 1 of the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of ACE-011 at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, ACE-011 had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal ACE concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The three starting dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg, 31.5 mg, and 52.5 mg, respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three ACE-011 doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to ACE-011. In this study, the starting dose level of 45.0 mg (during the dose finding Part 1) will be

implemented only after at least 10 subjects at each lower dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level) have been evaluated as well as following DMC review of safety data and assessment of dose effects on Hgb levels.

In addition, in the current NSCLC study, during the first 6-week treatment period for a 70 kg subject receiving the starting dose at 45.0 mg, the ACE-011 exposure ($C_{max,\ day\ 1\text{-}43}$ and $AUC_{1\text{-}43}$) is projected to be approximately 10% lower than the exposure for the dose regimen of 0.5 mg/kg once every 4 weeks. Afterwards, safety measures (Hgb and blood pressure) will be used to guide the adjustment of the second dose and beyond. Thus, the use of the 45.0 mg starting dose in the current study is not anticipated to significantly compromise subject safety.

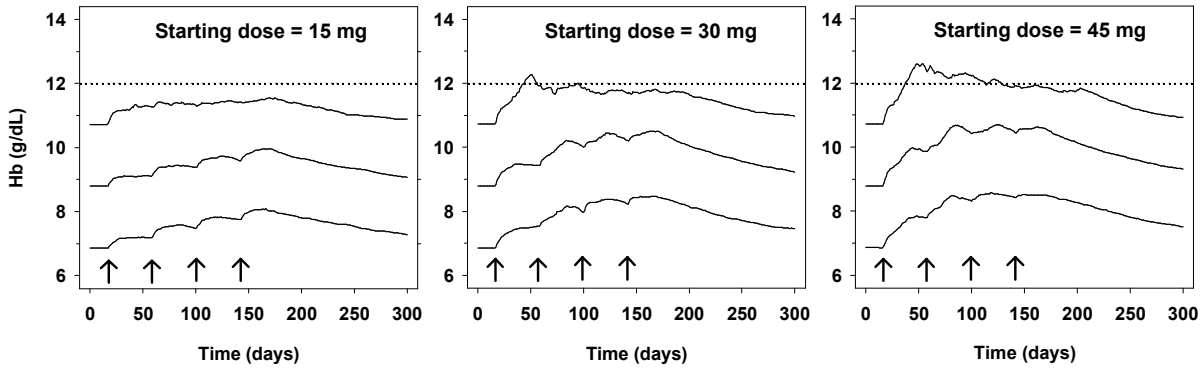
In the current study, the 45.0 mg group will have the highest starting dose, and it may be titrated up to 61.0 mg for the last dose (Dose 4). Assuming a 70 kg subject who receives the maximal amount of dose during the entire study (i.e., starting at 45.0 mg followed by dose escalation every 6 weeks to 50.0, 55.0, and 61.0 mg for Doses 2, 3, and 4, respectively), the projected cumulative AUC during the treatment period (168 days) would be approximately 60% of the steady state AUC cumulated during the same period at the NOAEL level of 1 mg/kg (given every 4 weeks for a total of 6 doses) as reported in the 9-month, repeat-dose toxicity study in monkeys. The projected highest C_{max} for the current study would be less than 50% of the steady state C_{max} in the monkey study.

4.2.4. Evaluation of Dosing Schema via Modeling/Simulation

The performance of the proposed dosing schema (three fixed starting dose levels, 6-week dosing interval, and dose adjustment rules [see Section 4.1.1 for details]) for this study was evaluated via PK/pharmacodynamic modeling/simulation. A tentative mechanistic PK/pharmacodynamic model for Hgb was developed using PK and Hgb data from healthy postmenopausal women and the model was extended to include MM subjects as a sub-population. The model was required to appropriately reproduce the observed PK and Hgb profiles in MM subjects. Monte Carlo simulations of the Hgb response to ACE-011 in a hypothetical anemic population (6.5 ≤ baseline Hgb < 11 g/dL; body weight 47 – 108 kg) were performed using the model parameterized with preliminary PK and pharmacodynamic parameters from MM subjects. In this simulation analysis, efficacy refers to an Hgb increase > 1 g/dL from the baseline for 28 consecutive days while safety refers to both the absolute Hgb levels and the rate of Hgb increase.

The simulation predicts that the desired efficacy would be achieved 6 weeks after the second dose in approximately 70% subjects of the 45 mg group and 6 weeks after the last dose in >70% subjects of the 30 mg group. Further, the simulation predicts the Hgb level would be maintained under 12 g/dL in 90% subjects and under 13 g/dL in 95% of subjects during the course of the study (Figure 2). No subjects are predicted to have a Hgb level above the upper limit of the normal range for Hgb (16 g/dL). Approximately 6% subjects are predicted to have an Hgb rise > 2 g/dL within 28 days of the first dose, mostly from the 45.0 mg group (4%); however, the fraction of subjects with an Hgb rise > 3 g/dL per 28 days is predicted to be similar between the three dose groups (approximately 2.5% for each group).

Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population



The middle solid lines represent the median Hgb level. The top and bottom solid lines represent the Hgb level at 5% and 95% percentile, respectively. The area between 5% and 95% percentiles represents 90% prediction interval. The straight dot lines represent the Hgb level of 12 g/dL. The arrows indicate the dosing time of ACE-011. The two level dose reductions upon ≥ 3 g/dL increase sustained for 28 days of a dose (Table 5) was not included in the simulation.

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects in Part 1 and 750 subjects in Part 2 will be randomized prior to receiving the fourth cycle of platinum-based chemotherapy for metastatic NSCLC. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of ACE-011 or ACE-011/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of ACE-011 or ACE-011/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of ACE-011 or ACE-011/placebo or until progression of their NSCLC, whichever comes first. All subjects will continue to be followed for survival up to 24 months from their first dose of ACE-011 or ACE-011/placebo.

5. TABLE OF EVENTS

Table 7: ACE-011 NSCLC Schedule of Assessments

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Complete Medical History	X																	
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X			X		X		X	X	X	X	X	X	X	
Vital Signs / Blood Pressure[b]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X			X		X		X		X		X		X	
12-Lead Electrocardiogram (ECG) – **Part 1**[c]	X	X	X				X				X							
12-Lead Electrocardiogram (ECG) – **Part 2**[c]	X	X									X							
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 7: ACE-011 NSCLC Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Serum Chemistry[f]	X	X		X			X				X		X			X	X	
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X							
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X		X					
Urinalysis[j]	X	X		X			X		X		X	X	X	X	X	X	X	
FSH and LH – Males and Females	X	X	X				X		X		X			X			X	
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X			X			X	
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X			X			X	
TSH[k]	X	X					X						X					
ACE-011 drug antibody test (pre-ACE-011 or ACE-011/placebo dose)		X		X			X				X			X		X		
Bone and other Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[l] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X			X				

Table 7: ACE-011 NSCLC Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X													X				
Activin A and other Proteins/Biomarkers in Blood and Tissue (pre-dose study treatment in a subset of subjects)		X	X									X						
Circulating Tumor Cells (pre-dose study treatment in a subset of subjects)		X									X	X		X				
Pharmacokinetics– **Part 1** and **Part 2**)[n]		Refer to Table 8 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X	Every 9 weeks ± 1 week																
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose only AEs assessed as related to study treatment are to be reported																
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X		X			X	X	
Concomitant Procedures	X	X		X			X		X		X		X			X	X	
Hospitalizations (Record)	X	X		X			X		X		X		X			X	X	
Randomization		X																

Table 7: ACE-011 NSCLC Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Administer ACE-011/Perform Drug Accountability[q]		X					X											
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice																
Maintenance chemotherapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[v]																		X
Post Treatment Anti-Neoplastic Therapy											X	X	X	X	X	X	X	X

[a]Include NSCLC history, date of original diagnosis, clinical stage at Screening and date of metastases and metastatic site involvement. Record prior ESA history, starting at diagnosis of NSCLC. Record RBC transfusion history, starting from diagnosis of metastatic NSCLC, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, at Treatment Discontinuation, and at Study Discontinuation. Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: For **Part 1**: At Screening, Day 1 pre and post ACE-011 or ACE-011/placebo dose, Day 8 post dose 1, every ACE-011/ACE-011/placebo dosing Visit and at end of study treatment (day 43 post last dose).

For **Part 2**: At Screening, Day 1 pre and post ACE-011 or ACE-011/placebo dose and at end of study treatment (day 43 post last dose).

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days prior to the start of ACE-011 or ACE-011/placebo or administration (Day 1) once the subject has been on effective contraception for at least 28 days. Subjects must agree to use highly effective birth control measures (eg, oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of ACE-011 or ACE-011/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of ACE-011 or ACE-011/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with ACE-011 or ACE-011/placebo to ensure levels are within normal limits and that ACE-011 dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (Part 1).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the treatment period, every month (except month 1) during the post treatment follow-up period and at study discontinuation .

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of ACE-011 or ACE-011/placebo and end of study treatment (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of ACE-011 or ACE-011/placebo. For full PK assessment, weekly after first dose of ACE-011.

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of the first and second dose of ACE-011 or ACE-011/placebo and at 2 month post-treatment follow-up visit.

[l]Bone Biomarkers- Collected for full PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. For all other subjects collected prior to dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of ACE-011. Approximately 10 subjects at each ACE-011 dose level, 15.0, 30.0 and 45.0 mg, will have more full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment.

Pharmacokinetics (**Part 2**): Blood samples will be collected to evaluate the blood or serum concentrations of ACE-011. ACE-011 doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening tumor assessments may be performed up to six weeks prior to randomization. Historical tumor assessment data from prior to initiation of platinum-based chemotherapy through randomization to the study will also be collected. Following randomization, tumor assessments will be performed every 9 weeks (± 7 days).

[p]QoL assessments, FACIT Fatigue Scale (Version 4) and LCSS questionnaire, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]ACE-011 or ACE-011/placebo dosing repeats every 42 days and will begin after the subject begins an every 3 week platinum-based chemotherapy regimen. The first dose of ACE011 or ACE-011/placebo should be given within +/- 3 days of a chemotherapy cycle. Subsequent cycles of the chemotherapy dosing schedule, included dose reductions and delays, should not affect the ACE-011 or ACE-011/placebo dosing schedule, unless determined to be necessary by the Investigator. ACE-011 or ACE-011/placebo can be administered at any time point during the chemotherapy cycle. If there is a chemotherapy dose delay, ACE-011 or ACE-011/placebo administration does not need to be delayed until start of next chemotherapy cycle.

[r]Every 3-week platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. ACE-011 or ACE-011/placebo administration should be given prior to chemotherapy administration on ACE-011 or ACE-011/placebo administration days.

[s]Pemetrexed maintenance chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose corresponds to the end of Treatment Period. Subjects who discontinue the ACE-011 or ACE-011/placebo Treatment Period early will continue to the Post Treatment Follow-Up Period and be followed for up to 6 months after their last dose of ACE-011/placebo.

[u]Study Discontinuation visit should occur 12 months after starting treatment with ACE-011 or ACE-011/placebo.

[v]Survival data will be collected monthly, via telephone contact, following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of ACE-011 or ACE-011/placebo).

Table 8: Schedule of Pharmacokinetic Assessments

Scheduled Time	Time relative to ACE-011/placebo dose[a]	Part 1[b]		Part 2[b]	Collection Window[e]
		Full PK[c]	Sparse PK[d]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	-	± 3 days
Dose 4, D43 (Dose 5, D1)	42 days after Dose 4 (pre-Dose 5 in **Part 2**)	X	X	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6 in **Part 2**	-	-	X	± 3 days
Follow up, 1 month	72 days after final dose	X	-	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	X	± 1 week

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first ACE-011 dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first ACE-011 dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 30 subjects (approximately 10 subjects in each dose group).

[d] To be collected in other subjects.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed within 28 days prior to randomization. Historical tumor assessment data from six weeks prior to initiation of platinum-based chemotherapy through randomization to the study will be collected. Hematology and chemistry laboratory assessments should be performed within 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac, renal and thromboembolic events
- NSCLC history, including date of original diagnosis, histopathology, clinical stage at screening, date of metastatic stage and site involvement
- Prior ESA treatment history starting from initial diagnosis of NSCLC
- RBC transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up two months prior to randomization
- 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, with a minimum sensitivity of 25mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to ACE-011 or ACE-011/placebo administration
- Serum chemistry, hematology, absolute reticulocyte count to be assessed within 14 days of randomization
- Creatinine clearance (per Cockroft-Gault formula) within 14 days prior to study treatment administration
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and red blood cell folate levels
- Serum erythropoietin
- Urinalysis

- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Bone imaging – DXA scan
- Tumor Assessment - Screening tumor assessments and tumor evaluation documentation, as per RECIST criteria, must be performed within 6 weeks prior to randomization to this study. Also, historical tumor assessment data from prior to initiation of platinum based chemotherapy through randomization to the study will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose ranging portion of the study), subjects who meet all eligibility criteria will be randomized by a single-blind procedure utilizing IVRS to receive one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

In **Part 2**, subjects meeting all inclusion and exclusion criteria will enter into the Treatment Period and be randomized by a double-blind procedure utilizing IVRS to receive ACE-011 or placebo (1:1 ratio).

A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of ACE-011 or ACE-011/placebo every 42 days during the Treatment Period, as specified in the Table of Events (see Section 5).

In **Part 1**, the Treatment Period will last approximately 6 months, where subjects randomized to ACE-011 will receive treatment on Day 1 every 42 days for a planned 4 doses.

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to ACE-011/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with and additional two doses of ACE-011/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP.
- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of ACE-011 or ACE-011/placebo and at subsequent ACE-011 or ACE-011/placebo doses collected at 7, 14 days and 28 days post-dose by local laboratory.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 43 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and 43 days after last dose of study treatment
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for ACE-011 drug antibody test (**pre-dose** on the day of ACE-011 or ACE-011/placebo administration)

- Bone or other biomarkers
- Activin A and other ACE-011-related proteins/biomarkers in blood and tissue (**pre-dose** on Day 1 and Day 8 after first dose of ACE-011 or ACE-011/placebo)
- Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo)
- Tumor Assessment and Response Evaluation, as per RECIST criteria, (every 9 weeks ± one week) following chemotherapy schedule
- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Evaluation and all AE/SAE reporting (regardless causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or maintenance chemotherapy
- Administration of ACE-011 or ACE-011/placebo at: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will enter the Post Treatment Follow-Up Period and be followed for 6 months after their last dose of ACE-011 or ACE-011/placebo. Upon completion of the Post Treatment Follow-Up Period, subjects will have a discontinuation visit and be followed for survival for up to 24 months from their first dose of ACE-011 or ACE-011/placebo.

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

Following completion or early discontinuation from the Treatment Period, subjects will enter the Post Treatment Follow-Up Period and continue to be followed for 6 months after their last dose of ACE-011 or ACE-011/placebo. Visits will occur every month. The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)

- Vitamin B12 and red blood cell folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH (at 2 month end of treatment follow-up visit)
- Serum for ACE-011 drug antibody test (pre-ACE-011 or ACE-011/placebo dose)
- Bone or other biomarkers
- Bone imaging – DXA scan (at 3 month end of treatment follow-up visit)
- Activin A and other ACE-011 related proteins/biomarkers in blood and tissue (**pre-dose** ACE-011 or ACE-011/placebo at 1 month end of treatment follow-up visit)
- Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo at day 43 post last dose and 1 month end of treatment follow-up visit)
- Pharmacokinetics
- Tumor Assessment and Response Evaluation, as per RECIST criteria, (every 9 weeks ± one week) following chemotherapy schedule
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of ACE-011 or ACE-011/placebo). After 6 weeks post last dose of ACE-011 or ACE-011/placebo, only AEs assessed as related to ACE-011 or ACE-011/placebo or study related procedures are to be reported.
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Study Discontinuation

Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects.

Subjects who discontinue from treatment early will enter the Post Treatment Follow-Up Period and be followed for 6 months from their last dose of ACE-011 or ACE-011/placebo. Follow-up for twelve months for TTP and PFS will be performed from the subject's first dose of ACE-011 or ACE-011/Placebo. Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of ACE-011 or ACE-011/placebo).

The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) – if Study Discontinuation date is ≤ 112 days following the last dose of ACE-011 or ACE-011/placebo.
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Estrogen and estradiol – females only
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Tumor Assessment and Response Evaluation, as per RECIST criteria (PFS at 12 months)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Reporting of adverse events (only AE/SAE assessed related to study treatment are to be reported)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Survival Follow-Up Period:

Monthly collection of survival data will begin following the Study Discontinuation Visit and continue for an additional 12 months (up to 24 months after first dose of ACE-011 or ACE-011/placebo).

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Additional Procedure Descriptions:

Central ECG

Part 1 – ECGs will be performed and read per Central ECG vendor.

Part 2 – ECGs will be performed locally and read per Central ECG vendor.

Please refer to vendor manual for procedures.

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone will be performed by a central laboratory.

Please refer to vendor manual for procedures.

Note: Local laboratory assessments are allowed in cases when timely results are needed (e.g., randomization, study treatment and chemotherapy dosing decisions, hematology assessments between clinic visits). Local laboratory data should be collected in the eCRF.

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population in a subset of subjects.

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio, and other serum biomarkers will also be evaluated from all subjects.

Circulating Tumor Cell Enumeration and Molecular Studies

Analysis will be performed in a subset of subjects.

Pharmacokinetics

- Part 1 - Full PK blood samples will be collected to evaluate the full PK profile of ACE-011 from approximately 30 subjects at select centers (approximately 10 subjects for each ACE-011 dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.
- Part 2- Sparse PK blood samples will be collected from all subjects.

Detailed PK sampling schedule is presented in Table 8: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of ACE-011 or ACE-011/placebo administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

Bone Biomarkers

Bone or other biomarkers will be evaluated in all subjects. The serum and urine biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

Bone Imaging

DXA scan to evaluate overall bone health will be performed on approximately 200 subjects at select site(s)

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire will be completed by the subject upon arrival at clinic and prior to any study procedures or testing.

Independent External Radiology Review

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC): The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each patient. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

7. STUDY POPULATION

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

7.1. Number of Subjects

This NSCLC platinum-based CIA study will enroll approximately 840 subjects in **Part 1** and **Part 2**.

In **Part 1**, up to 90 subjects will be randomized to receive one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC
- ACE-011 45.0 mg SC

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)

In **Part 2**, an additional 750 subjects will be randomized to receive either ACE-011, at the dose determined in Part 1, or placebo at a ratio of 1:1. Subjects will be randomized to receive either ACE-011 or placebo and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
4. ECOG Performance Status 0-1 vs. 2

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document
2. Histologically confirmed (cytology or biopsy) non-small cell carcinoma of the lung
3. Documented metastatic (Stage IV) disease, including pleural or pericardial effusion involvement
4. Measurable or non-measurable disease evaluable by RECIST criteria (Appendix A)
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L)
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 25,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function (creatinine < 1.5 x upper limit of normal [ULN] or ≥ 50 mL/min)
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤5 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL), previous hypercalcemia treatment is allowed
6. Subjects may have received up to 3 cycles of a current first line platinum-based chemotherapy treatment regimen for metastatic NSCLC. Allowed regimens are:
   - gemcitabine plus cisplatin or carboplatin ± bevacizumab
   - pemetrexed plus cisplatin or carboplatin ± bevacizumab
   - paclitaxel plus carboplatin ± bevacizumab

   Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.
7. ≥ 28 days must have elapsed since previous treatment with ESA
8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 56 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)
10. If currently receiving bisphosphonate therapy, be on a stable dose for ≥ 2 months before Day 1 (ongoing bisphosphonate therapy is allowed during study provided it is kept at a stable level, bisphosphonate therapy may not be started on study, other than for the treatment of hypercalcemia). Subjects not currently on bisphosphonates must not have received bisphosphonates within 2 months prior to Day 1.

11. 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 at least 112 days following the last dose of ACE-011 or ACE-011/placebo.

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days prior to ACE-011 or ACE-011/placebo administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).

12. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of ACE-011 or ACE-011/placebo, even if he has undergone a successful vasectomy.
13. Life expectancy of ≥ 3 months
14. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements
15. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C] at the time of screening, except for the following disease related toxicities: hematological events [e.g. anemia, thrombocytopenia or neutropenia] or non hematological events [e.g. 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 subject participation in the study, at the discretion of the Investigator.

3. History of prior regimen(s) of platinum-based chemotherapy for metastatic NSCLC.
4. CNS metastases (exception: CNS metastases treated with whole brain radiotherapy > 6 months prior to randomization).
5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying NSCLC.
6. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).
7. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.
8. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
9. 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).
10. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
11. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (BP) must be < 160 mmHg and diastolic BP must be < 100 mmHg.
12. Known infection with human immunodeficiency virus (HIV).
13. Known active hepatitis B or C antibody defined by positive serology.
14. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or folate. Subjects may be re-screened following treatment with supplements and normalization of levels.
15. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
16. History of anemia due to autoimmune or hereditary hemolysis or gastrointestinal bleeding.
17. Urine protein / creatinine ratio < 1.0
18. 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.
19. Any prior use of ACE-011.
20. Pregnant or lactating females or females planning to become pregnant.
21. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).
22. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Process IIa Clinical Drug Product

ACE-011 will be provided as a 1 mL solution of 50 mg/mL in phosphate buffered saline (PBS), pH 7.5, in labeled 2 mL vials with rubber stoppers, providing 50 mg per vial. ACE-011 is recommended to be stored at ≤ -65˚C (colder than -65˚C) until thawed for administration. ACE-011 should be used within 6 hours of thawing.

In **Part 2**, the ACE-011 placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Sterile, normal saline will be supplied by the investigational site's pharmacy. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

8.2. Treatment Administration and Schedule

ACE-011 or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh. Vials of ACE-011 must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.

At the time of randomization all subjects must be receiving their first-line regimen of platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects will be randomized to this study during the time period in which they are receiving Cycle 1 to Cycle 3 of their first regimen of first-line platinum-based chemotherapy. Subjects must not have received any prior regimens of platinum-based chemotherapy for metastatic NSCLC.

Allowed concomitant platinum-based chemotherapy regimens are:

- gemcitabine plus cisplatin or carboplatin ± bevacizumab
- pemetrexed plus cisplatin or carboplatin ± bevacizumab
- paclitaxel plus carboplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Subjects may receive 4-6 cycles of the allowed platinum-based regimen selected by the Investigator. The addition of up to 2 cycles of platinum-based chemotherapy may be given following cancer response. The platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

Maintenance chemotherapy with a pemetrexed-containing regimen will only be allowed following completion of the subject's platinum-based chemotherapy, with a best response of at least stable disease.

Subjects must be given ACE-011 or ACE-011/placebo prior to chemotherapy administration on the dose administration days.

In **Part 1** and **Part 2**, ACE-011 or ACE-011/placebo dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb. Dose delays of ACE-011 or ACE-011/placebo and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

In **Part 1**, subjects will be randomized to one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of ACE-011, a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of $\geq$ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions and/or ESAs. In order to determine the optimal dose of ACE-011 to be used in Part 2, evaluation of hematopoietic response will be determined from ACE-011 dose 1/day 1 through and including dose 2/day 43 (prior to dose 3).
- In addition to the hematopoietic response, safety profile, dose modifications and extent of exposure will be taken into account for dose level selection for Part 2.

Hematopoietic response will be determined by laboratory analysis.

In **Part 2**, subjects will be randomized to receive either ACE-011 (at the dose determined in Part 1) or placebo.

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive ACE-011 or ACE-011/placebo starting on Day 1 (one SC dose every 42 days) and continuing during the six month Treatment Period, as outlined in the Table of Events (see Section 5).

In **Part 1**, subjects will be randomized to receive one of three doses of ACE-011, with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive ACE-011 or placebo at a ratio of 1:1.

Each subject will return to the site on Day 1 of each scheduled visit. During the Treatment Period, subjects will receive ACE-011 or ACE-011/placebo every 42 days as determined by Hgb

levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated by local lab weekly after the first dose of ACE-011 or ACE-011/placebo then at 7, 14 and 28 days after each subsequent dose of ACE-011 or ACE-011/placebo.

The **first** dose of ACE-011 or ACE-011/placebo should be given within +/- 3 days of **Day 1** of a platinum-based chemotherapy **Cycle**. Subsequent cycles of the chemotherapy dosing schedule, included dose reductions and delays, should not affect the ACE-011 or ACE-011/placebo dosing schedule, unless determined to be necessary by the Investigator. ACE-011 or ACE-011/placebo can be administered at any time point during the chemotherapy cycle. If there is a chemotherapy dose delay, ACE-011 or ACE-011/placebo administration does not need to be delayed until the start of the next chemotherapy cycle. ACE-011 or ACE-011/placebo should be given prior to chemotherapy administration.

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of ACE-011 or ACE-011/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of ACE-011 or ACE-011/placebo, or until progression of their NSCLC, whichever comes first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of NSCLC that requires the initiation of another treatment.

Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of ACE-011 or ACE-011/placebo).

8.2.3. Discontinuation

Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from ACE-011 treatment:

- AE(s)
  - Medically significant hypertension which 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)
  - Creatinine clearance < 40 ml/min
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)

  - Persistent hematuria
- Lack of ACE-011 therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of ACE-011 or ACE-011/placebo
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- ACE-011 or ACE-011/placebo Dose Modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL
  - In **Part 2:** > 3 dose reductions and/or delays
- Disease Progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

The reason for treatment discontinuation should be recorded in the eCRF 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 (subject has completed six to nine month Treatment Period plus up to six month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- AE(s)
- Disease progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF 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.

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to 4 doses of ACE-011 in Part 1. In Part 2, subjects will be randomized at a ratio of 1:1 and receive up to 4 doses of study treatment with an additional 2 doses of ACE-011/placebo allowed, if clinically indicated, at the discretion of the Investigator. A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

8.4. Packaging and Labeling

The label(s) for investigational product (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 secured 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 investigational medicinal product.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF 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

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 and 7.3 Inclusion Criteria and 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 eCRF throughout the course of the study.

Concomitant therapies considered as supportive care are acceptable while participating in this study including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting and palliative radiation and bisphosphonates (Refer to Inclusion Criterion, Section 7.2) for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

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.

Iron supplementation

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

Erythropoiesis-stimulating agents (ESAs)

The use of ESAs are not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study sponsor and Medical Monitor, as well as to the unblinded clinical site pharmacist, so that **no further dosing with ACE-011 in that study subject will occur. Subjects will not be unblinded.** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

In **Part 1**, all subjects who receive an ESA will be discontinued from the study treatment period and continue to the post treatment follow-up period. In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of ACE-011 or ACE-011/placebo will be discontinued from the study treatment period and continue to the post treatment follow-up period. Subjects who receive an ESA at ≥ 4 months from their first dose of ACE-011/placebo will continue in the treatment period. **The unblinded pharmacist will ensure that subjects randomized to receive**

treatment with ACE-011 are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo.

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is > 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, ACE-011 should be administered no sooner than 7 days from the date of the RBC transfusion.

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate therapy (see Section 7.2), other than for the treatment of hypercalcemia, must not be started on study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a single-blind, randomized, phase 2a, dose ranging study of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of ACE-011 for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. In **Part 1**, subjects will be randomized to one of three doses of ACE-011 plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected ACE-011 dosing schedule from Part 1 plus platinum-based chemotherapy.

A DMC will be used to monitor the study conduct.

10.2. Study Population Definitions

Three study populations will be used for analyses.

- The Intent-to-Treat (ITT) Population – All randomized subjects.
- Safety Population – All subjects who take at least one dose of study medication.
- Efficacy Evaluable (EE) Population – All ITT subjects who take at least one dose of study medication and have baseline and at least one post-baseline efficacy assessment without major protocol deviation.

10.3. Sample Size and Power Considerations

In **Part 1**, up to 90 subjects will be randomized among three dosing groups. This sample size is for the purpose of hypothesis generation. However, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a two-sided significance level (alpha) of 0.05.

In **Part 2**, subjects will be enrolled in two stages. In the first stage, approximately 180 subjects will be randomized in a 1:1 ratio to the selected ACE-011 dose group or placebo group. An interim analysis of transfusion rate will be performed after these 180 subjects have received at least two doses of ACE-011/placebo, and have been followed for at least 4 months from randomization. A Data Monitoring Committee will review the results and provide recommendations on continuing or stopping the study. Based on the results of the futility analysis, further enrollment in the second stage of Part 2 of the study could be continued.

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in Part 2 (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude more than 15% risk reduction in the ACE-011 arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:ACE-011) of 0.87, assuming the ACE-011 arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:ACE-011) of 1.11.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics by treatment arm, 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 by treatment arm. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

In **Part 1**, the primary endpoint will be the hematopoietic response defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the first ACE-011 treatment. It will be estimated based on Kaplan-Meier estimates for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects with a documented RBC transfusion will be considered having the event. Subjects without documented RBC transfusion will be censored on the date of last contact or a month after the last dose of study treatment, or termination of the concomitant chemotherapy, whichever is earlier. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test.

As secondary endpoints for Part 2 of the study, time to progression, progression free survival and overall survival will be analyzed based on the ITT population.

Time to progression (TTP) is defined as the time between the randomization date and date of disease progression. **Disease progression is based on the IRC reviewed progression date.** If a subject dies due to reasons other than disease progression, the subject will be censored at the death date. If a subject does not have disease progression, then the subject will be censored at the last tumor assessment (prior to or on the first day of the first subsequent antitumor therapy).

Progression free survival (PFS) is defined as the time between the randomization and disease progression or death. **Disease progression is based on the IRC reviewed progression date.** Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the subject is censored at the time of last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. The date of progression is taken as the earliest date of: Date of PD as evaluation of response, date of new lesion on tumor measurements page, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who did

not progress nor died (lost to follow-up or still being treated without documented disease progression or started subsequent antitumor therapy) will be censored at the date of the last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. PFS based on investigators' assessment will also be analyzed.

Overall survival (OS) is defined as the time between the randomization and death. A subject that dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the distribution function, six-month and one-year survival rates, as well as the medians and 95% confidence intervals will be provided. The stratified log rank test will be used to compare the distributions of TTP, PFS and OS respectively. The stratification factors are described in Section 4.1 . The associated hazard ratios and confidence intervals will be provided using stratified Cox proportional hazard model respectively for each endpoint.

Sensitivity analyses will be performed on TTP, PFS, and efficacy analyses will also be performed using EE population. Data listings will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.

10.7. Safety Analysis

All safety subjects will be used for safety analyses. 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 study part and treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized. Safety information obtained during the Post Treatment Follow-Up Period during each segment will be incorporated into these analyses.

10.8. Interim Analysis

There are two interim analyses planned for this study. At the first interim analysis, the transfusion rate result will be used for go/no go decision, and overall survival will also be analyzed. At the second interim analysis, only the overall survival will be analyzed.

The first interim analysis on transfusion rate will be conducted after the first 180 eligible subjects randomized in Part 2 of the study (stage 1) who have received at least two doses of ACE-011/placebo, have been followed for at least 4 months from randomization. This sample size would allow at least 90% power to detect a 15% difference between two arms (ACE-011 arm 15% vs. placebo 30%) in 4 month transfusion rates at two-sided 5% significance level based on the stratified log rank test and the assumption of exponential distribution for time to RBC transfusion. If the p-value at the interim analysis does exceed significance level of 0.05, the result will be considered as lack of efficacy. If the p-value is less than or equal to 0.05, additional subjects will be enrolled and the study will move on to the Part 2; however, the futility analysis result based on RBC transfusion rate may be up to DMC evaluation. For superiority,

Type I error 0.0001 will be spent at this interim for transfusion rate, and the remaining 0.0499 will be spent at the final analysis after 750 subjects being enrolled.

Overall survival will also be analyzed at this interim, Type I error spending will be based on O'Brien and Fleming Boundary.

The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. Type I error spending will be based on O'Brien and Fleming boundary.

The final analysis will be performed when approximately 536 deaths are observed in Part 2.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of Part 1. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for ACE-011, such as t_{max}, C_{max}, AUC_{42}, CL/F, Vz/F, and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

In exploratory population PK analysis, covariates to be tested may include type of chemotherapy, the presence of anti-ACE-011 antibodies, demographics (age, race, gender, and body weight), markers for hepatic and renal function, and other factors as deemed appropriate. Both full and sparse PK data will be included for population PK analyses.

The relationship between ACE-011 exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) will be explored.

10.10. Data Monitoring Committee (DMC)

A DMC will review safety and efficacy data to ensure the protection of study subjects. The DMC will receive periodic updates of all serious treatment-related toxicities and SAEs leading to deaths from all causes. The first planned review by the DMC will be conducted following the randomization and treatment of twenty subjects. The DMC will continue to monitor safety on an ongoing basis including recommendation of ACE-011 dose selection for Part 2. The first interim analysis will be conducted after the first 180 eligible subjects in Part 2 of the study (stage 1) have been followed for at least 4 months for RBC transfusion rate. The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. The final analysis will be performed when approximately 536 deaths are observed in Part 2.

Ad hoc meetings will be scheduled as needed.

The DMC will have a consultative role with respect to the Sponsor. The Sponsor will make the final decision regarding the recommendation proposed by the committee. A separate DMC charter will detail the activities of this committee.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately (i.e., 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. Seriousness

An 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF 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

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of 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

The Investigator will provide a record of the start and stop dates of the AE/SAE.

The duration of the AE and the SAE may vary within one event. For example, a non-serious AE may begin on 01-Jan. The event will become serious when it meets one of the criteria for seriousness (e.g., the subject is hospitalized on 05-Jan). The SAE will continue until it no longer

meets the seriousness criteria (e.g., the subject is discharged on 07-Jan). However, the AE continues until 10-Jan when the event resolves. The AE dates may extend from before and beyond the SAE dates, but not the reverse.

11.2.5. Action Taken

The Investigator will report the discontinuation or reduction of IP following an AE and report if concomitant and/or additional treatments were given for the AE.

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 (delay) 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 an SAE.

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential:

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

The female should be referred to an obstetrician-gynecologist.

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 Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), 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

Female partners of male subjects taking IP should be advised to call their healthcare provider immediately if they become pregnant, and male subjects should notify the Investigator.

11.5. Immediate 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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

The SAE report should provide a detailed description of the SAE and include copies 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 Institutional Review Board (IRB)/Ethics Committee (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.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

- Any AE associated with 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 SAE Report Form.

12. DISCONTINUATIONS

Please refer to Section 8.2.3.

Stopping Rules

In addition to Celgene routine pharmacovigilance surveillance, a DMC will review unblinded data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

In both Part 1 and Part 2 the blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.

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 eCRFs 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.

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

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

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

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

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

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

- Information on serious or unexpected 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via an electronic data capture (EDC) system rather than paper. Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. The Clinical team and investigational site personnel will be alerted of discrepant data by the functionality of the system. 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g. FDA, EMEA, 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.

18. REFERENCES

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. Submitted 2008.

Chen Y-G, Lui HM, Lin S-L, Lee JM, and Ying S-Y. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. *Exp Biol Med* 2002; 227: 75-87.

Dang TP, Carbone DP: Cancer of the Lung, in DeVita, VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 8th edition, Philadelphia, PA. Lippincott Williams & Wilkens, 2008, 887-971.

Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F Version 4. *http://www.facit.org/qview/qlist.aspx*, last accessed 21Jul2010.

Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *Journal of the National Cancer Institute* 1999, 91, 1616-1634.

Hollen PJ, Gralla RJ, Kris MG 'Lung Cancer Symptom Scale (LCSS)', *Administration, Scoring and Procedures Manual*, (1995) Ver.1.1.

Hong WK, Tsao AS, in Lung Carcinoma: Tumors of the Lungs: Merck Manuals Online Medical Library for Healthcare Professionals, 2008.
http://www.merck.com/mmpe/print/sec05/ch062/ch062b.html

Lotinun S, Fajardo RJ, Pearsall RS, Bouxsein ML, and Baron R. A soluble activin receptor type IIA fusion protein, ACE-011, increases bone mass by stimulating bone formation and inhibiting bone resorption in cynomolgus monkeys. ASBMR 30th annual meeting, 2008.

Mathews LS. Activin receptors and cellular signaling by the receptor serine kinase family. *Endocr Rev* 1994; 15: 310-25.

Murata M, Onomichi K, Eto Y, Shibai H, and Muramatsu M. Expression of erythroid differentiation factor (EDF) in Chinese hamster ovary cells. *Biochem Biophys Res Commun* 1988; 151: 230-5.

Nakao K, Kosaka M and Saito S. Effects of erythroid differentiation factor (EDF) on proliferation and differentiation of human hematopoietic progenitors. *Exp Hematol* 1991; 19: 1090-5.

National Heart, Lung, and Blood Institute, National Institutes of Health. New York Heart Association Classification. 2008.

NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, V.2. 2010 http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf; 2009.

Non-small Cell Lung cancer Collaborative Group 'Chemotherapy in non-small cell lung cancer: a metaanalysis using updated data on individual patients from 52 randomized clinical trials', *British Medical Journal* 1995 vol. 311, no.7010, 899-909.

Oken, MM., Creech, R.H., Tormey, D.C., et. al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982; 5:649-655.

Parker SL, Tong T, Bolden S, et. al. Cancer statistics, 1997. *CA Cancer J Clin*, 1997, 47, no. 1, 5-27.

Pearsall RS, Canalis E, Cornwall-Brady M, Underwood KW, Haigis B, Ucran J, Kumar R, Pobre E, Grinberg A, Werner ED, Glatt V, Stadmeyer L, Smith D, Seehra J, and Bouxsein ML. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. Proc Natl Acad Sci USA 2008, 105: 7082-7.

Perrien DS, Akel NS, Edwards PK, et. al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology* 2007; 148: 1654-65.

Rivier J, Spiess J, McClintock R, Vaughan J and Vale W. Purification and partial characterization of inhibin from porcine follicular fluid. *Biochem Biophys Res Commun* 1985; 133: 120-7.

Rossi A, Maione P, Gridelli C Cetuximab in advanced non-small cell lung cancer. *Critical Reviews in Oncology/Hematology*, 2006 59, 139-149.

Ruckle J, Jacobs M, Kramer W, et. al. A single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res* 2009; 24 (4): 744-52.

Sandler A, Gray R, Perry M, et al Paclitaxel-Carboplatin alone or with Bevacizumab for Non Small Cell Lung Cancer, *NEJM*, 2006 vol.355, no.24, 2542-50.

Scagliotti G, Parikh P, von Pawel J, et al Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve patients With Advanced-Stage Non-Small-Cell Lung Cancer, JCO, 2008, 26 (21): 3543-51.

Schiller J, Harrington D, Belani C, et al Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Seder C, Hartojo W, Lin L, et al Upregulated INHBA Expression May Promote Cell Proliferation and Is Associated with Poor Survival in Lung Adenocarcinoma, Neoplasia, 2009, 11: 388-396.

Shedden K, Taylor J, Enkemann S, et al Gene Expression-Based Survival prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validaion Study: Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Nat Med, 2008, 14 (8): 822-827.

Shiozaki M, Sakai R, Tabuchi M, et. al. Evidence for the participation of endogenous activin A/erythroid differentiation factor in the regulation of erythropoiesis. *Proc Natl Acad Sci USA* 1992; 89: 1553-6.

Shiozaki M, Sakai R, Tabuchi M, et. al. In vivo treatment with erythroid differentiation factor (EDF/activin A) increases erythroid precursors (CFU-E and BFU-E) in mice. *Biochem Biophys Res Commun* 1989; 165: 1155-61.

Vansteenkiste J, Pirker R, Massuti B, et.al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute, 2002, 94: 16: 1211-1220.

Woodruff TK. Regulation of cellular and system function by activin. *Biochem Pharmacol* 1998; 55: 953-63.

Ying S-Y. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine Rev* 1988; 9: 267-93.

19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Terms	**Definition**
Measurable disease	The presence of at least one measurable lesion by CT or MRI. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions	Lesions that can be accurately measured in least one dimension by CT scan with longest diameter $\geq$ 10 mm (CT scan thickness no greater than 5 mm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Non-measurable lesion	All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

RECIST Criteria-Response Evaluation

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
***Partial Response (PR)*:**	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
***Stable Disease (SD)*:**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
***Progressive Disease (PD)*:**	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

RECIST Criteria-Response Evaluation (continued)

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of best overall response	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (2009). European Journal of Cancer 45, 228-247.

Appendix B: 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 9: 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 C: 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 D: New York Heart Association - Classification of Heart Failure

Table 10: 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

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	Sotatercept (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
ORIGINAL DATE:	17 SEPTEMBER 2010
AMENDMENT No. 1 DATE:	22 MARCH 2011 (FINAL)
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

CONTACT INFORMATION:

PPD

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD	22March2011
Signature of Celgene Therapeutic Area Head	**dd mmm yyy**
PPD	
Printed Name of Celgene Therapeutic Area Head and Title	

By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below. These changes were based on feedback obtained from the FDA, investigators/sites and internal discussions:

1. FDA approval of use of Sotatercept (ACE-011) Process III Clinical Drug Product – Lyophilized Powder.
2. USAN/INN approval of "sotatercept" as the generic name for ACE-011.
3. Objectives
    a. Clarification of Part 2 primary objective of transfusion rate.
    b. Clarification of Parts 1 and 2 secondary objectives to evaluate the hematopoietic response and duration associated with ACE-011.
    c. Clarification of exploratory objectives
        i. Defined Activin A and other proteins/biomarkers, including mysostatin and follistatin, assessed in blood.
        ii. Defined Activin A and other proteins/biomarkers assessed in tumor tissue.
        iii. Deleted circulating tumor cell assessment.
4. Endpoints
    a. Clarification of Part 2 primary endpoint of transfusion rate.
    b. Addition of secondary endpoint – Duration of hematopoietic response.
    c. Specification of renal biomarkers for renal function assessment.
5. Clarification of metastatic non small cell lung cancer patient population.
6. Clarification of hemoglobin level and RBC transfusion for chemotherapy-induced anemia and timeframe of RBC transfusion versus ACE-011 (sotatercept) administration.
7. Revision of Introduction Section to include updated nonclinical findings and deletion of comparator claims.
8. Modification to increase the allowed dosing time period of the **first** dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to and following a cycle of platinum-based chemotherapy.
9. Clarification of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule versus platinum-based chemotherapy dosing schedule and order of dosing, if administered on the same day.
10. Clarification of randomization in Part 1 to describe the analysis of safety data following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12 week follow-up period from first dose and the subsequent decision to add a third dose level of 45.0 mg to the randomization schema.

11. Revision of Inclusion Criteria:
    a. Revised typographical error – Platelet count ≥75,000/mm^3 instead of ≥25,000/mm^3
    b. Defined adequate renal function as creatinine clearance ≥ 40 mL/min or ≥ 50 mL/min if cisplatin concomitantly administered.
    c. Addition of concomitant platinum-based chemotherapy regimen docetaxel plus cisplatin ± bevacizumab.
    d. Clarification that subjects are expected to be eligible to receive at least two additional cycles of platinum-based chemotherapy at the time of randomization.
    e. Revision of timeframe of pre-dose Day 1 RBC transfusion ≥ 14 days and receipt of ≤ 2 units in past 30 days.
    f. Addition of denosumab (XGEVA™) as an acceptable concomitant therapy for the treatment of bone metastases.
12. Revision of Exclusion Criteria:
    a. Clarification of exclusion of subjects with ≥ Grade 3 toxicities or major end-organ dysfunction, irrespective of whether they are considered disease related, except for hematotoxicity and non hematologic events occurring during the chemotherapy period and resolving.
    b. Modified to exclude CNS metastases that have not been treated and stable for at least 2 weeks prior to randomization.
    c. Modified to exclude subjects with ≥ 150mm Hg systolic or diastolic blood pressure ≥ 100mm Hg.
    d. Modified to exclude subjects with a history of gastrointestinal bleeding occurring with the past 6 months.
    e. Correction of typographical error to – urine protein / creatinine ratio > 1.0.
13. Revision of dose modification algorithm for hypertension and additional clarification of dose modification rules.
14. Clarification of collection of historical tumor assessment data and acceptable screening tumor assessment timeframes. Modification of post - randomization tumor assessment timeframes.
15. Addition of erlotinib (Tarceva®) - based regimens as allowed maintenance therapy.
16. Clarification of Treatment Discontinuation Rules:
    a. Revised language to instruct investigators regarding criteria for study therapy discontinuation.
    b. Addition of specific blood pressure parameters.
    c. Addition of definition of persistent hematuria.

17. Clarification of Study Discontinuation Rules to define events that **are** considered reasons for study discontinuation versus events that **may be** considered reasons for discontinuing a subject from the study.
18. Revisions to Schedule of Assessments
    a. Addition of blood pressure measurement at Day 29 following dosing of sotatercept (ACE-011).
    b. Clarification that blood pressure measurements should be confirmed by two measurements obtained five minutes apart.
    c. Addition of measurement of weight to correspond with creatinine clearance assessments.
    d. Addition of serum chemistry assessments to correspond with creatinine clearance assessments.
    e. Clarification that renal biomarkers are assessed at the same visits as urinalysis.
    f. Clarification that tumor tissue is an archival sample and not required to be collected on study.
19. Clarification of Pharmacokinetic Assessments
    a. Clarification that subjects not participating in the full pharmacokinetic assessment in Part 1 of the study will participate in the sparse pharmacokinetic assessment.
    b. Clarification that sparse pharmacokinetic samples will be collected from approximately 300 subjects in Part 2 of the study.
    c. Addition of a separate Schedule of Pharmacokinetic Assessments Table for Part 2 of the study.
20. Revision of term in Iron Supplementation from 'iron deficient' to 'iron replete'.
21. Revisions to Statistical Analyses
    a. Clarification that data from Parts 1 and 2 of the study will not be combined in safety and efficacy analyses.
    b. Correction of typographical error in Sample Size and Power Considerations from '15% risk reduction' to '15% hazard increase'.
    c. Clarification of Efficacy Analysis to better define the primary endpoint, transfusion rate, in Part 2 of the study.
22. Data Monitoring Committee – clarification throughout the protocol on the role and responsibilities of the DMC.
23. Revision of serious adverse event reporting period from 112 to 42 days for events not suspected to be related to investigational product.

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

2. ITEMIZED CHANGES

2.1. Section: Title Page, (page 1)

Original Text:

A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE RANGING STUDY (PART 1) OF ACE-011 THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF ACE-011 FOR CHEMOTHERAPY INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

Revised Text:

A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY- INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

Rationale:

The USAN/INN approved the name sotatercept for ACE-011. The term “ACE-011” has been replaced with “sotatercept (ACE-011)” throughout the protocol.

2.2. Section: Title Page, (page 1)

Original Text:

INVESTIGATIONAL PRODUCT (IP):	ACE-011
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

Revised Text:

INVESTIGATIONAL PRODUCT (IP):	Sotatercept (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
AMENDMENT 1.0 DRAFT:	15 MARCH 2011 (DRAFT)
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

Rationale:

Updated to include amendment version and date.

2.3. Section: MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION, (page 2)

Original Text:

Contact Information:	
PPD	

Revised Text:

Contact Information:	
PPD	

Rationale:

Addition of Medical Monitor to the header information to align with the current protocol template. Also, updated information to include the new Clinical Research Physician.

2.4. Section: Protocol Summary, (page 6)

Original Text:

Study Title

A single-blind, randomized, phase 2a, dose ranging study (**Part 1**) of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of ACE-011 for chemotherapy induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapeutic regimens.

Revised Text:

Study Title

A single-blind, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia ~~(CIA)~~ in subjects with metastatic non-small cell lung cancer ~~(NSCLC)~~ treated with first-line platinum-based chemotherapeutic regimens.

Rationale:

The USAN/INN approved the name sotatercept. The term ACE-011 has been replaced with sotatercept (ACE-011) throughout the protocol.

2.5. Section: Protocol Summary, (pages 6-7)

Original Text:

The primary objectives are:

- **Part 1**: To determine an effective dose of ACE-011 showing a hematopoietic response in the treatment of CIA in advanced NSCLC subjects.
- **Part 2**: To assess transfusion rate within 4 months following initiation ACE-011 treatment.

The secondary objectives are:

Part 1 and **Part 2**:

- To estimate the effect of ACE-011 treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in advanced NSCLC subjects with CIA.
- To evaluate the safety and tolerability of ACE-011 treatment for advanced NSCLC subjects with CIA.
- To determine the PK of ACE-011 in subjects with advanced NSCLC receiving platinum-based chemotherapy.
- To estimate the duration of hematopoietic response associated with ACE-011.
- To evaluate the effect of ACE-011 treatment on the quality of life (QoL) of NSCLC subjects with CIA.

Part 2:

- To evaluate hematopoietic response

Revised Text:

Objectives

The primary objectives are:

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate ~~within 4 months~~ following initiation of sotatercept (ACE–011)/placebo treatment.

The secondary objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in ~~advanced~~metastatic NSCLC subjects with CIA.

- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment ~~for advanced~~in metastatic NSCLC subjects with CIA.
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects with ~~advanced~~metastatic NSCLC receiving platinum-based chemotherapy.
- To ~~estimate~~evaluate the ~~duration of~~ hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

~~**Part 2**:~~

- ~~To evaluate hematopoietic response~~

Rationale:

Primary objectives – Revised to clarify patient population and primary objective.

Secondary objectives – Revised to clarify patient population and analysis of hematopoietic response and delete redundant wording.

Original Text:

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of each ACE-011 treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between ACE-011 exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population.
- To assess circulating tumor cells and molecular studies
- To assess renal function biomarkers

Revised Text:

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of ~~each~~ sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression~~/overexpression~~ of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue ~~in the NSCLC population.~~
- ~~Circulating tumor cell enumeration and molecular studies.~~ .
- To assess renal function biomarkers.

Rationale:

Updated to provide clarification and specification of Parts 1 and 2 of exploratory objectives. Evaluating expression of Activin A, myostatin and follistatin as well as other additional biomarkers in both serum and in tumor tissue may help to better understand sotatercept (ACE-011) mechanism of action. Assessment of circulating tumor cells was deleted because the expression is very low in patients undergoing treatment with chemotherapy and because, to date, there is little evidence that tumor cells circulate at quantifiable levels in NSCLC patients.

2.6. Section: Protocol Summary, (page 7)

Original Text:

Study Population

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Revised Text:

Study Population

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles and must be randomized prior to receiving Cycle 4 of this current first-line platinum-based regimen to be eligible for the study. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Rationale:

Modified to include additional erlotinib-based maintenance regimen per investigator recommendation. Also, per FDA's recommendation clarification of study population description based on subjects being eligible to continue to receive platinum-based chemotherapy following randomization.

2.7. Section: Protocol Summary, (page 8)

Original Text:

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days of randomization, as outlined in the Table of Events, Section 5. **Historical tumor assessment data from six weeks prior to initiation of platinum-based chemotherapy through randomization to the study will be collected.**

Revised Text:

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days of randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks prior to randomization. **Also, h~~H~~istorical tumor assessment data, from ~~from six weeks~~ prior to the initiation of platinum-based chemotherapy through the screening period, ~~randomization to the study~~ will ~~-~~be collected and used for assessment of tumor response.**

Rationale:

Updated description of collection of tumor assessment data from prior to randomization. Clarification of the screening period timeframe and of the additional collection of historical tumor assessment data, from prior to initiation of first line platinum-based chemotherapy, to be used as the baseline tumor assessment.

2.8. Section: Protocol Summary, (pages 8-10)

Original Text:

Treatment Period (up to 6-9 months):

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

Evaluation of response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the optimal dose for Part 2.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is > 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, ACE-011 should be administered ≥ 7 days from the date of the RBC transfusion.

Revised Text:

Treatment Period (up to 6-9 months):

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12 week follow-up period from first dose. Following this analysis, the addition of a third dose level:

S~~Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:~~

- ~~ACE-011~~otatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the optimal dose for Part 2.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ~~>~~≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered ~~>~~≥ 7 days from the date of the RBC transfusion.

Rationale:

Revised per FDA's recommendation to clarify when safety analysis of the first 10 subjects treated with 15 and 30 mg dose levels of sotatercept (ACE-011) would occur.

Addition of term 'hemoglobin' to clarify the type of response to be evaluated for the optimal dose decision for Part 2 of the study.

Clarification of recommended RBC transfusion for the treatment of CIA per Hgb level and timeframe for RBC transfusion and sotatercept (ACE-011) administration.

Original Text:

In **Part 1**, full PK blood samples will be collected to evaluate the full PK profile of ACE-011 from approximately 30 subjects at select centers in approximately 10 subjects for each ACE-011 dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose.

In **Part 2**, sparse PK blood samples will be collected.

Revised Text:

In **Part 1**, full PK blood samples will be collected to evaluate the full PK profile of ~~ACE-011~~sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each ~~ACE-011~~sotatercept (ACE-011) dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

In **Part 2**, the sparse PK assessment will be performed in approximately 300 (40%) of 750~~blood samples will be collected~~ subjects (approximately 150 subjects in each arm).

Rationale:

Section updated to provide clarification of PK requirements in Parts 1 and 2 of the study.

Original Text:

The following events are considered sufficient reasons for discontinuing a subject from the Treatment Period:

- AE(s)
  - Medically significant hypertension which cannot be adequately controlled with antihypertensive therapy
  - Creatinine clearance < 40 ml/min
  - Persistent hematuria

Revised Text:

Subjects will be discontinued from Study Treatment due to the following:~~The following events are considered sufficient reasons for discontinuing a subject from the Treatment Period:~~

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mm Hg or diastolic blood pressure [DBP] ≥ 100mm Hg), confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.
  - ~~Creatinine clearance < 40 ml/min~~
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.

Rationale:

Updated to comply with FDA's feedback to use command language to instruct investigators to discontinue study therapy, provide blood pressure parameters and define persistent hematuria. Discontinuation based on creatinine clearance was deleted based on updated toxicology study data and investigator recommendation.

2.9. Section: Protocol Summary, (pages 10-11)

Original Text:

Post Treatment Follow-Up Period (monthly for up to 6 months)

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

- Completed study, per protocol (subject has completed six to nine month Treatment Period plus up to six month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- AE(s)
- Disease Progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

Revised Text:

Post Treatment Follow-Up Period (monthly for up to 6 months)

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- ~~AE(s)~~
- ~~Disease Progression of NSCLC~~
- Withdrawal of consent
- Death
- Lost to follow-up
- ~~Protocol violation~~

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

- AE(s)
- Disease progression of NSCLC
- Protocol violation

Rationale:

Separated the reasons for study discontinuation into two types to better define the reasons that will necessitate study discontinuation and reasons that may lead to study discontinuation.

2.10. Section: Protocol Summary, (page 12)

Original Text:

Overview of Exploratory Assessments

- Bone or other protein/biomarkers
- Circulating tumor cell enumeration and molecular studies

Revised Text:

Overview of Exploratory Assessments

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- ~~Circulating tumor cell enumeration and molecular studies~~

Rationale:

Updated to clarify exploratory assessments and delete circulating tumor cell assessment due to very low expression in patients undergoing treatment with chemotherapy and because, to date, there is little evidence that tumor cells circulate at quantifiable levels in NSCLC patients.

2.11. Section 1: Introduction, (page 18)

Original Text:

This is a single-blind, randomized, phase 2a, dose ranging study of ACE-011 therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of ACE-011 for chemotherapy induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects will be randomized to one of three ACE-011 dose treatment arms. A Data Monitoring Committee (DMC), composed of both internal Celgene and external independent reviewers, will review data from Part 1 to define the recommended ACE-011 dose to be used in Part 2 which is the phase 2b/3, randomized, double-blind, placebo-controlled segment of the study. **Part 2** will be performed in two stages. In the first stage approximately 180 subjects will be randomized to receive ACE-011, at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

Revised Text:

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. ~~A Data Monitoring Committee (DMC), composed~~Continuous monitoring of ~~both internal Celgene and external independent reviewers,~~ safety data will be conducted, including the review ~~data from~~ of Part 1 data to define the recommended sotatercept (ACE-011) dose to be used in **Part 2** ~~which is~~, the phase 2b/3, ~~randomized,~~ double-blind, randomized placebo-controlled segment of the study.

Part 2 will be performed in two stages. In the first stage approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Rationale:

Updated to confirm continuous safety data monitoring and better clarify the role and composition of the DMC consistently throughout the protocol.

Original Text:

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 the terminal differentiation step in erythropoiesis to allow additional rounds of erythroid cell replication before cells enter the terminal differentiation phase. The result is a substantial increase in mature erythrocytes released into circulation. Since this proposed mechanism is different to that of known agents, ACE-011 may provide a different clinical profile in the treatment of CIA.

Revised Text:

Although the mechanism(s) underlying the stimulation effect of sotatercept (ACE-011) on erythropoiesis are not yet fully understood, the result of clinical experience showed a rapid and sustainable increase in mature erythrocytes released into circulation. The sotatercept (ACE-011) proposed mechanism of action may be different than that of known erythropoiesis-stimulating agents (ESAs) and may provide a different clinical profile in the treatment of CIA.

Rationale:

Updated to reflect clinical experience and nonclinical findings.

2.12. Section 1: Introduction, (page 19-20)

Original Text:

Treatment of Chemotherapy-Induced Anemia

The ability for ACE-011 to rapidly increase and sustain Hgb levels in anemic subjects, while showing a safety benefit as well as no decrement in Overall Survival (as part of this study design endpoints), suggests that ACE-011 may then serve as an alternative therapeutic agent for the treatment of CIA.

Revised Text:

Treatment of Chemotherapy-Induced Anemia

The ability for ~~ACE-011~~sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of~~, while showing a safety benefit as well as no decrement in Overall Survival (as part of this study design endpoints), suggests that~~ ACE-~~00~~11 ~~may then serve as an alternative therapeutic agent~~ for the treatment of CIA.

Rationale:

Updated per FDA's recommendation to avoid comparator claims.

2.13. Section 1: Introduction, (pages 20-23)

Original Text:

Activin Biology

The activin signaling pathway has been shown to induce terminal erythroid differentiation in some preclinical models. 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 anemia associated with a variety of disorders, such as in chronic renal failure and CIA.

Pharmacology Studies

The data demonstrate that RAP-011 treatment acts to inhibit MDA-MB-231 metastasis to bone and may also play a role in inhibiting tumor growth in soft tissue. Furthermore, in the presence of tumor cells, RAP-011 is able to prevent lytic disease through an anabolic mechanism of bone formation. Lastly, inhibition of tumor growth and metastasis with RAP-011 leads to a greater than 25% survival benefit in this model.

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model of myeloma in which the extra-cellular domain of the murine activin type II receptor, fused to a murine IgG-Fc fragment, (RAP-011) was shown to prevent the development of osteolytic bone disease in a preventative setting. Additionally, RAP-011, an antagonist of activin, was shown to reverse ovariectomy-induced bone loss *in vivo*.

The effect of this antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in isolated 5T2MM murine myeloma cells from the bone marrow of disease bearing animals.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

This study showed that, in the preclinical murine model for myeloma, RAP-011 stimulates bone formation by increasing osteoblast perimeter and number, mineralisation and bone formation rate but had no effect on osteoclast activity. RAP-011 also prevented the development of osteolytic bone disease.

Revised Text:

Activin Biology

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

Pharmacology Studies

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

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model ~~of myeloma in which the extra-cellular domain of the murine activin type II receptor, fused to a murine IgG-Fc fragment, (~~demonstrated that RAP-011~~) was shown to~~ could prevent the development of osteolytic bone disease in a preventative setting. ~~Additionally, RAP-011, an antagonist of activin, was shown to reverse ovariectomy-induced bone loss *in vivo*.~~

The effect of this activin antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in ~~isolated~~ 5T2MM murine myeloma cells isolated from the bone marrow of disease bearing animals.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

This study showed that, in the preclinical murine model for myeloma, RAP-011 stimulates bone formation by increasing osteoblast perimeter and number, mineralisation and bone formation rate but had no effect on osteoclast activity. RAP-011 also ~~prevented the development~~appeared to directly inhibit tumor growth as demonstrated by decreased serum M protein, indicative of ~~osteolytic bone disease~~decreased tumor burden.

Rationale:

Modified to update preclinical data.

2.14. Section 2.1: Primary Objectives, (page 34)

Original Text:

The primary objectives are:

- **Part 1**: To determine an effective dose of ACE-011 showing a hematopoietic response in the treatment of CIA in advanced NSCLC subjects.
- **Part 2**: To assess transfusion rate within 4 months following initiation ACE-011 treatment.

2.15. Section 2.2: Secondary Objectives, (page 34)

Original Text:

The secondary objectives are:

Part 1 and **Part 2**:

- To estimate the effect of ACE-011 treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in advanced NSCLC subjects with CIA.
- To evaluate the safety and tolerability of ACE-011 treatment for advanced NSCLC subjects with CIA.
- To determine the PK of ACE-011 in subjects with advanced NSCLC receiving platinum-based chemotherapy.
- To estimate the duration of hematopoietic response associated with ACE-011.
- To evaluate the effect of ACE-011 treatment on the quality of life (QoL) of NSCLC subjects with CIA.

Part 2:

- To evaluate hematopoietic response

Revised Text:

The primary objectives are:

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in ~~advanced~~metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate ~~within 4 months~~ following initiation of sotatercept (ACE-011) treatment.

The secondary objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in ~~advanced~~metastatic NSCLC subjects with CIA.
- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment ~~for advanced~~in metastatic NSCLC subjects with CIA.
- To determine the PK of sotatercept (ACE-011) in subjects with ~~advanced~~metastatic NSCLC receiving platinum-based chemotherapy.
- To ~~estimate~~evaluate the ~~duration of~~ hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

~~**Part 2**:~~

- ~~To evaluate hematopoietic response~~

Rationale:

Primary objectives – Revised to clarify patient population and primary objective.

Secondary objectives – Revised to clarify patient population and analysis of hematopoietic response and delete redundant wording.

2.16. Section 2.3: Exploratory Objectives, (page 34)

Original Text:

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of each ACE-011 treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between ACE-011 exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population.
- To assess circulating tumor cells and molecular studies
- To assess renal function biomarkers

Revised Text:

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of ~~each~~ sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression~~/overexpression~~ of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue~~ in the NSCLC population.~~ .
- ~~To assess circulating tumor cells and molecular studies~~
- To assess renal function biomarkers

Rationale:

Updated to provide clarification and specification of Parts 1 and 2 exploratory objectives. Evaluating expression of Activin A, myostatin, folistatin as well as other additional biomarkers in both serum and in tumor tissue may help to better understand sotatercept (ACE-011) mechanism of action. Assessment of circulating tumor cells was deleted because the expression is very low in patients undergoing treatment with chemotherapy and because, to date, there is little evidence that tumor cells circulate at quantifiable levels in NSCLC patients.

2.17. Section 3.1: Primary Endpoint(s), (page 35)

Original Text:

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following ACE-011/placebo treatment

Revised Text:

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following the date of randomization to sotatercept (ACE-011)/placebo treatment

2.18. Section 3.2: Secondary Endpoint(s), (page 36)

Original Text:

(Text not previously present.)

Revised Text:

- Duration of hematopoietic response

Rationale:

Primary Endpoint - Revised per FDA's recommendation to provide a detailed definition of the primary endpoint, transfusion rate.

Secondary Endpoint - Added to better clarify hematopoietic response endpoint.

2.19. Section 3.3: Exploratory Endpoint(s), (page 36)

Original Text:

- Change in time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression

Revised Text:

- ~~Change in time~~Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression

Rationale:

Revised to clarify SRE assessment.

Original Text:

- Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other serum biomarkers

Revised Text:

- Change in r~~R~~enal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin~~ measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other serum biomarkers~~

Rationale:

Revised to provide specification of renal biomarkers for renal function assessment.

2.20. Section 4.1: Study Design, (pages 37-38)

Original Text:

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects will be randomized to one of three ACE-011 dose treatment arms. A DMC, will conduct periodic data reviews, including the review of Part 1 data, to define the recommended ACE-011 dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Three starting ACE-011 dose levels, 15.0, 30.0, and 45.0 mg, were selected for Part 1 of the study. Up to approximately 90 subjects will be randomized to one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following DMC review, analysis of safety data and assessment of dose effects of Hgb levels, a decision will be made to start concurrent randomization to:

- ACE-011 45.0 mg SC

Each dose level will be administered every 42 days for four doses.

The DMC will continue to monitor safety of the ACE-011 45.0 mg dose level.

At the time of randomization, all subjects must be receiving a first-line platinum-containing chemotherapy regimen, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles of this first-line platinum-based regimen to be eligible for the study. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Maintenance chemotherapy with a pemetrexed-containing regimen will only be allowed following completion of the subject's platinum-based chemotherapy, with a best response of at least stable disease.

Revised Text:

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects will be randomized to one of three ~~ACE-011~~sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including~~A DMC, will conduct periodic data reviews, including~~ the review of Part 1 data~~,~~ to define the recommended ~~ACE-011~~sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

A DMC will monitor the conduct of the study.

Three starting ~~ACE-011~~sotatercept (ACE-011) dose levels, 15.0, 30.0, and 45.0 mg, were selected for Part 1 of the study. Up to approximately 90 subjects will be randomized to one of the following ~~ACE-011~~sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- S~~ACE-011~~otatercept (ACE-011) 15.0 mg SC
- S~~ACE-011~~otatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12 week follow-up period from first dose. Following this analysis, the addition of a third dose level:~~Following DMC review, analysis of safety data and assessment of dose effects of Hgb levels, a decision will be made to start concurrent randomization to:~~

- S~~ACE-011~~otatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for four doses. ~~The DMC will continue to monitor safety of the ACE-011 45.0 mg dose level.~~

At the time of randomization~~,~~ all subjects must be receiving ~~a~~their first regimen of first-line platinum-containing chemotherapy ~~regimen~~, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles of this first-line platinum-based regimen to be eligible for the study. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles ~~or~~while on study treatment prior to initiating any maintenance ~~therapy with a pemetrexed-based regimen following randomization.~~

~~Maintenance~~ chemotherapy ~~with a pemetrexed-containing regimen will only be allowed following completion of~~for the ~~subject's platinum-based chemotherapy, with a best response~~treatment of ~~at least stable disease.~~ metastatic NSCLC.

Rationale:

Revised to clarify study design, confirm continuous safety monitoring, clarify the role and composition of consistently throughout the protocol.

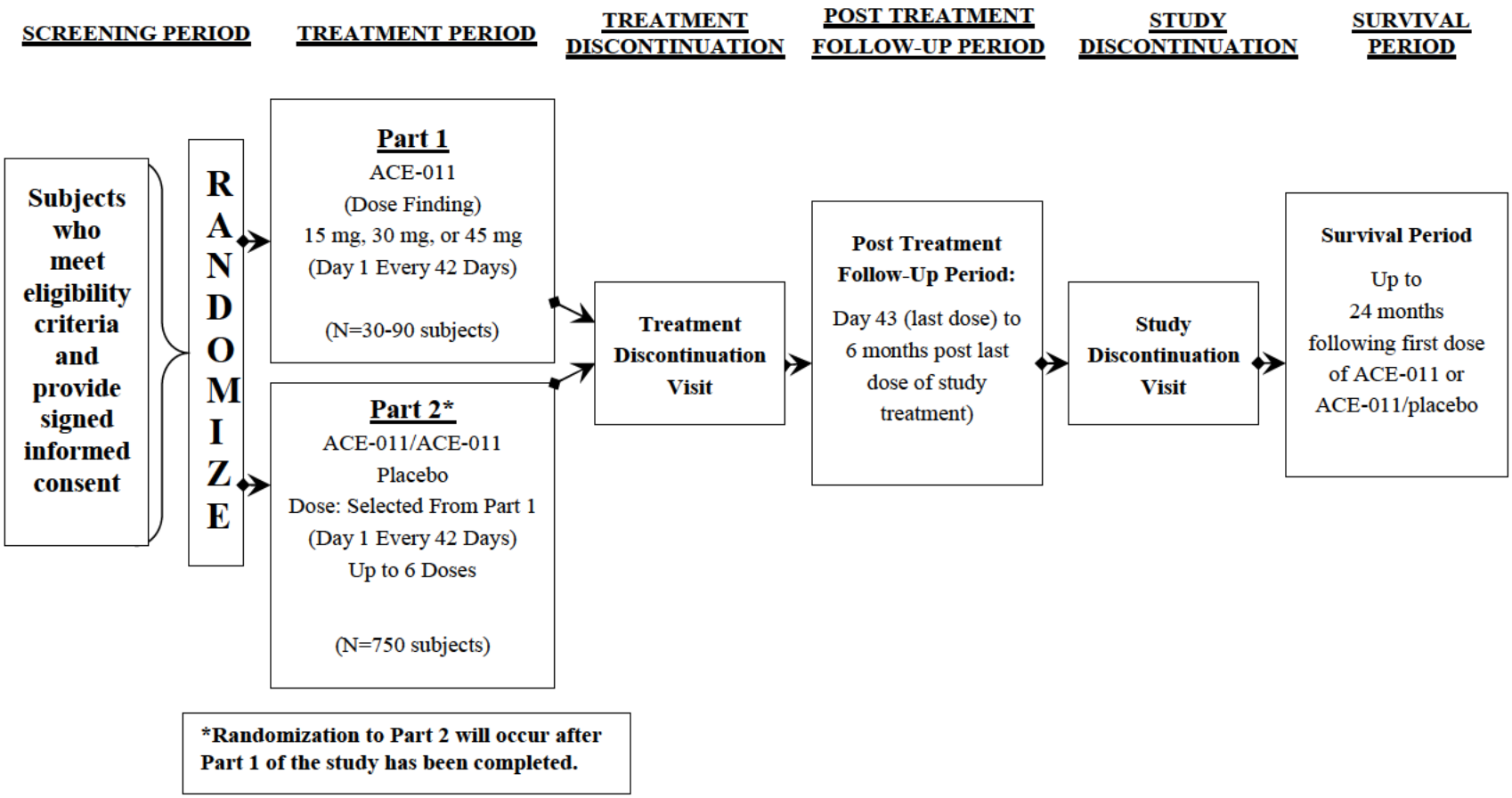
Modified to include clarification on when maintenance can be initiation and, per investigator recommendation, to add erlotinib-based maintenance regimen.

Revised per FDA's recommendations, clarification of when safety analysis of the first 10 subjects treated with 15 and 30 mg dose levels of sotatercept (ACE-011) would occur and clarification of study population description based on subjects being eligible to continue to receive platinum-based chemotherapy following randomization.

2.21. Section 4.1: Study Design, (page 39)

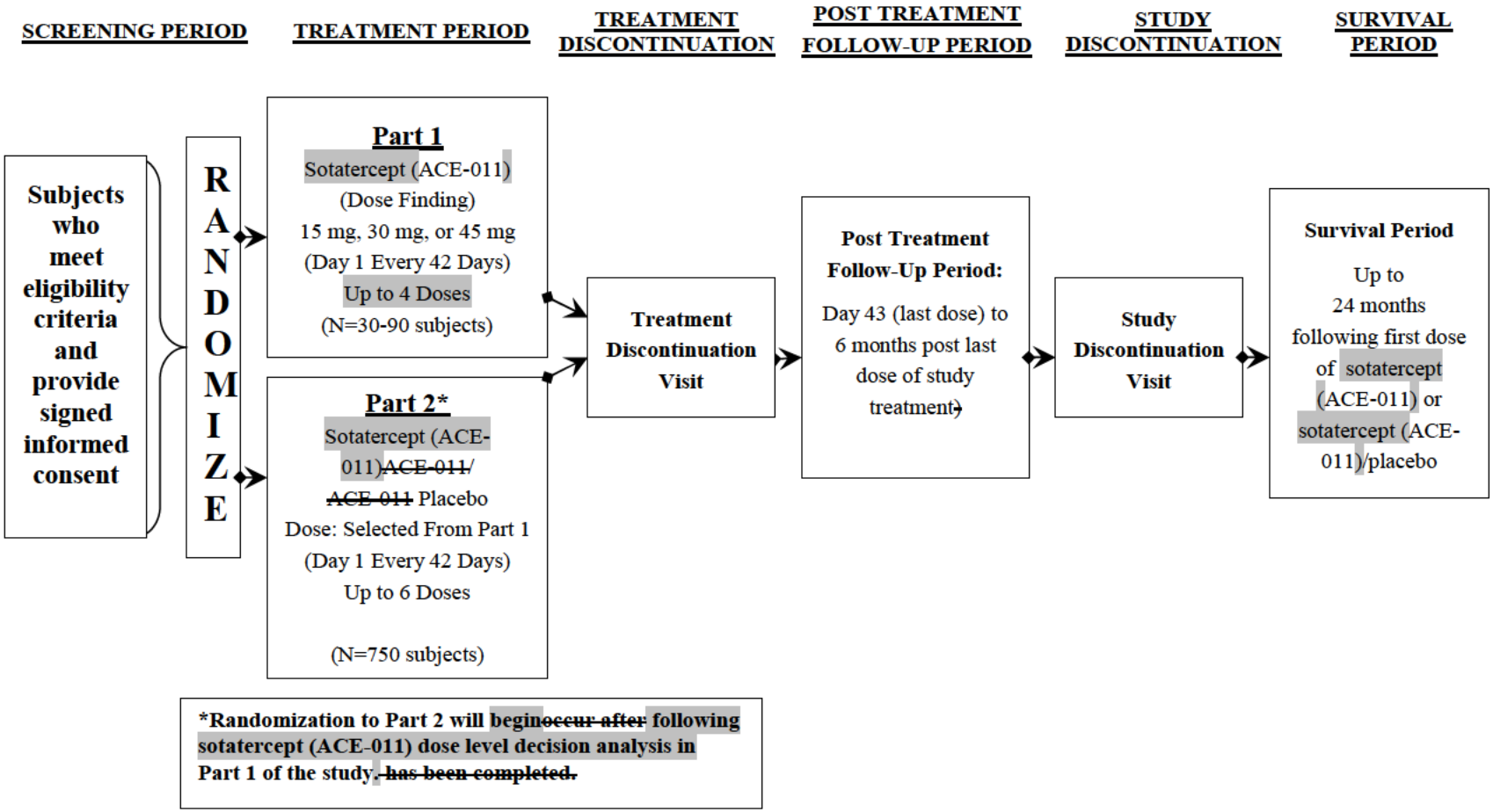
Original Text:

Figure 1: Study Design



Revised Text:

Figure 1: Study Design



Rationale:

Revised to clarify number of sotatercept (ACE-011) doses allowed in Part 1 and that randomization to Part 2 will be subsequent to Part 1 and not performed concurrently.

Section 4.1.1: ACE-011 Dose Modification, Reduction and Escalation Rules, (pages 40-41)

Original Text:

4.1.1. ACE-011 Dose Modification, Reduction and Escalation Rules

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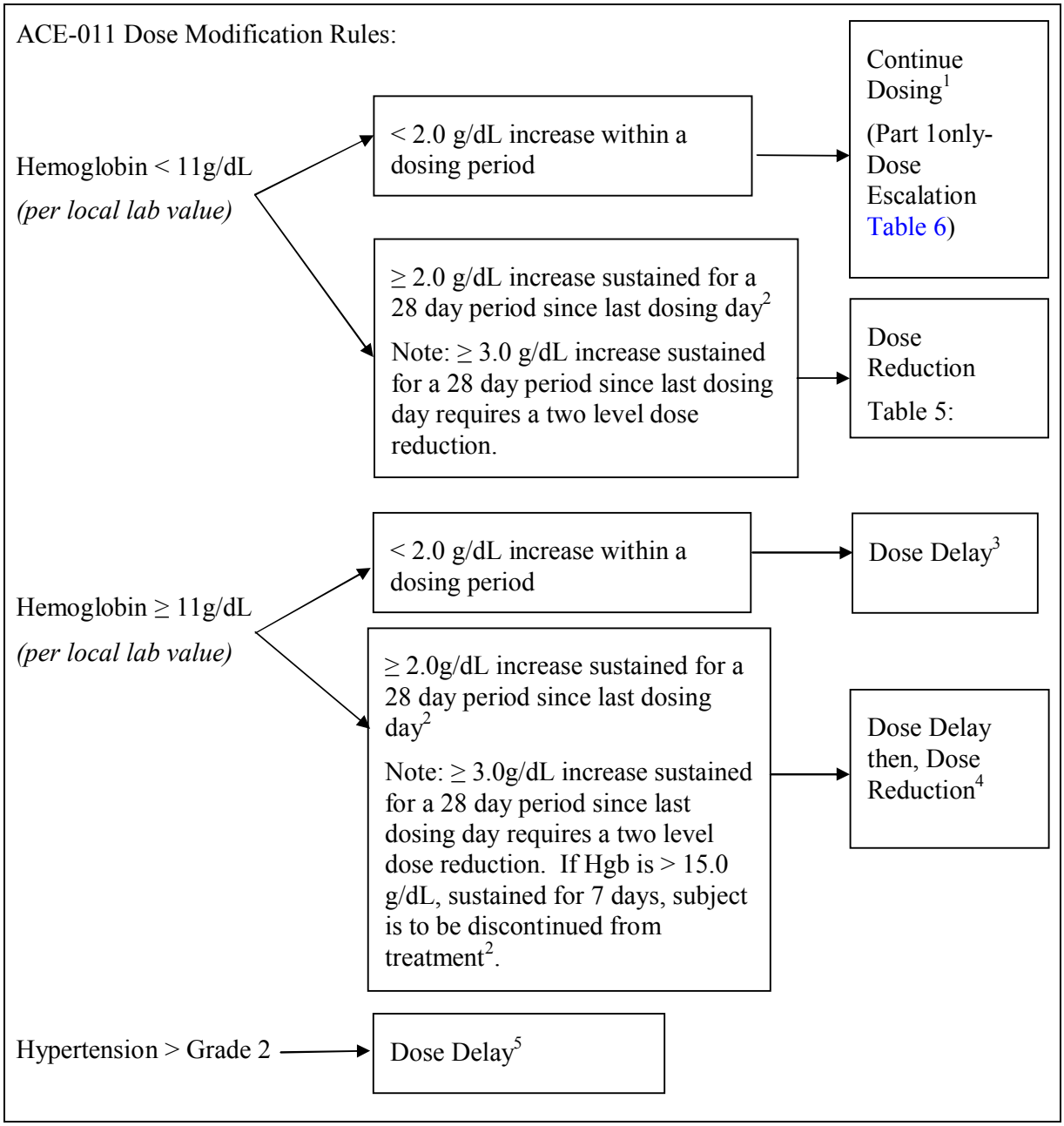


[1]Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** ACE-011 dosing level if the transfusion was given greater than 7 days from the previous dose of ACE-011 (or ACE-011/placebo) AND the Hgb level is < 11 g/dL AND hypertension is ≤ Grade 2 on the day of dosing. ACE-011 (or ACE-011/placebo) should not be administered within 7 days post RBC transfusion.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of ACE-011, the subsequent dose of ACE-011 will be **increased** one dose level (Refer to ACE-011 Dose Escalation Levels-Table 6).

---

[3]ACE-011 should be **delayed** until Hgb is < 11g/dL and hypertension ≤ Grade 2. The follow-up dosing can commence at 7 days or later after the originally planned ACE-011/placebo dose that was **delayed**. Subsequent ACE-011/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** ACE-011/placebo dose is defined as a dose not administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > Grade 2, and/or ACE-011 related toxicity).

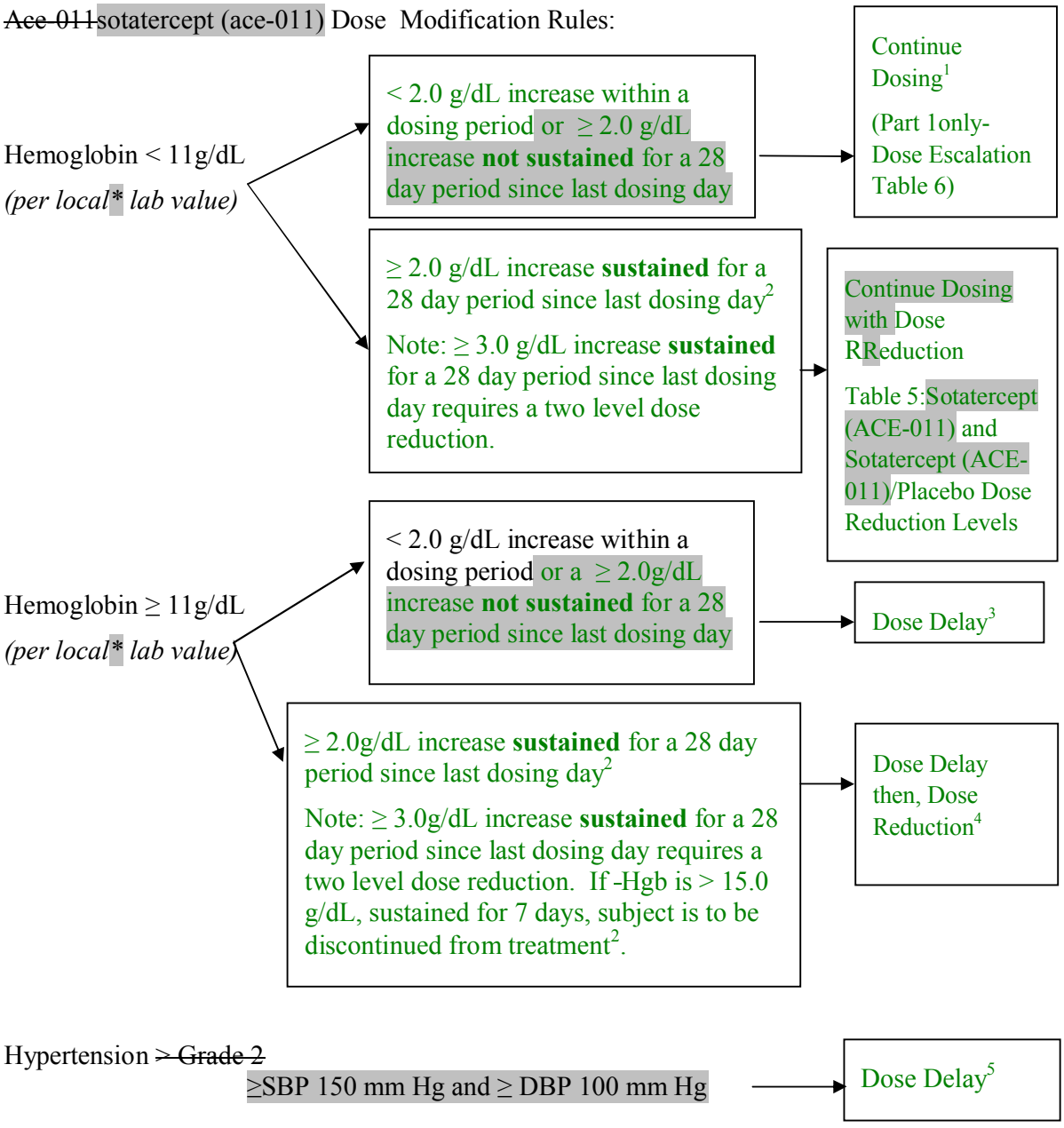
---

[5]ACE-011 should be held until hypertension resolves to ≤ Grade 2 (current active minor version NCI CTCAE v4.0) and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Revised Text:

4.1.1: ~~ACE-011~~Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

~~Ace-011~~sotatercept (ace-011) Dose Modification Rules:



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

[1] If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150mm Hg and < DBP 100 mm Hg on the day of dosing. Sotatercept (ACE-011) should not be administered within 7 days post RBC transfusion.

For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** ~~ACE-011-~~ sotatercept (ACE-011)/placebo dose ~~ing level~~ if the transfusion was given greater than 7 days from the previous dose of ~~ACE-011 (or~~ACE-011sotatercept (ACE-011)/placebo~~)~~ AND the Hgb level is < 11 g/dL AND hypertension is ~~<~~ SBP 150mm Hg and < DBP 100 mm Hg ~~≤ Grade 2~~ on the day of dosing. ~~ACE-011 (or~~ACE-011Sotatercept (ACE-011)/placebo~~)~~ should not be administered within 7 days post RBC transfusion.

---

[3] ~~ACE-011~~Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. ~~≤ Grade 2~~. ~~The follow-up D~~dosing can commence at ≥7 days ~~or later~~after the originally planned sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo dose is defined as a dose not administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension ~~>~~ < SBP 150mm Hg and < DBP 100 mm Hg ~~Grade 2,~~and/or ~~ACE-011~~sotatercept (ACE-011) related toxicity).

---

[5] ~~ACE-011~~Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be held until hypertension resolves to < SBP 150mm Hg and < DBP 100 mm Hg ~~≤ Grade 2 (current active minor version NCI CTCAE v4.0)~~ and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Rationale:

Revised per FDA's recommendation to modify dose modification algorithm for hypertension. Additional revisions to better clarify dosing based on hemoglobin level and duration sustained, RBC transfusion timepoints and use of local laboratory assessments.

Section 4.1.1: Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules (pages 42)

Original Text:

ACE-011 Dose Escalation Levels:

- Hgb level must be < 11.0 g/dL and hypertension ≤ Grade 2
- Dose escalation to begin at next every 42 day scheduled dosing visit.

Revised Text:

Sotatercept (ACE-011) Dose Escalation Levels:

- Hgb level must be < 11.0 g/dL and hypertension < ~~Grade 2~~SBP 150mm Hg and < DBP 100 mm Hg
- Dose escalation to begin at next ~~every 42 day scheduled dosing~~ treatment visit.

Rationale:

Revised per FDA's recommendation to revise dose modification algorithm for hypertension.

Clarification of wording to describe the visit at which when dose escalation would occur.

2.22. Section 5: Table Of Events, (pages 46-51)

Original Text:

Table 7: ACE-011 NSCLC Schedule of Assessments

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Vital Signs / Blood Pressure[b]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X			X		X		X		X		X		X	
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[f]	X	X		X			X				X		X			X	X	
Urinalysis[j]	X	X		X			X		X		X	X	X	X	X	X	X	
TSH[k]	X	X					X						X					

Table 7: ACE-011 NSCLC Schedule of Assessments

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		ACE-011 Dose 1 Schedule (± 3 days)					ACE-011 Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Activin A and other Proteins/Biomarkers in Blood and Tissue (pre-dose study treatment in a subset of subjects)		X	X									X						
Circulating Tumor Cells (pre-dose study treatment in a subset of subjects)		X									X	X		X				
Pharmacokinetics– **Part 1** and **Part 2**)[n]		Refer to Table 8 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X	Every 9 weeks ± 1 week																
Maintenance chemotherapy[s]		Dosing of allowed regimen(s) per standard practice																

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, at Treatment Discontinuation, and at Study Discontinuation. Investigators are to report any clinically significant abnormal findings as adverse events.

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days prior to the start of ACE-011 or ACE-011/placebo or administration (Day 1) once the subject has been on effective contraception for at least 28 days. Subjects must agree to use highly effective birth control measures (eg, oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of ACE-011 or ACE-011/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of ACE-011 or ACE-011/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with ACE-011 or ACE-011/placebo to ensure levels are within normal limits and that ACE-011 dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (Part 1).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

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[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of the first and second dose of ACE-011 or ACE-011/placebo and at 2 month post-treatment follow-up visit.

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[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of ACE-011. Approximately 10 subjects at each ACE-011 dose level, 15.0, 30.0 and 45.0 mg, will have more full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment.

Pharmacokinetics (**Part 2**): Blood samples will be collected to evaluate the blood or serum concentrations of ACE-011. ACE-011 doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening tumor assessments may be performed up to six weeks prior to randomization. Historical tumor assessment data from prior to initiation of platinum-based chemotherapy through randomization to the study will also be collected. Following randomization, tumor assessments will be performed every 9 weeks (± 7 days).

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[q]ACE-011 or ACE-011/placebo dosing repeats every 42 days and will begin after the subject begins an every 3 week platinum-based chemotherapy regimen. The first dose of ACE011 or ACE-011/placebo should be given within +/- 3 days of a chemotherapy cycle. Subsequent cycles of the chemotherapy dosing schedule, included dose reductions and delays, should not affect the ACE-011 or ACE-011/placebo dosing schedule, unless determined to be necessary by the Investigator. ACE-011 or ACE-011/placebo can be administered at any time point during the chemotherapy cycle. If there is a chemotherapy dose delay, ACE-011 or ACE-011/placebo administration does not need to be delayed until start of next chemotherapy cycle.

[r]Every 3-week platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. ACE-011 or ACE-011/placebo administration should be given prior to chemotherapy administration on ACE-011 or ACE-011/placebo administration days.

[s]Pemetrexed maintenance chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

Revised Text:

Table 7: ~~ACE-011~~Sotatercept (ACE-011) NSCLC Schedule of Assessments

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		~~ACE-011~~Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					~~ACE-011~~Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X		X	X	X	X	X	
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[f]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X	X	X	X	X	X	X	
TSH[k]	X	X					X[k]						X					

Table 7: ~~ACE-011~~Sotatercept (ACE-011) NSCLC Schedule of Assessments

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		~~ACE-011~~Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					~~ACE-011~~Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Activin A and other ~~Proteins/ Biomarkers~~proteins/biomarkers in Blood ~~and Tissue~~ (pre-dose study treatment in a subset of subjects)		X	X				X					X						
~~Circulating Tumor Cells (pre-dose study treatment in a subset of subjects)~~ Activin and other proteins/biomarkers in archival tumor tissue	X	~~X~~									~~X~~	~~X~~		~~X~~				
Pharmacokinetics– **Part 1** and **Part 2**)[n]		Refer to Table 8 and Table 9 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X	≤ Every 9 weeks ± 1 week or per standard of care at study site																
Maintenance ~~chemotherapy~~Therapy[s]		Dosing of allowed regimen(s) per standard practice																

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) or sotatercept (ACE-011)/ placebo dose, at Treatment Discontinuation, and at Study Discontinuation. Blood pressure measurements should be confirmed by two measurements obtained five minutes apart. Investigators are to report any clinically significant abnormal findings as adverse events.

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days prior to the start of ~~ACE-011~~sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo ~~or~~ administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo during the treatment period. ~~-~~ Subjects must agree to use highly effective birth control measures (eg, oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of ~~ACE-011~~sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of ~~ACE-011~~sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with ~~ACE-011~~sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo to ensure levels are within normal limits and that ~~ACE-011~~sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (Part 1).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at 2 month post-treatment follow-up visit.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of ~~ACE-011~~sotatercept (ACE-011). Approximately 10 subjects at each ~~ACE-011~~sotatercept (ACE-011) dose level, 15.0, 30.0 and 45.0 mg, will have ~~more~~full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

Pharmacokinetics (**Part 2**): Sparse PK blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011) in approximately 300 (40%) of 750 subjects. Sotatercept (ACE-011) doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8 and Table 9, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening period tumor assessments may be performed up to six weeks prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Following randomization, tumor assessments will be performed at a maximum of every 9 weeks (± 7 days) or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

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[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins an every 3 week platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days following Day 1 of a platinum-based chemotherapy cycle**. **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.
Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.
If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

[r]Every 3-week platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

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[s]Pemetrexed or erlotinib maintenance ~~chemo~~therapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

Rationale:

1. Addition of additional blood pressure measurement on Day 29 based on FDA's recommendation of at least one additional blood pressure measurement between Day 15 and Day 43 post sotatercept (ACE-011) dosing.
2. Clarification that blood pressure measurements should be confirmed by two measurements obtained five minutes apart.
3. Clarification that pregnancy testing is to be performed up to 3 days prior to sotatercept (ACE-011) dosing versus ± 3 days.
4. Addition of MCV to hematology assessments.
5. Addition of lipase to serum chemistry assessments.
6. Addition of measurement of weight to correspond with creatinine clearance calculations.
7. Addition of serum chemistry assessments to correspond with creatinine clearance assessments.
8. Clarification that renal biomarkers are assessed at the same visits as urinalysis.
9. Addition of superscript 'k' to further clarify TSH assessment only on Day 1 of first and second dose of sotatercept (ACE-011).
10. Clarification of PK assessments in Part 1 and Part 2.
11. Clarification that tumor tissue is an archival sample and not required to be collected on study.
12. Clarification of tumor assessment schedule and collection of historical tumor assessment data and modification of post- randomization tumor assessment timeframes.
13. Modified to increase the allowed dosing time period of the **first** dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to and following a cycle of platinum-based chemotherapy.
14. Clarification of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule versus platinum-based chemotherapy dosing schedule and order of dosing, if administered on the same day.
15. Addition of erlotinib as allowed maintenance therapy.

2.23. Section 5: Table Of Events, (page 52)

Original Text:

Table 8: Schedule of Pharmacokinetic Assessments

Scheduled Time	Time relative to ACE-011/placebo dose[a]	Part 1[b]		Part 2[b]	Collection Window[c]
		Full PK[c]	Sparse PK[d]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	-	± 3 days
Dose 4, D43 (Dose 5, D1)	42 days after Dose 4 (pre-Dose 5 in **Part 2**)	X	X	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6 in **Part 2**	-	-	X	± 3 days
Follow up, 1 month	72 days after final dose	X	-	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	X	± 1 week

Revised Text:

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

Scheduled Time	Time relative to ACE-011/placebo dose[a]	Part 1[b]		Part 2[b]	Collection Window[c]
		Full PK[c]	Sparse PK[d]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	-	± 3 days
Dose 4, D43 (Dose 5, D1)	42 days after Dose 4 (pre-Dose 5 in **Part 2**)	X	X	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6 in **Part 2**	-	-	X	± 3 days
Follow up, 1 month	72 days after final dose	X	-	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	X	± 1 week

Scheduled Time	Time relative to Sotatercept (ACE-011)	Part 1[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days
PT[f] Follow up, 1 month	72 days after final dose	X	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	± 1 week

Original Text:

(Text not previously present.)

Revised Text:

Table 9: Schedule of Pharmacokinetic Assessments (Part 2)

Scheduled Time	Time relative to Sotatercept (ACE-011)/placebo dose	Sparse PK[a,b,c]	Collection Window[d]
Dose 1, D1	pre-Dose 1	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	±1 hour
Dose 1, D8	7 days after Dose 1	X	± 3 day
Dose 1, D15	14 days after Dose 1	X	± 3 day
Dose 1, D29	28 days after Dose 1	X	± 3 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	± 3 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	± 3 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	± 3 days
Dose 4, D43 (Dose 5, D1)	pre-Dose 5	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6	X	± 3 days
PT[e] Follow up, 3 month	132 days after final dose	X	± 1 week
PT Follow up, 5 month	192 days after final dose	X	± 1 week

[a] For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

[d] Except for Day 1 (Dose 1, D1), the collection window will be the same as the visit window defined in Table 7.

[e] PT = Post Treatment

Rationale:

Table 8 and Table 9

Addition of a separate table - Table 9 - to display Part 2 pharmacokinetic assessments.
Modification of Table 8 to now display only pharmacokinetic assessments in Part 1.

2.24. Section 6: Procedures, (pages 53-54)

Original Text:

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed within 28 days prior to randomization. Historical tumor assessment data from six weeks prior to initiation of platinum-based chemotherapy through randomization to the study will be collected. Hematology and chemistry laboratory assessments should be performed within 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Tumor Assessment - Screening tumor assessments and tumor evaluation documentation, as per RECIST criteria, must be performed within 6 weeks prior to randomization to this study. Also, historical tumor assessment data from prior to initiation of platinum based chemotherapy through randomization to the study will be collected.

Revised Text:

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed within 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization. Historical tumor assessment data, from ~~six weeks~~ prior to the initiation of platinum-based chemotherapy through the screening period,~~randomization to the study~~ will be collected. Hematology and chemistry laboratory assessments should be performed within 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks prior to randomization to this study. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period,~~randomization to the study~~ will be collected.

Rationale:

Updated description of collection of tumor assessment data from prior to randomization. Clarification of the screening period timeframe and of the additional collection of historical tumor assessment data, from prior to initiation of first line platinum-based chemotherapy, to be used as the baseline tumor assessment.

2.25. Section 6: Procedures, (page 54-56)

Original Text:

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

In **Part 1** (the dose ranging portion of the study), subjects who meet all eligibility criteria will be randomized by a single-blind procedure utilizing IVRS to receive one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

Revised Text:

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized by a single-blind procedure utilizing IVRS to receive one of the following ~~ACE-011~~sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- ~~ACE-011~~Sotatercept (ACE-011) 15.0 mg SC
- ~~ACE-011~~Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

~~Following analysis of at least 10 subjects at each dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level), a third dose level will be added to the randomization schema:~~

- ~~ACE-011~~Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

Rationale:

Revised per FDA's recommendation to clarify when safety analysis of the first 10 subjects treated with 15 and 30 mg dose levels of sotatercept (ACE-011) would occur.

Original Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP.

Revised Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration.

Rationale:

Clarified pregnancy testing is to be performed up to 3 days prior to sotatercept (ACE-011) dosing versus +/- 3 day procedure window as shown in Table 7 – Schedule of Assessments.

Original Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of ACE-011 or ACE-011/placebo and at subsequent ACE-011 or ACE-011/placebo doses collected at 7, 14 days and 28 days post-dose by local laboratory.

Revised Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses collected at 7, 14 days and 28 days post-dose. ~~by local laboratory.~~

Rationale:

Revised to add MCV to hematology laboratory evaluation.

Clarification of use of local laboratory is now provided in Section 6 Procedures – Clinical Laboratory Assessments.

Original Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Bone or other biomarkers
- Activin A and other ACE-011-related proteins/biomarkers in blood and tissue (**pre-dose** on Day 1 and Day 8 after first dose of ACE-011 or ACE-011/placebo)
- Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo)

Revised Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- ~~Bone or other biomarkers~~
- Activin A and other ~~ACE-011~~sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - ~~and tissue (~~**pre- dose** on Day 1 and Day 8 after first dose of ~~ACE-011~~sotatercept (ACE-011) or ~~ACE-011~~sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in~~)~~ archival tumor tissue
- ~~Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo)~~

Rationale:

Updated to clarify exploratory assessments and delete circulating tumor cell assessment due to very low expression in patients undergoing treatment with chemotherapy.

Original Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Tumor Assessment and Response Evaluation, as per RECIST criteria, (every 9 weeks ± one week) following chemotherapy schedule

Revised Text:

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week or per standard of care at the study site, starting from the previous [screening] tumor assessment) and following the chemotherapy schedule

Rationale:

Revised to modify the allowed tumor assessment timeframe starting from the Screening Period.

2.26. Section 6: Procedures, (pages 56-57)

Original Text:

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- Bone or other biomarkers

- Activin A and other ACE-011 related proteins/biomarkers in blood and tissue (**pre-dose** ACE-011 or ACE-011/placebo at 1 month end of treatment follow-up visit)
- Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo at day 43 post last dose and 1 month end of treatment follow-up visit)

Revised Text:

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- Bone or other potential mechanistic or disease-related proteins/biomarkers

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- Activin A and other ~~ACE-011~~sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood ~~and tissue (**pre-dose** ACE-011 or ACE-011/placebo~~ at 1 month end of treatment follow-up visit)~~)~~
- ~~Circulating Tumor Cells (**pre-dose** ACE-011 or ACE-011/placebo at day 43 post last dose and 1 month end of treatment follow-up visit)~~

Rationale:

Clarification to include bone and other potential biomarkers and defined in exploratory objectives that Activin A and other proteins/biomarkers, including mysostatin and follistatin, will be assessed in blood and Activin A and other proteins/biomarkers assessed in tumor tissue.

Deletion of circulating tumor cell assessment due to very low expression in patients undergoing treatment with chemotherapy.

Original Text:

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- Tumor Assessment and Response Evaluation, as per RECIST criteria, (every 9 weeks ± one week) following chemotherapy schedule

Revised Text:

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week or per standard of care at the study site), and following the chemotherapy schedule

Rationale:

Revised to modify the allowed tumor assessment timeframe through the Post Treatment Follow-Up Period.

3. SECTION 6: PROCEDURES, (PAGE 59)

Original Text:

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone will be performed by a central laboratory.

Please refer to vendor manual for procedures.

Note: Local laboratory assessments are allowed in cases when timely results are needed (e.g., randomization, study treatment and chemotherapy dosing decisions, hematology assessments between clinic visits). Local laboratory data should be collected in the eCRF.

Revised Text:

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone) will be performed by a central laboratory.

Please refer to vendor manual for procedures.

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

Rationale:

Modified to clarify folate levels to be assessed and central laboratory requirements when a local laboratory is utilized.

3.1. Section 6: Procedures, (page 59)

Original Text:

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression/overexpression of Activin A and other proteins/biomarkers related to ACE-011 mechanism of action in blood and tumor tissue in the NSCLC population in a subset of subjects.

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio, and other serum biomarkers will also be evaluated from all subjects.

Circulating Tumor Cell Enumeration and Molecular Studies

Analysis will be performed in a subset of subjects.

Revised Text:

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression~~/overexpression~~ of Activin A and other proteins/biomarkers related to ~~ACE-011~~sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in the NSCLC population in a subset of subjects.

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and~~-~~ other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin ~~measuring urine albumin / creatinine ratio, urine protein / creatinine ratio, and other serum biomarkers~~ will ~~also~~be evaluated in~~from~~ all subjects.

~~**Circulating Tumor Cell Enumeration and Molecular Studies**~~

~~Analysis will be performed in a subset of subjects.~~

Rationale:

Defined in exploratory objectives that Activin A and other proteins/biomarkers, including mysostatin and follistatin, will be assessed in blood and Activin A and other proteins/biomarkers assessed in tumor tissue.

Clarification of renal biomarkers to be assessed for renal function.

Deletion of circulating tumor cell assessment due to very low expression in patients undergoing treatment with chemotherapy.

3.2. Section 6: Procedures, (page 59)

Original Text:

Pharmacokinetics

- Part 1 - Full PK blood samples will be collected to evaluate the full PK profile of ACE-011 from approximately 30 subjects at select centers (approximately 10 subjects for each ACE-011 dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.
- Part 2- Sparse PK blood samples will be collected from all subjects.

Revised Text:

Pharmacokinetics

- Part 1 - Full PK blood samples will be collected to evaluate the full PK profile of ~~ACE-011~~sotatercept (ACE-011) from approximately 30 subjects at select centers (approximately 10 subjects for each ~~ACE-011~~sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.
- Part 2- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 ~~all~~ subjects (approximately 150 subjects in each arm).

Rationale:

Revised to clarify pharmacokinetic assessments required in Part 1 and 2 of the study and modify Part 2 sparse pharmacokinetic requirements.

3.3. Section 6: Procedures, (page 59)

Original Text:

Bone Biomarkers

Bone or other biomarkers will be evaluated in all subjects. The serum and urine biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Revised Text:

Bone Biomarkers

Bone ~~or other~~ biomarkers -will be evaluated in all subjects. The serum and urine bone biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Rationale:

Revised to clarify bone biomarker in urine versus renal biomarkers also required in this study.

3.4. Section 6: Procedures, (page 60)

Original Text:

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire will be completed by the subject upon arrival at clinic and prior to any study procedures or testing.

Independent External Radiology Review

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC): The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each patient. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

Revised Text:

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Independent External Radiology Review (Part 2 Only)

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC~~):~~) (Part 2 Only)

The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each ~~patient.~~subject. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

Rationale:

Revised to clarify required scales within the LCSS.

Clarification that the required independent reviews to be performed in Part 2 only.

Revised to correct typographical error ‘patient’ and replace with ‘subject’.

3.5. Section 7: Study Population, (page 61)

Original Text:

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

Revised Text:

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles ~~or maintenance therapy with a pemetrexed-based regimen following randomization~~while on study treatment.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

Rationale:

Updated per FDA's recommendation to clarify study population description based on subjects being eligible to continue to receive platinum-based chemotherapy following randomization.

3.6. Section 7.2: Inclusion Criteria, (page 62-63)

Original Text:

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

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5. All of the following laboratory values:
    - Platelet count ≥ 25,000/mm^3 (> 72 hours since prior platelet transfusion)

Revised Text:

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

---

5. All of the following laboratory values:
    - Platelet count ≥ ~~25~~75,000/mm^3 (> 72 hours since prior platelet transfusion)

Rationale:

Revised to correct typographical error.

Original Text:

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

---

5. All of the following laboratory values:
    - Adequate renal function (creatinine < 1.5 x upper limit of normal [ULN] or ≥ 50 mL/min)

Revised Text:

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

---

5. All of the following laboratory values:
    - Adequate renal function (~~creatinine < 1.5 x upper limit of normal [ULN] or~~ creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin concomitantly administered)

Rationale:

Defined adequate renal function as creatinine clearance ≥ 40 mL/min or ≥ 50 mL/min if cisplatin concomitantly administered based on investigator and data monitoring committee feedback. Updated toxicology results showed renal findings were due to anti-drug antibody reaction rather than ACE-011 nephrotoxicity.

Original Text

6. Subjects may have received up to 3 cycles of a current first line platinum-based chemotherapy treatment regimen for metastatic NSCLC. Allowed regimens are:

   - gemcitabine plus cisplatin or carboplatin ± bevacizumab
   - pemetrexed plus cisplatin or carboplatin ± bevacizumab
   - paclitaxel plus carboplatin ± bevacizumab

   Subjects are expected to be eligible to receive 2 platinum-based chemotherapy cycles or maintenance therapy with a pemetrexed-based regimen following randomization.

Revised Text:

6. Subjects may have received up to 3 cycles of ~~a current~~their first regimen of first line platinum-based chemotherapy treatment ~~regimen~~ for metastatic NSCLC. Allowed regimens are:

   - gemcitabine plus cisplatin or carboplatin ± bevacizumab
   - pemetrexed plus cisplatin or carboplatin ± bevacizumab
   - paclitaxel plus carboplatin ± bevacizumab
   - docetaxel plus cisplatin ± bevacizumab

   At randomization ~~S~~subjects are expected to be eligible to continue to receive ~~2~~at least two additional platinum-based chemotherapy cycles ~~or maintenance therapy with a pemetrexed-based regimen following randomization.~~ while on study.

Rationale:

Modified per FDA's recommendation, to provide clarification of study population description based on subjects being eligible to continue to receive platinum-based chemotherapy following randomization.

Original Text

8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 56 days (prior to Day 1)

Revised Text:

8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past ~~56~~30 days (prior to Day 1)

Rationale:

Updated to correct typographical error.

Original Text

10. If currently receiving bisphosphonate therapy, be on a stable dose for ≥ 2 months before Day 1 (ongoing bisphosphonate therapy is allowed during study provided it is kept at a stable level, bisphosphonate therapy may not be started on study, other than for the treatment of hypercalcemia). Subjects not currently on bisphosphonates must not have received bisphosphonates within 2 months prior to Day 1.

Revised Text:

10. If currently receiving bisphosphonate or denosumab (XGEVA™) therapy for bone metastases, must be on a stable dose for ≥ 2 months before Day 1 (ongoing bisphosphonate or denosumab therapy is allowed during study provided it is kept at a stable level). Bisphosphonate or denosumab therapy may not be started on study. Bisphosphonate therapy may be started on study for the treatment of hypercalcemia. Subjects not currently on bisphosphonates or denosumab must not have received bisphosphonates or denosumab within 2 months prior to Day 1.

Rationale:

Modified per investigator recommendation in alignment with standard of care.

3.7. Section 7.3: Exclusion Criteria, (pages 63-64)

Original Text:

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C] at the time of screening, except for the following disease related toxicities: hematological events [e.g. anemia, thrombocytopenia or neutropenia] or non hematological events [e.g. nausea, vomiting, fatigue, or muscle or bone/joint pain]).

Revised Text:

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C] at the time of screening, including ~~except for~~ Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g. asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non hematological events (e.g. nausea, vomiting, fatigue, or muscle or bone/joint pain) occurring during the chemotherapy period and resolving. ~~the following disease related toxicities: hematological events [e.g. anemia, thrombocytopenia or neutropenia] or non hematological events [e.g. nausea, vomiting, fatigue, or muscle or bone/joint pain]).~~

Rationale:

Revised per FDA's recommendation to exclude patients with Grade 4 toxicities or major end-organ dysfunction, irrespective of whether they are considered disease related. Clarification of exception for hematotoxicity and non hematologic events occurring during the chemotherapy period and resolving was added.

Original Text:

4. CNS metastases (exception: CNS metastases treated with whole brain radiotherapy > 6 months prior to randomization).

Revised Text:

4. CNS metastases (exception:- subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks ~~> 6 months~~ prior to randomization)~~)~~.

Rationale:

Modified per investigator recommendation to allow for broader eligible patient population.

Original Text:

11. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (BP) must be < 160 mmHg and diastolic BP must be < 100 mmHg.

Revised Text:

11. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (SBP) must be < ~~160~~150 mmHg ~~and~~or diastolic ~~BP~~blood pressure (DBP) must be < 100 mmHg.

Rationale:

Modified per FDA's recommendation.

Original Text:

14. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or folate. Subjects may be re-screened following treatment with supplements and normalization of levels.

Revised Text:

14. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.

Rationale:

Revised to clarify folate assessment.

Original Text:

16. History of anemia due to autoimmune or hereditary hemolysis or gastrointestinal bleeding.

Revised Text:

16. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.

Rationale:

Revised to allow inclusion of patients who may have had a history of bleeding (e.g. ulcers), that has now resolved.

Original Text:

17. Urine protein / creatinine ratio < 1.0

Revised Text:

17. Urine protein / creatinine ratio ~~><~~ 1.0

Rationale:

Corrected typographical error.

3.8. Section 8.1: Description of Investigational Product(s), (page 65)

Original Text:

Process IIa Clinical Drug Product

ACE-011 will be provided as a 1 mL solution of 50 mg/mL in phosphate buffered saline (PBS), pH 7.5, in labeled 2 mL vials with rubber stoppers, providing 50 mg per vial. ACE-011 is recommended to be stored at ≤ -65˚C (colder than -65˚C) until thawed for administration. ACE-011 should be used within 6 hours of thawing.

Revised Text:

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

Note: Subjects receiving Process IIa clinical drug product will begin to receive Process III clinical drug product as soon as it becomes available at the study site.

Process IIa Clinical Drug Product – Frozen Liquid Formulation:

The clinical drug product consists of ~~ACE-011~~sotatercept (ACE-011) ~~will be provided as a 1 mL solution of 50 mg/mL~~ in phosphate buffered saline (PBS), pH 7.5. It is supplied as a 1 mL solution of 50 mg/mL sotatercept (ACE-011) ~~,~~in labeled,~~-~~ rubber stoppered, 2 mL vials ~~with rubber stoppers,~~providing 50 mg per vial. The recommended storage temperature for ~~ACE-011~~sotatercept (ACE-011) ~~is recommended to be stored at ≤ -65˚C (colder than -65˚C) until thawed for administration.~~ Process IIa frozen liquid drug product is ≤ -65˚C (colder than -65˚C) until thawed for administration. Vials of sotatercept (ACE-011) frozen liquid must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.

~~ACE-011 should be used within 6 hours of thawing.~~ **Process III Clinical Drug Product-Lyophilized Powder:**

The clinical drug product consists of sotatercept (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 sotatercept (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 sotatercept (ACE-011). The reconstituted sotatercept (ACE-011), in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.

Rationale:

Investigational product information updated based on FDA's approval of sotatercept (ACE-011) Process III lyophilized material. Subjects receiving Process IIa clinical drug product will begin to receive Process III clinical drug product as soon as it becomes available at the study site.

3.9. Section 8.2: Treatment Administration and Schedule, (page 68)

Original Text:

ACE-011 or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh. Vials of ACE-011 must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.

Allowed concomitant platinum-based chemotherapy regimens are:

- gemcitabine plus cisplatin or carboplatin ± bevacizumab
- pemetrexed plus cisplatin or carboplatin ± bevacizumab
- paclitaxel plus carboplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Subjects may receive 4-6 cycles of the allowed platinum-based regimen selected by the Investigator. The addition of up to 2 cycles of platinum-based chemotherapy may be given following cancer response. The platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

Maintenance chemotherapy with a pemetrexed-containing regimen will only be allowed following completion of the subject's platinum-based chemotherapy, with a best response of at least stable disease.

Revised Text:

Sotatercept (ACE-011) or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh. ~~Vials of ACE-011 must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.~~

Allowed concomitant platinum-based chemotherapy regimens are:

- gemcitabine plus cisplatin or carboplatin ± bevacizumab
- pemetrexed plus cisplatin or carboplatin ± bevacizumab
- paclitaxel plus carboplatin ± bevacizumab
- docetaxel plus cisplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Subjects may receive 4-6 cycles of the allowed platinum-based regimen selected by the Investigator. Up to ~~The addition of up to~~ 2 additional cycles (8 total cycles) of platinum-based chemotherapy may be given as determined by ~~following~~ cancer response. The platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

While on treatment subjects will be allowed to receive m~~M~~aintenance ~~chemo~~therapy with a pemetrexed or erlotinib-containing regimen when indicated. ~~will only be allowed following completion of the subject's platinum-based chemotherapy, with a best response of at least stable disease.~~

Rationale:

Revised to move Process IIa preparation instructions to Section 8.1 –Description of Investigational Products.

Modified to include additional platinum-based chemotherapy regimen, clarify maximum number of cycles allowed and add erlotinib-based maintenance regimen per investigator recommendation. Also, per FDA's recommendation, clarification of study population description based on subjects being eligible to continue to receive platinum-based chemotherapy following randomization.

Section 8.2.1: Selection of Dose for the Study, (page 66)

Original Text:

In **Part 1**, subjects will be randomized to one of the following ACE-011 dose levels, with 10-30 subjects per arm:

- ACE-011 15.0 mg SC
- ACE-011 30.0 mg SC

Following analysis of at least 10 subjects at each dose level (10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level), a third dose level will be added to the randomization schema:

- ACE-011 45.0 mg SC

Revised Text:

In **Part 1**, subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

~~Following analysis~~Analysis of safety data will be performed following the treatment of at least 10 subjects at ~~each dose level (10 subjects at~~ the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level~~),~~, with at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level ~~will be added~~ :

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema~~:~~ will be determined.

- ~~ACE-011 45.0 mg SC~~

Each dose level will be administered every 42 days for up to four doses.

Rationale:

Revised per FDA's recommendation to clarify when safety analysis of the first 10 subjects treated with 15 and 30 mg dose levels of sotatercept (ACE-011) would occur.

Section 8.2.2: Selection and Timing of Dosing for Each Subject (Page 66)

Original Text:

In **Part 1**, subjects will be randomized to receive one of three doses of ACE-011, with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive ACE-011 or placebo at a ratio of 1:1.

Each subject will return to the site on Day 1 of each scheduled visit. During the Treatment Period, subjects will receive ACE-011 or ACE-011/placebo every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated by local lab weekly after the first dose of ACE-011 or ACE-011/placebo then at 7, 14 and 28 days after each subsequent dose of ACE-011 or ACE-011/placebo.

Revised Text:

In **Part 1**, subjects will be randomized to receive one of three ~~doses~~ dose levels of sotatercept (ACE-011), with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive sotatercept (ACE-011) or placebo at a ratio of 1:1.

Each subject will return to the site on ~~Day 1 of~~ each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated ~~by local lab~~ weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Rationale:

Revised to clarify three dose **levels** of sotatercept (ACE-011) and that subjects are to return to the study site for each clinic visit.

Original Text:

The **first** dose of ACE-011 or ACE-011/placebo should be given within +/- 3 days of **Day 1** of a platinum-based chemotherapy **Cycle**. Subsequent cycles of the chemotherapy dosing schedule, included dose reductions and delays, should not affect the ACE-011 or ACE-011/placebo dosing schedule, unless determined to be necessary by the Investigator. ACE-011 or ACE-011/placebo can be administered at any time point during the chemotherapy cycle. If there is a chemotherapy dose delay, ACE-011 or ACE-011/placebo administration does not need to be delayed until the start of the next chemotherapy cycle. ACE-011 or ACE-011/placebo should be given prior to chemotherapy administration.

Revised Text:

The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days <u>of administration</u> of a platinum-based chemotherapy cycle**. **Subsequent doses** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

Rationale:

Modified to increase the allowed dosing time period of the **first** dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to and following a cycle of platinum-based chemotherapy.

Clarification of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule versus platinum-based chemotherapy dosing schedule.

Clarification of the order of study treatment and platinum-based chemotherapy dosing, when administered on the same day.

Section 8.2.3: Discontinuation, (pages 67-68)

Original Text:

Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from ACE-011 treatment:

- AE(s)
  - Medically significant hypertension which 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)
  - Creatinine clearance < 40 ml/min
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria

Revised Text:

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

~~The following events are considered sufficient reasons for discontinuing a subject from ACE-011 treatment:~~

- Adverse events(s)
  - – Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100mm Hg), confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy. ~~Medically significant hypertension which cannot be adequately controlled with antihypertensive therapy~~
  - Any AE > Grade 2 assessed to be related to ~~ACE-011~~sotatercept (ACE-011) therapy

- Any persistent AE > Grade 1 considered to be related to ~~ACE-011~~sotatercept (ACE-011) treatment and causing a subject to miss three months ~~ACE-011~~sotatercept (ACE-011) therapy
- Any thromboembolic event > Grade 2
- Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
- ~~Creatinine clearance < 40 ml/min~~
- Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
- Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living and persisting for one week.

Rationale:

Updated to comply with FDA's feedback to use command language to instruct investigators to discontinue study therapy, provide blood pressure parameters and define persistent hematuria. Discontinuation based on creatinine clearance was deleted based on updated toxicology study data and investigator recommendation.

Section 8.2.3: Discontinuation, (page 68)

Original Text:

Study Discontinuation:

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

- Completed study, per protocol (subject has completed six to nine month Treatment Period plus up to six month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- AE(s)
- Disease progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

Revised Text:

Study Discontinuation:

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

- Completed study, per protocol (subject has completed six- to nine-month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- ~~AE(s)~~
- ~~Disease progression of NSCLC~~
- ~~W~~Withdrawal of consent
- Death
- Lost to follow-up
- ~~Protocol violation~~

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

- Adverse events(s)

- Disease progression of NSCLC
- Protocol violation

Rationale:

Separated the reasons for study discontinuation into two types to better define the reasons that will necessitate study discontinuation and reasons that may lead to study discontinuation.

3.10. Section 9.1: Permitted Concomitant Medications and Procedures, (page 70-71)

Original Text:

Iron supplementation

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

Revised Text:

Iron supplementation

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

Rationale:

Modified per FDA's recommendation to replace term "replete" with "deficient".

Original Text:

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is > 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, ACE-011 should be administered no sooner than 7 days from the date of the RBC transfusion.

Revised Text:

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ~~></~~≤ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered no sooner than 7 days from the date of the RBC transfusion.

Rationale:

Clarification of recommended RBC transfusion for the treatment of CIA per Hgb level and timeframe for RBC transfusion and sotatercept (ACE-011) administration.

3.11. Section 10.1: Overview, (page 72)

Original Text:

(Text not previously present.)

Revised Text:

Data from Part 1 will not be combined with data from Part 2 in all safety and efficacy analyses.

Rationale:

Revised to clarify Part 1 and Part 2 analyses.

3.12. Section 10.3: Sample Size and Power Considerations (page 72)

Original Text:

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in Part 2 (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude more than 15% risk reduction in the ACE-011 arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:ACE-011) of 0.87, assuming the ACE-011 arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:ACE-011) of 1.11.

Revised Text:

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in Part 2 (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude more than 15% ~~risk reduction~~hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

Rationale:

Revised to correct typographical error.

3.13. Section 10.6: Efficacy Analysis, (page 73)

Original Text:

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the first ACE-011 treatment. It will be estimated based on Kaplan-Meier estimates for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects with a documented RBC transfusion will be considered having the event. Subjects without documented RBC transfusion will be censored on the date of last contact or a month after the last dose of study treatment, or termination of the concomitant chemotherapy, whichever is earlier. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test.

Overall survival (OS) is defined as the time between the randomization and death. A subject that dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

Revised Text:

In **Part 1**, the primary endpoint will be the hematopoietic response defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the ~~first ACE-011 treatment.~~date of randomization. It will be estimated based on Kaplan-Meier ~~estimates~~ method for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects ~~with a~~ who have documented RBC transfusion~~ will be considered having the event. Subjects without documented RBC transfusion will be censored on the date of last contact or a month after~~(s) from randomization until the last dose of ~~study treatment, or termination of the~~ concomitant platinum-based chemotherapy~~-~~ plus 30 days or from the initiation date of non-platinum-based chemotherapy ,whichever is earlier , will be considered as having the event on the date of first RBC transfusion. Subjects who are discontinued from study treatment due to reasons other than disease progression or death will be considered as having the event on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Subjects who discontinue from study treatment due to disease progression or death will be censored on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Otherwise subjects will be censored on the date of last contact, or on the date of last dose of concomitant platinum-based chemotherapy plus 30 days or on the initiation date of non-platinum-based chemotherapy, whichever is earliest. The comparison on the distribution

difference between the treatment groups will be based on the stratified log-rank test~~.~~, and the associated hazard ratio and 95% confidence interval will be provided using Cox proportional hazard model. The proportion of subjects receiving a transfusion based on Kaplan-Meier estimates at specific time points will also be provided by treatment arms.

Overall survival (OS) is defined as the time between the randomization and death. A subject ~~that~~ who dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

Rationale:

Modified per FDA's recommendation to provide a detailed definition of the Part 2 primary endpoint, transfusion rate.

Revised typographical error.

3.14. Section 11.2: Evaluation of Adverse Events (pages 78-79)

Section 11.2.4: Duration, (pages 78-79)

Original Text:

The Investigator will provide a record of the start and stop dates of the AE/SAE.

The duration of the AE and the SAE may vary within one event. For example, a non-serious AE may begin on 01-Jan. The event will become serious when it meets one of the criteria for seriousness (e.g., the subject is hospitalized on 05-Jan). The SAE will continue until it no longer meets the seriousness criteria (e.g., the subject is discharged on 07-Jan). However, the AE continues until 10-Jan when the event resolves. The AE dates may extend from before and beyond the SAE dates, but not the reverse.

Revised Text:

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

~~The Investigator will provide a record of the start and stop dates of the AE/SAE.~~

~~The duration of the AE and the SAE may vary within one event. For example, a non-serious AE may begin on 01-Jan. The event will become serious when it meets one of the criteria for seriousness (e.g., the subject is hospitalized on 05-Jan). The SAE will continue until it no longer meets the seriousness criteria (e.g., the subject is discharged on 07-Jan). However, the AE continues until 10-Jan when the event resolves. The AE dates may extend from before and beyond the SAE dates, but not the reverse.~~

Rationale:

Updated in alignment with current protocol template.

Section 11.2.5: Action Taken, (page 79)

Original Text:

The Investigator will report the discontinuation or reduction of IP following an AE and report if concomitant and/or additional treatments were given for the AE.

Revised Text:

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. ~~The Investigator will report the discontinuation or reduction of IP following an AE and report if concomitant and/or additional treatments were given for the AE.~~

Rationale:

Updated in alignment with current protocol template.

3.15. Section 11.4: Pregnancy

Section 11.4.1: Females of Childbearing Potential, (pages 79-80)

Original Text:

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

The female should be referred to an obstetrician-gynecologist.

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 Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), 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.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

Revised Text:

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

The female subject should be referred to an 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 ~~Pregnancy~~ Report Form, or approved equivalent form.

Rationale:

Updated in alignment with current protocol template.

Section 11.4.2: Male Subjects, (page 80)

Original Text:

Female partners of male subjects taking IP should be advised to call their healthcare provider immediately if they become pregnant, and male subjects should notify the Investigator.

Revised Text:

~~Female partners~~If a female partner of a male ~~subjects~~subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately ~~if they become pregnant, and male subjects should notify the Investigator~~.

Rationale:

Updated in alignment with current protocol template.

3.16. Section 11.5: Immediate Reporting of Serious Adverse Events, (page 80)

Original Text:

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

The SAE report should provide a detailed description of the SAE and include copies of hospital records and other relevant documents.

Revised Text:

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

The SAE report should provide a detailed description of the SAE and include summaries~~copies~~ of hospital records and other relevant documents.

Rationale:

Modified serious adverse event reporting period from 112 to 42 days for events not suspected to be related to investigational product to be in alignment with AE reporting and current protocol template.

3.17. Section 11.6: Expedited Reporting of Adverse Events, (page 80-81)

Original Text:

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

- Any AE associated with the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);

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 SAE Report Form.

Revised Text:

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

- Any AE suspected of being related ~~assoc~~to~~iated with~~ the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);

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~~SAE~~ Report Form / Completion Guidelines.

Rationale:

Updated in alignment with current protocol template.

3.18. Section 14.6: Institutional Review Board/Independent Ethics Committee Review and Approval, (page 86)

Original Text:

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative.

Revised Text:

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.

Rationale:

Updated in alignment with current protocol template.

3.19. Section 17: Publications, (page 90)

Original Text:

(Text not previously present.)

Revised Text:

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.

Rationale:

Updated in alignment with current protocol template.

A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
AMENDMENT 1.0 FINAL:	22 MARCH 2011
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

MEDICAL MONITOR / **EMERGENCY CONTACT INFORMATION**

Contact Information:	
PPD	

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:	PPD

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

Signature of Celgene Therapeutic Area Head

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:_____** By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A single-blind, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Metastatic Non-Small Cell Lung Cancer (NSCLC).

Objectives

The primary objectives are:

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011)/placebo treatment.

The secondary objectives are:

- Part 1 and Part 2:
- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in metastatic NSCLC subjects with CIA.
- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment in metastatic NSCLC subjects with CIA.
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects with metastatic NSCLC receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).

- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue.
- To assess renal function biomarkers.

Study Design

This is a single-blind, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for CIA subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Part 2 is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During **Part 2** (first and second stage) overall survival will be assessed. The total sample size of 750 subjects will allow observation of at least 536 deaths and thus, at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Study Population

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles and must be randomized prior to receiving Cycle 4 of this current first-line platinum-based regimen to be eligible for the study. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening, Treatment Period, Post Treatment Follow-Up Period, and Survival Follow-Up Period. Study treatment is defined as sotatercept (ACE-011) in Part 1 and sotatercept (ACE-011)/placebo in Part 2.

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days of randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks prior to randomization. **Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected and used for assessment of tumor response.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from initial diagnosis of NSCLC and red blood cell (RBC) transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up to two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the screening period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Treatment Period (up to 6-9 months):

The treatment period is approximately six months (four doses of study treatment given on Day 1, every 42 days), two additional sotatercept (ACE-011)/placebo doses may be given only in **Part 2**, at the discretion of the Investigator.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The effective dose of sotatercept (ACE-011) is defined as follows:

> An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks during the first two doses of sotatercept (ACE-011) (Dose 1/Day 1 through and including Dose 2/Day 43 [prior to Dose 3]), in approximately 70% of subjects, in at least one or more treatment arms (in the absence of RBC transfusions and/or ESAs).

Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the optimal dose for Part 2.

In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

In **Part 2**, a total of 750 subjects will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses. Up to two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011) (at the dose determined from Part 1) or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered > 7 days from the date of the RBC transfusion.

In **Part 1**, full PK blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

In **Part 2**, the sparse PK assessment will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mm Hg or diastolic blood pressure [DBP] ≥ 100mm Hg), confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy. Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months of sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.
- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥ 3.0 g/dL following a two-level dose reduction due to a Hgb increase ≥ 3.0 g/dL
  - In **Part 2**: > 3 dose reductions and/or delays
- Disease progression of NSCLC
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

Post Treatment Follow-Up Period (monthly visits for up to 6 months)

Subjects who enter the Post Treatment Follow-Up Period will be followed monthly for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to one year from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first.

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

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

- Adverse event(s)
- Disease progression of NSCLC
- Protocol violation

Survival Follow-up Period (monthly for up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo)

In both **Part 1** and **Part 2**, survival data will be collected monthly via telephone contact for up to 24 months following the subject's first dose of sotatercept (ACE-011) (Part 1) or sotatercept (ACE-011)/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit.

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Overview of Efficacy Assessments

- Serum hematology, absolute reticulocyte counts
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Tumor Assessments
- Documentation of concomitant RBC transfusions

Overview of Safety Assessments

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac and thromboembolic events
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- AE(s)
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy testing
- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone).
- QoL Assessment (FACIT Fatigue Scale [Version 4]) and Lung Cancer Symptom Scale (LCSS) questionnaire.
- Documentation of concomitant medications / procedures.

Overview of Exploratory Assessments

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- DXA scan
- Renal function biomarkers

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 18
2. STUDY OBJECTIVES 34
2.1. Primary Objective 34
2.2. Secondary Objectives 34
2.3. Exploratory Objectives 34
3. STUDY ENDPOINTS 35
3.1. Primary Endpoint(s) 35
3.2. Secondary Endpoint(s) 35
3.3. Exploratory Endpoint(s) 36
4. OVERALL STUDY DESIGN 37
4.1. Study Design 37
4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules 40
4.2. Study Design Rationale 43
4.2.1. Fixed Dose 44
4.2.2. Dosing Schedule 44
4.2.3. Starting Dose Levels in Part 1 44
4.2.4. Evaluation of Dosing Schema via Modeling/Simulation 45
4.3. Study Duration 46
5. TABLE OF EVENTS 47
6. PROCEDURES 55
7. STUDY POPULATION 63
7.1. Number of Subjects 63
7.2. Inclusion Criteria 64
7.3. Exclusion Criteria 65
8. DESCRIPTION OF STUDY TREATMENTS 68
8.1. Description of Investigational Product(s) 68
8.2. Treatment Administration and Schedule 68
8.2.1. Selection of Dose for the Study 69
8.2.2. Selection and Timing of Dosing for Each Subject 70

8.2.3. Discontinuation 71
8.3. Method of Treatment Assignment 72
8.4. Packaging and Labeling 72
8.5. Investigational Product Accountability And Disposal 73
8.6. Investigational Product Compliance 73
9. CONCOMITANT MEDICATIONS AND PROCEDURES 74
9.1. Permitted Concomitant Medications and Procedures 74
9.2. Prohibited Concomitant Medications and Procedures 75
9.3. Required Concomitant Medications and Procedures 75
10. STATISTICAL ANALYSES 76
10.1. Overview 76
10.2. Study Population Definitions 76
10.3. Sample Size and Power Considerations 76
10.4. Background and Demographic Characteristics 77
10.5. Subject Disposition 77
10.6. Efficacy Analysis 77
10.7. Safety Analysis 78
10.8. Interim Analysis 79
10.9. Other Topics 79
10.10. Data Monitoring Committee (DMC) 80
11. ADVERSE EVENTS 81
11.1. Monitoring, Recording and Reporting of Adverse Events 81
11.2. Evaluation of Adverse Events 81
11.2.1. Seriousness 81
11.2.2. Severity / Intensity 82
11.2.3. Causality 83
11.2.4. Duration 83
11.2.5. Action Taken 84
11.2.6. Outcome 84
11.3. Abnormal Laboratory Values 84
11.4. Pregnancy 84
11.4.1. Females of Childbearing Potential: 84
11.4.2. Male Subjects 85

11.5. Immediate Reporting of Serious Adverse Events 85
11.5.1. Safety Queries 85
11.6. Expedited Reporting of Adverse Events 85
12. DISCONTINUATIONS 87
13. EMERGENCY PROCEDURES 88
13.1. Emergency Contact 88
13.2. Emergency Identification of Investigational Products 88
14. REGULATORY CONSIDERATIONS 89
14.1. Good Clinical Practice 89
14.2. Investigator Responsibilities 89
14.3. Subject Information and Informed Consent 89
14.4. Confidentiality 90
14.5. Protocol Amendments 90
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 90
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 91
14.8. Closure of the Study 91
15. DATA HANDLING AND RECORDKEEPING 92
15.1. Data/Documents 92
15.2. Data Management 92
15.3. Record Retention 92
16. QUALITY CONTROL AND QUALITY ASSURANCE 94
16.1. Study Monitoring and Source Data Verification 94
16.2. Audits and Inspections 94
17. PUBLICATIONS 95
18. REFERENCES 96
19. APPENDICES 99
Appendix A: Response Evaluation Criteria in Solid Tumors 99
Appendix B: ECOG Performance Status Scale 101
Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 102
Appendix D: New York Heart Association - Classification of Heart Failure 103

LIST OF TABLES

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation 26
Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall 29
Table 3: Summary of SAEs Reported 30
Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days 30
Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels 42
Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only) 43
Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments 47
Table 8: Schedule of Pharmacokinetic Assessments (Part 1) 53
Table 9: Schedule of Pharmacokinetic Assessments (Part 2) 54
Table 10: ECOG Performance Status Scale 101
Table 11: Classification of Heart Failure 103

LIST OF FIGURES

Figure 1: Study Design 39
Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population 46

1. INTRODUCTION

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to define the recommended sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 2 will be performed in two stages. In the first stage approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The chemical structure of sotatercept (ACE-011) is composed of a disulfide-linked, glycosylated, dimeric protein. Sotatercept (ACE-011) competes with the activin receptor IIA and binds a number of TGF-β superfamily ligands including activin, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

In both a single and a multiple dose phase 1 study of sotatercept (ACE-011) in healthy volunteer, postmenopausal women, a dose and time dependent increase in hemoglobin (Hgb) and hematocrit (HCT), and red blood cell (RBC) levels were observed following sotatercept (ACE-011) treatment and remained elevated over the course of study.

Although the mechanism(s) underlying the stimulation effect of sotatercept (ACE-011) on erythropoiesis are not yet fully understood, the result of clinical experience showed a rapid and sustainable increase in mature erythrocytes released into circulation. The sotatercept (ACE-011) proposed mechanism of action may be different than that of known erythropoiesis-stimulating agents (ESAs) and may provide a different clinical profile in the treatment of CIA.

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

Non-Small Cell Lung Cancer Current Therapy Status

Lung cancer is the leading cause of cancer death in the world, accounting for 32% of cancer deaths in males and 25% in females, affecting approximately 171,000 people annually in the US (Parker, 1997; Sandler, 2006) and more than 200,000 people in Europe (Rossi, 2006). Of these patients, approximately 85% have NSCLC, including squamous carcinoma, adenocarcinoma and

large cell carcinoma (Rossi, 2006; Sandler, 2006). These histologies are typically classified together because the approaches to diagnosis, staging and prognosis, and treatment are similar.

Patients are often diagnosed with an advanced stage of disease. Studies of advanced NSCLC patients treated with platinum-based chemotherapy report a one year survival rate that ranges from 30 to 43 percent and a median survival that ranges from seven to ten months (Dang, 2008). The 5-year survival rate of patients with NSCLC varies by stage, from 60 to 70% for patients with stage I disease to < 1% for patients with stage IV disease (Hong, 2008). Patients having stage IIIb/IV NSCLC are not considered to be candidates for curative resection surgery or radiation, and radiation therapy is primarily used as palliative treatment in advanced stages of NSCLC.

The role of chemotherapy is now well established as the recommended treatment of advanced NSCLC (Non-small Cell Lung Cancer Collaborative, Group 1995). The current globally accepted standard of treatment for NSCLC is platinum-based combination therapy. In advanced-stage (stage IIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine (Gemzar®), vinorelbine, taxanes (paclitaxel or docetaxel) or pemetrexed are reference regimens. When compared head-to-head in phase III studies, these doublets have shown comparable efficacy, in regards to overall survival (Schiller, 2002) with differences in toxicity profiles (Schiller, 2002). When administered in a 3-week schedule, cisplatin plus gemcitabine, or cisplatin plus pemetrexed are effective and are widely used regimens for first-line treatment of NSCLC. A recent phase III study in NSCLC compared cisplatin plus gemcitabine with cisplatin plus pemetrexed (Scagliotti, 2008). Both had similar efficacy, with cisplatin plus pemetrexed having better tolerability and more convenient administration than cisplatin/gemcitabine. This study was also the first prospective phase III study in NSCLC to show a survival difference based on histologic type (non-squamous benefited from pemetrexed plus cisplatin). Drug-related grade (G) 3 or 4 anemia was at the rate of 6% for cisplatin/pemetrexed versus 10% for cisplatin/gemcitabine. The incidence of RBC transfusion was 16.1% versus 27.3% and administration of erythropoietic agents 10.4% versus 18.1% respectively. There was no significant difference between treatment arms in the incidence of or reason for deaths (7%).

Treatment of Chemotherapy-Induced Anemia

Chemotherapy-induced anemia is an area of unmet medical need. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these patients, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002).

The current treatment options for CIA include blood transfusion and ESAs. However, the blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients in chemotherapy has therefore been

rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. In the pivotal Aranesp study for CIA in NSCLC, 27 % of patients were transfused with Packed Red Blood Cells (PRBC's) at 4 months vs. 52% in the placebo arm. In a subsequent recent Phase III study of pemetrexed (Alimta®) plus cisplatin vs. gemcitabine plus cisplatin where all first-line NSCLC patients with anemia or not were enrolled, 16.1% vs 27.3% of patients respectively were transfused with PRBC's during that study (Scagliotti, 2008).

Chemotherapy-induced anemia is a significant problem for patients with cancer, causing fatigue and reducing quality-of-life (QoL). Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two Phase 1 studies in healthy volunteers, as well as in a Phase 2a study for multiple myeloma (MM). The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

Activin Biology

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

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

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

In a retrospective study (Seder, 2009) activin immunoreactivity was found in 78% of lung adenocarcinomas surveyed (n=164). Expression ranged from moderate in the majority of individuals to high in approximately 19.7% of samples evaluated. Gene expression analysis was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples. An average of three-fold more activin transcript was detected in diseased tissue relative to normal samples and particularly high levels of overexpression were associated with worse overall survival in stage I patients with NSCLC.

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

Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below.

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 (IP) twice per week for 3 months resulted in a 16-26% increase in RBC counts compared to control animals. Rats treated with sotatercept (ACE-011) at 0.3, 3 and 30 mg/kg once per week for 3 months showed RBC count increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of sotatercept (ACE-011) twice per month for 3 months, there was a 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 sotatercept (ACE-011).

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

RAP-011 has also been shown to significantly increase bone mineral density (BMD) and strength in normal animals and in a variety of animal models of bone loss (Chantry, 2008;

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

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

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

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model demonstrated that RAP-011 could prevent the development of osteolytic bone disease in a preventative setting.

The effect of this activin antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in 5T2MM murine myeloma cells isolated from the bone marrow of disease bearing animals.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

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

In addition, the RAP-011 was highly effective in restoring bone mineral density (BMD) when administered therapeutically in a murine model of postmenopausal osteoporosis. RAP-011 has also been shown to increase trabecular bone density in normal mice.

The efficacy of RAP-011 was also examined in two orthotopic metastatic models of breast cancer using luciferase-tagged human MCF-7 and MDA-MB-231 breast cancer cells (estrogen receptor positive and negative, respectively). Mice were pretreated for 2 weeks with RAP-011 (10 mg/kg, biweekly, SC) prior to the intra-cardiac implantation of tumor cells into female nude mice. Treatment with RAP-011 was continued for an additional 7 weeks following tumor implantation at which time mice were sacrificed and assessed for tumor burden. RAP-011 either modestly decreased the tumor burden (in the case of mice bearing MCF-7 tumors) or delayed tumor growth by approximately 3 weeks (MDA-MB-231 model) as measured by bio-luminescence. In addition, in the MCF-7 model, a 60% reduction in tumor weight was observed in the RAP-011 treated mice.

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

Toxicology

Sotatercept (ACE-011) has been evaluated for toxicological effects in two species, Sprague-Dawley rats and cynomolgus monkeys. The dose levels ranged from 0.3 to 30 mg/kg in rats and from 1 to 50 mg/kg in monkeys. These dose ranges were designed to support phase 1a single-dose levels of 0.01 to 3.0 mg/kg IV and phase 1b multiple doses of 0.1 to 2 mg/kg (monthly, SC). Weekly (rat and IV monkey studies) or every 2 week (SC monkey studies) dosing in animals was designed to provide continuous, but fluctuating serum concentrations of sotatercept (ACE-011), which would be mimicked by a one-month dosing interval in humans.

Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney

findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-sotatercept (ACE-011) antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats. However, high plasma concentrations of sotatercept (ACE-011) in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (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, the NOAEL from the 6 month monkey study is < 10 mg/kg. A 9-month monkey study to evaluate the effects of lower concentrations of sotatercept (ACE-011) has been completed (refer to Potential Risks for Human Use).

Summary of Clinical Experience

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

Sotatercept (ACE-011) was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal females (Ruckle, 2009). Sotatercept (ACE-011) was diluted in normal saline administered as an IV infusion (over approximately 1 hour) or as a SC injection on Day 1. Dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg IV and 0.03 and 0.1 mg/kg SC. A total of 48 subjects were enrolled; 5 active and 1 placebo at each of the IV and SC dose levels. All subjects were followed for 4 months following a single dose administration.

The pharmacokinetics (PK) of sotatercept (ACE-011) was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (CL) ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half life in serum ($t_{1/2,}$ z) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, sotatercept (ACE-011) was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs was mild in severity and were judged to be unrelated to sotatercept (ACE-011). No deaths, serious AEs (SAEs), or AEs leading to discontinuation were reported. Changes in RBCs, Hgb, reticulocytes, liver function tests, glucose, uric acid, amylase and lipase occurred in some subjects. Mild, transient elevations in pancreas enzymes, liver enzymes, or glucose were reported as AEs in five subjects.

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

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

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

Sotatercept (ACE-011) was studied in a phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalating study to evaluate the safety, tolerability and pharmacodynamics of sotatercept (ACE-011) in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following dose levels: 0.1, 0.3, 1.0, and 2.0 mg/kg administered SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of sotatercept (ACE-011) or placebo every 28 days for a total of 4 doses. All subjects were to be followed for 12 weeks after the last dose.

The treatment phase of the study was terminated early after a dose-limiting pharmacodynamic effect was observed. While on study, one subject in the 1.0 mg/kg cohort experienced an SAE of progressive and persistent hypertension that was attributed to a rapid and significant rise in Hgb levels, up to 20 g/dL and HCT levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting pharmacodynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and treated. Dose levels of sotatercept (ACE-011) administered included 0.1, 0.3, and 1.0 mg/kg (Cohorts 1, 2, and 3 respectively). All subjects randomized to active treatment in Cohort 1 received all 4 planned doses of sotatercept (ACE-011). Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of sotatercept (ACE-011), and subjects randomized to active treatment in Cohort 3 received 2 doses of sotatercept (ACE-011). Subjects randomized to placebo treatment received between 1 and 4 doses of study treatment.

In the analysis of the data, after the administration of the first dose, a dose and time dependent increase in Hgb, 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]	**Sotatercept (ACE-011) 0.1 mg/kg N=8**	**Sotatercept (ACE-011) 0.3 mg/kg N=8**	**Sotatercept (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

Other than the serious case of Hgb increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the

subjects in the 1.0 mg/kg group with elevated Hgb levels underwent phlebotomies and all Hgb elevations were resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups.

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

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

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

The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ((apparent) volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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

Study A011-04 is a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety, tolerability and efficacy of sotatercept (ACE-011) in subjects with osteolytic lesions of multiple myeloma (MM).

In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of sotatercept (ACE-011) (0.1, 0.3 and 0.5 mg/kg) or placebo, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept (ACE-011) was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg sotatercept (ACE-011), 8 subjects received 0.3 mg/kg sotatercept (ACE-011), and 8 subjects received 0.5 mg/kg sotatercept (ACE-011). Twenty six (86.7%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

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

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

Fourteen out of 24 subjects (58%) who received study treatment (sotatercept [ACE-011]) did receive 3 doses or more (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level).

Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (ie, those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept (ACE-011) or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg sotatercept (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to sotatercept (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups and Table 3 is a summary of SAEs reported.

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

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

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

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug (sotatercept (ACE-011) or placebo).

Table 3: Summary of SAEs Reported

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

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

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

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hgb values were observed within 28 days after administration of the first dose of sotatercept (ACE-011)/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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

Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies

were as a result of the expected biologic activity of 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 sotatercept (ACE-011) treatment and is being targeted as a therapeutic intervention for conditions associated with anemia.
- In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~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 sotatercept (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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, 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 lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg (~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 sotatercept (ACE-011) is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all sotatercept (ACE-011) protocols describe pregnancy prevention requiring females of child-bearing potential to use highly effective methods of birth control. In addition, since it is unknown if sotatercept (ACE-011) is found in breast milk, breast feeding is prohibited in all protocols.

- Fertility
  - In male rats, sperm granulomas and testicular degeneration were observed histologically. In addition, sperm analysis revealed a reduction in sperm counts and motility as well as sperm fragmentation in isolated animals (2/10 males) at doses of 30 mg/kg IV. Sperm fragmentation was also noted in 2/5 males administered 10 mg/kg IV at the end of the recovery period. Overall, there was some evidence of recovery (motility similar to controls) at the end of the 4-week recovery period. There was no evidence of a treatment-related impact on reproductive organs (testes, ovary, uterus) of monkeys in the toxicity studies; however, the monkeys on these studies, were too immature to fully assess the potential impact on reproductive organs. The NOAEL for reproductive effects (testicular or ovarian) was 1 mg/kg IV. Serum exposure (AUC_{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 sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) is targeted toward patient groups for whom the potential benefits outweigh the perceived risks.

Because of the potential risks sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) was first studied in healthy postmenopausal in two completed phase 1 clinical trials. In

addition, due to the potential for effects on hormones in the pituitary, levels of growth hormone, ACTH, and thyroid stimulating hormone (TSH) were monitored closely in the phase 1 studies.

Completed studies in humans carried out in postmenopausal females showed a dose-dependent decrease in circulating levels of FSH, with mean levels in the multi-dose study in the two higher dose groups remaining below baseline at study end. FSH will continue to be evaluated in ongoing studies. No abnormal effects of sotatercept (ACE-011) on growth hormone, ACTH, and TSH and kidney toxicities were observed.

Based on the safety data from the two completed phase 1 studies, single doses of sotatercept (ACE-011) up to 3.0 mg/kg IV and multiple doses of sotatercept (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 sotatercept (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 sotatercept (ACE-011).

2. STUDY OBJECTIVES

2.1. Primary Objective

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment.

2.2. Secondary Objectives

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in metastatic NSCLC subjects with CIA.
- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment in metastatic NSCLC subjects with CIA.
- To determine the PK of sotatercept (ACE-011) in subjects with metastatic NSCLC receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

2.3. Exploratory Objectives

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue.
- To assess renal function biomarkers

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Part 1: Dose Finding

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the optimal dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).
- In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

Hematopoietic response will be determined by laboratory analysis.

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following the date of randomization to sotatercept (ACE-011)/placebo treatment

3.2. Secondary Endpoint(s)

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- TTP
- PFS (including at 6 and 12 months)
- OS (at 12 months and up to 24 months)
- ORR
- Duration of hematopoietic response
- Sotatercept (ACE-011) concentration in serum
- Non-compartmental PK parameters for sotatercept (ACE-011) (**Part 1** only)
- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1995)

3.3. Exploratory Endpoint(s)

- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or sotatercept (ACE-011) mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- A population PK model for sotatercept (ACE-011)
- A population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics
- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in the NSCLC population
- Change in renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to define the recommended sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

A DMC will monitor the conduct of the study.

Part 1 is planned to be conducted at selected US sites. The study will be extended to additional global sites for the conduct of Part 2.

Study treatment is defined as sotatercept (ACE-011) in Part 1 and sotatercept (ACE-011)/placebo in Part 2.

Three starting sotatercept (ACE-011) dose levels, 15.0, 30.0, and 45.0 mg, were selected for Part 1 of the study. Up to approximately 90 subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for four doses.

In **Part 2**, a total of 750 subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses; two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

The Treatment Period for Part 1 is up to approximately six months and for Part 2 up to nine months. Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first.

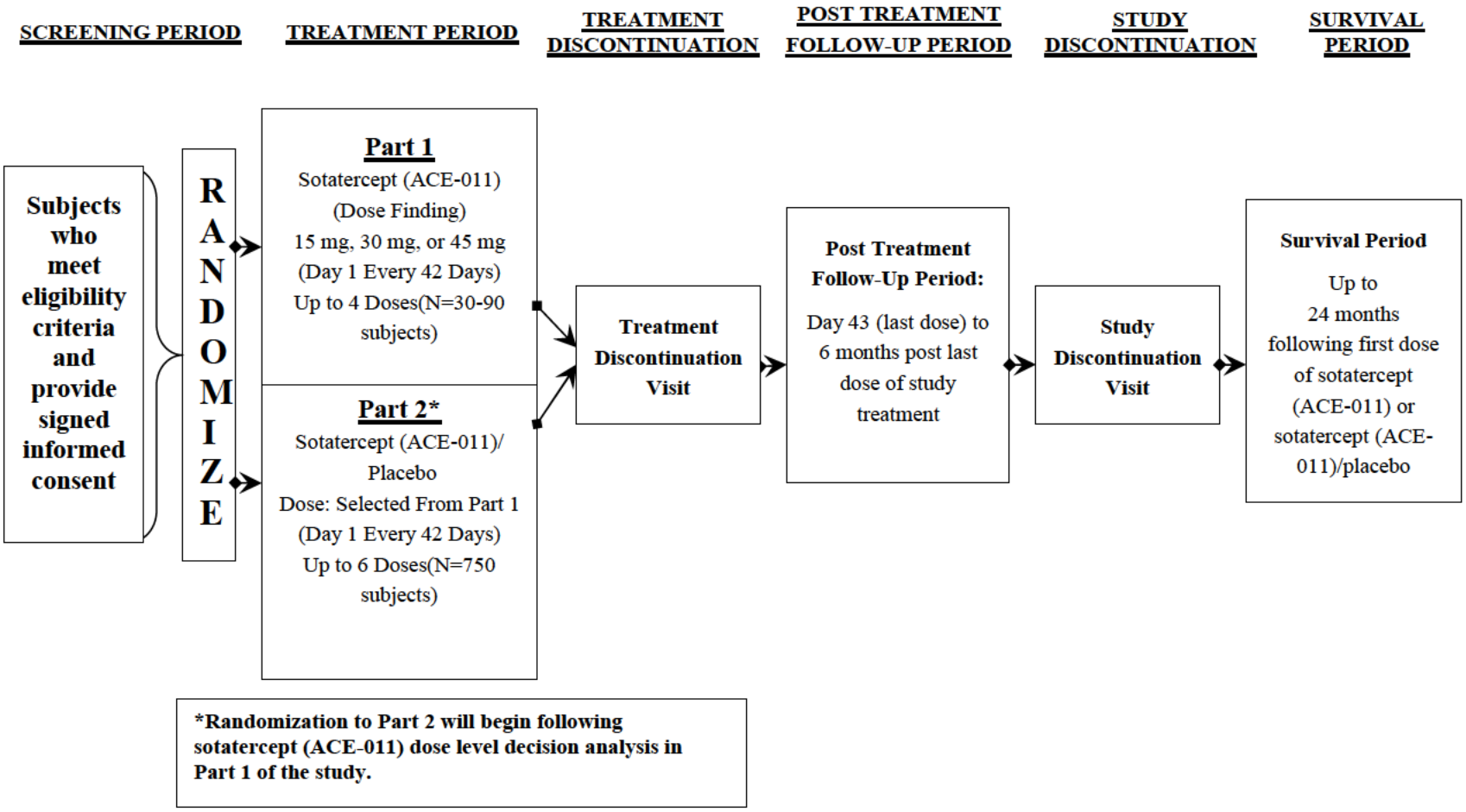
Survival data will be collected monthly for up to 24 months following the subject's first dose of sotatercept (ACE-011) in Part 1 or sotatercept (ACE-011)/placebo in Part 2.

At the time of randomization all subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles of this first-line platinum-based regimen to be eligible for the study. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment prior to initiating any maintenance chemotherapy for the treatment of metastatic NSCLC.

Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

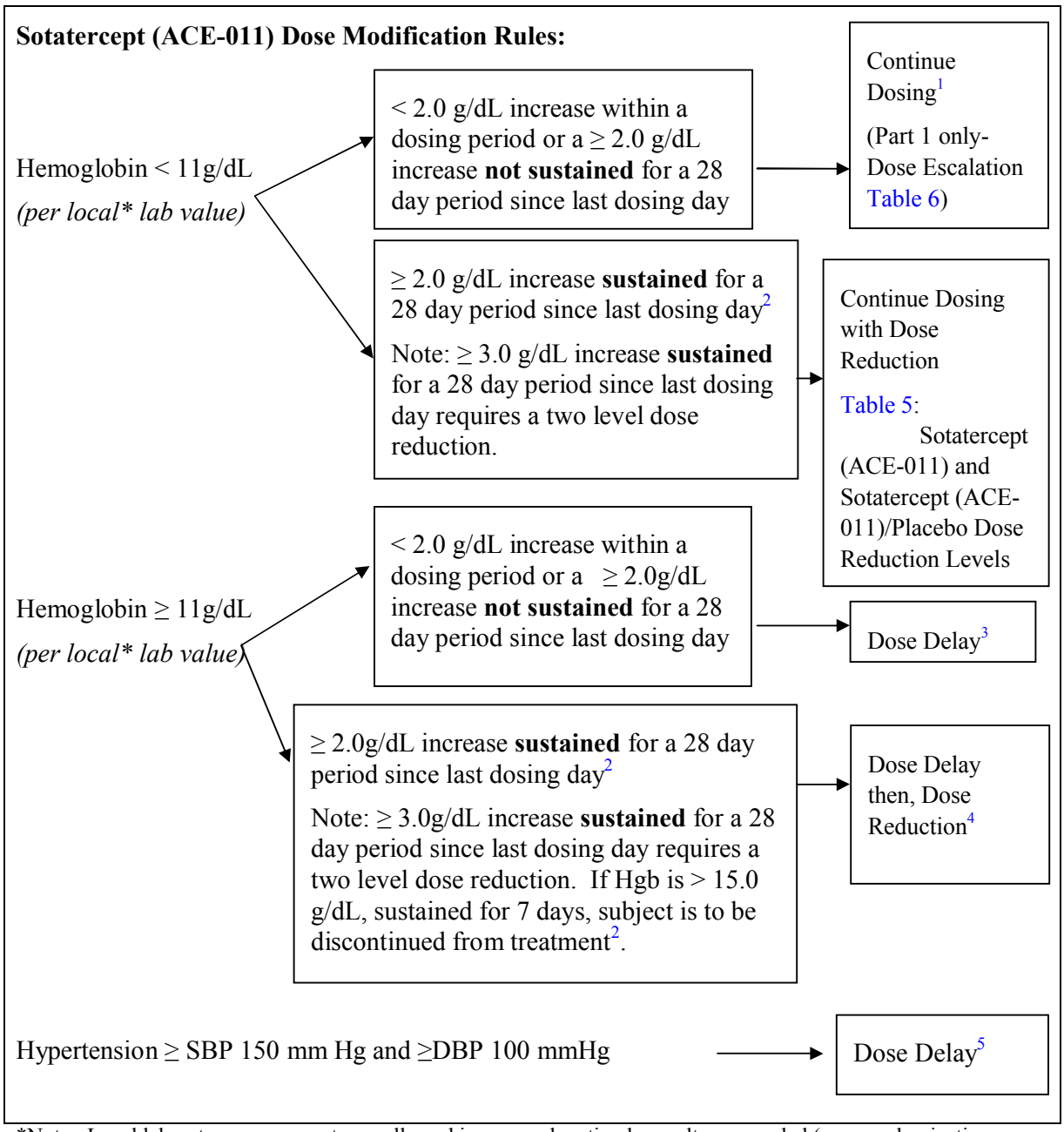
- In **Part 1**, subjects will be randomized to one of three sotatercept (ACE-011) dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
- In **Part 2** subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
  3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
  4. ECOG Performance Status 0-1 vs. 2

Figure 1: Study Design



4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) or sotatercept (ACE-011)/placebo for the subject's **second** dose of study treatment and beyond.



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

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150mm Hg and < DBP 100 mm Hg on the day of dosing. Sotatercept (ACE-011) should not be administered within 7 days post RBC transfusion.

For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** sotatercept (ACE-011)/placebo dose if the transfusion was given greater than 7 days from the previous dose of sotatercept (ACE-011)/placebo AND the Hgb level is < 11 g/dL AND hypertension is < SBP 150mm Hg and < DBP 100 mm Hg on the day of dosing. Sotatercept (ACE-011)/placebo should not be administered within 7 days post RBC transfusion.

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , 22 (after first dose of study treatment) and 28 days after dosing, and reviewed in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels (Refer to sotatercept (ACE-011) and sotatercept (ACE-011)/Placebo Dose Reduction Levels (Table 5). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg.. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose not administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension < SBP 150mm Hg and < DBP 100 mm Hg and/or sotatercept (ACE-011) related toxicity).

[4]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be held until hypertension resolves to < SBP 150mm Hg and < DBP 100 mm Hg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels

When required, per dose modification rules above, sotatercept (ACE-011) dose(s) in **Part 1** and sotatercept (ACE-011)/placebo dose(s) in **Part 2** should be reduced as follows:

Dose Schedule Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days- 45.0 mg	38.0 mg	33.0 mg	28.0 mg
Every 42 days- 30.0 mg	26.0 mg	22.0 mg	18.0 mg
Every 42 days- 15.0 mg	13.0 mg	11.0 mg	9.0 mg

*Note: Any Hgb increase of ≥3.0 g/dL will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for four doses. An additional two doses (total of 6 doses) may be given only during **Part 2** at the discretion of the Investigator.

Blood pressure (confirmed by two measurements obtained five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

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. A dose level may not be increased following a dose reduction.

Dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. In Part 2, subjects in the placebo group who are designated by their treating physician to undergo dose reduction will continue to receive placebo.

Placebo will be administered at the same volume as the corresponding sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction.

Sotatercept (ACE-011) Dose Escalation Levels:

The following dose escalation rules apply for sotatercept (ACE-011) dose(s) in **Part 1** only. Dose escalations are not allowed in **Part 2**:

- Less than 1.0 g/dL increase in Hgb in response to prior sotatercept (ACE-011) dose
- Hgb level must be < 11.0 g/dL and hypertension < SBP 150mm Hg and
  < DBP 100 mm Hg
- Dose escalation to begin at next treatment visit

- Sotatercept (ACE-011) should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of Sotatercept (ACE-011) at the subsequent visit per the escalation table below.

Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only)

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45.0 mg	50.0 mg	55.0 mg	61.0 mg
Every 42 days-30.0 mg	33.0 mg	36.0 mg	40.0 mg
Every 42 days-15.0 mg	17.0 mg	20.0 mg	23.0 mg

Blood pressure (confirmed by two measurements obtained five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

Dose increase steps and the subsequent administration of the increased dose(s) of sotatercept (ACE-011) will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject.

4.2. Study Design Rationale

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a significant 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 sotatercept (ACE-011), suggests an entirely novel mechanism of RBC production.

Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Guidelines, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

4.2.1. Fixed Dose

Sotatercept (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 sotatercept (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 sotatercept (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 sotatercept (ACE-011) exposure. Because the Hgb response is dependent on sotatercept (ACE-011) exposure and because body weight is not a major source for the intersubject variability of sotatercept (ACE-011) exposure, a fixed dosing approach is considered to be appropriate for the current study.

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 by taking into consideration the rapid and prolonged Hgb response to sotatercept (ACE-011) as well as the dosing schedule for the platinum-based chemotherapies. The Hgb-increasing effect of sotatercept (ACE-011) was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks. In addition, as platinum-based chemotherapy is often administered once every 3 weeks, a once every 6 weeks dosing schedule allows administration of sotatercept (ACE-011) at the same visit for the chemotherapy, which is convenient to both subjects and study sites.

4.2.3. Starting Dose Levels in Part 1

Three starting dose levels, 15.0, 30.0, and 45.0 mg, were chosen for Part 1 of the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of sotatercept (ACE-011) at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, sotatercept (ACE-011) had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal sotatercept (ACE-011) concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The three starting dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg, 31.5 mg, and 52.5 mg, respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three sotatercept (ACE-011) doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to sotatercept (ACE-011). In this study, the starting dose level of 45.0 mg (during the dose finding Part 1) will be implemented only after at least 10 subjects at each lower dose level (10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level) have been evaluated as well as following DMC review of safety data and assessment of dose effects on Hgb levels.

In addition, in the current NSCLC study, during the first 6-week treatment period for a 70 kg subject receiving the starting dose at 45.0 mg, the sotatercept (ACE-011) exposure ($C_{max,\ day\ 1\text{-}43}$ and $AUC_{1\text{-}43}$) is projected to be approximately 10% lower than the exposure for the dose regimen

of 0.5 mg/kg once every 4 weeks. Afterwards, safety measures (Hgb and blood pressure) will be used to guide the adjustment of the second dose and beyond. Thus, the use of the 45.0 mg starting dose in the current study is not anticipated to significantly compromise subject safety.

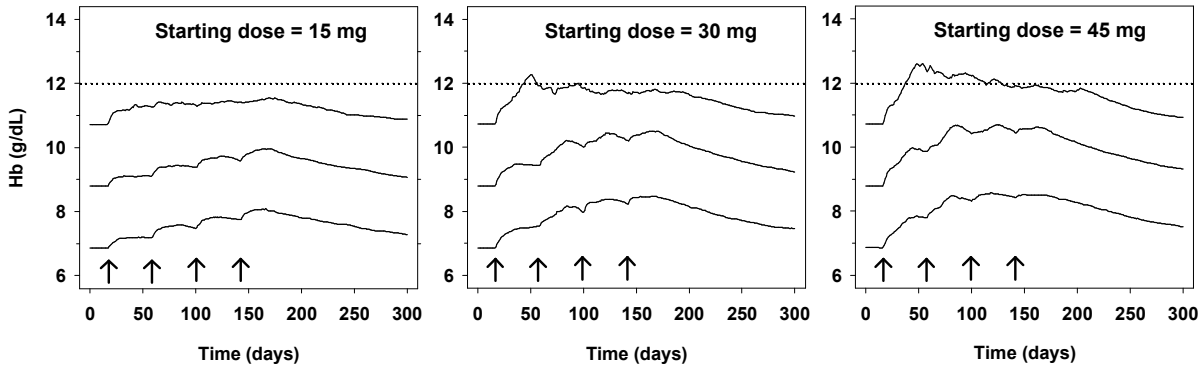
In the current study, the 45.0 mg group will have the highest starting dose, and it may be titrated up to 61.0 mg for the last dose (Dose 4). Assuming a 70 kg subject who receives the maximal amount of dose during the entire study (i.e., starting at 45.0 mg followed by dose escalation every 6 weeks to 50.0, 55.0, and 61.0 mg for Doses 2, 3, and 4, respectively), the projected cumulative AUC during the treatment period (168 days) would be approximately 60% of the steady state AUC cumulated during the same period at the NOAEL level of 1 mg/kg (given every 4 weeks for a total of 6 doses) as reported in the 9-month, repeat-dose toxicity study in monkeys. The projected highest C_{max} for the current study would be less than 50% of the steady state C_{max} in the monkey study.

4.2.4. Evaluation of Dosing Schema via Modeling/Simulation

The performance of the proposed dosing schema (three fixed starting dose levels, 6-week dosing interval, and dose adjustment rules [see Section 4.1.1 for details]) for this study was evaluated via PK/pharmacodynamic modeling/simulation. A tentative mechanistic PK/pharmacodynamic model for Hgb was developed using PK and Hgb data from healthy postmenopausal women and the model was extended to include MM subjects as a sub-population. The model was required to appropriately reproduce the observed PK and Hgb profiles in MM subjects. Monte Carlo simulations of the Hgb response to sotatercept (ACE-011) in a hypothetical anemic population ($6.5 \leq$ baseline Hgb < 11 g/dL; body weight 47 – 108 kg) were performed using the model parameterized with preliminary PK and pharmacodynamic parameters from MM subjects. In this simulation analysis, efficacy refers to an Hgb increase > 1 g/dL from the baseline for 28 consecutive days while safety refers to both the absolute Hgb levels and the rate of Hgb increase.

The simulation predicts that the desired efficacy would be achieved 6 weeks after the second dose in approximately 70% subjects of the 45 mg group and 6 weeks after the last dose in >70% subjects of the 30 mg group. Further, the simulation predicts the Hgb level would be maintained under 12 g/dL in 90% subjects and under 13 g/dL in 95% of subjects during the course of the study (Figure 2). No subjects are predicted to have a Hgb level above the upper limit of the normal range for Hgb (16 g/dL). Approximately 6% subjects are predicted to have an Hgb rise > 2 g/dL within 28 days of the first dose, mostly from the 45.0 mg group (4%); however, the fraction of subjects with an Hgb rise > 3 g/dL per 28 days is predicted to be similar between the three dose groups (approximately 2.5% for each group).

Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population



The middle solid lines represent the median Hgb level. The top and bottom solid lines represent the Hgb level at 5% and 95% percentile, respectively. The area between 5% and 95% percentiles represents 90% prediction interval. The straight dot lines represent the Hgb level of 12 g/dL. The arrows indicate the dosing time of sotatercept (ACE-011). The two level dose reductions upon ≥ 3 g/dL increase sustained for 28 days of a dose (Table 5) was not included in the simulation.

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects in Part 1 and 750 subjects in Part 2 will be randomized prior to receiving the fourth cycle of platinum-based chemotherapy for metastatic NSCLC. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

5. TABLE OF EVENTS

Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments

	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Complete Medical History	X																	
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X			X		X		X	X	X	X	X	X	X	
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X		X	X	X	X	X	
12-Lead Electrocardiogram (ECG) – **Part 1**[c]	X	X	X				X				X							
12-Lead Electrocardiogram (ECG) – **Part 2**[c]	X	X									X							
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	

Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[f]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X							
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X		X					
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X	X	X	X	X	X	X	
FSH and LH – Males and Females	X	X	X				X		X		X			X			X	
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X			X			X	
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X			X			X	
TSH[k]	X	X					X[k]						X					

Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Sotatercept (ACE-011) drug antibody test (pre-dose)		X		X			X				X			X		X		
Bone Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[l] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X			X				
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X													X				
Activin A and other proteins/biomarkers in Blood (pre-dose study treatment in a subset of subjects)		X	X				X					X						
Activin and other proteins/biomarkers in archival tumor tissue	X																	
Pharmacokinetics– **Part 1** and **Part 2**)[n]		Refer to Table 8 and Table 9 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X	≤ Every 9 weeks ± 1 week or per standard of care at study site																
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose only AEs assessed as related to study treatment are to be reported																
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X		X			X	X	

Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments (Continued)

	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Concomitant Procedures	X	X		X			X		X		X		X			X	X	
Hospitalizations (Record)	X	X		X			X		X		X		X			X	X	
Randomization		X																
Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X											
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice																
Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[v]																		X
Post Treatment Anti-Neoplastic Therapy											X	X	X	X	X	X	X	X

[a]Include NSCLC history, date of original diagnosis, clinical stage at Screening and date of metastases and metastatic site involvement. Record prior ESA history, starting at diagnosis of NSCLC. Record RBC transfusion history, starting from diagnosis of metastatic NSCLC, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) or sotatercept (ACE-011)/ placebo dose, at Treatment Discontinuation, and at Study Discontinuation. Blood pressure should be confirmed by two measurements obtained five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: For **Part 1**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011) dose, Day 8 post dose 1, every sotatercept (ACE-011) dosing Visit (post-dose) and at end of study treatment (day 43 post last dose).

For **Part 2**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011)/placebo dose and at end of study treatment (day 43 post last dose).

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days **prior** to the start of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo during the treatment period. Subjects must agree to use highly effective birth control measures (e.g., oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo to ensure levels are within normal limits and that sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (Part 1).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the treatment period, every month (except month 1) during the post treatment follow-up period and at study discontinuation .

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and end of study treatment (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. For full PK assessment, weekly after first dose of sotatercept (ACE-011).

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at 2 month post-treatment follow-up visit.

[l]Bone Biomarkers- Collected for **full** PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. For all other subjects collected prior to dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15.0, 30.0 and 45.0 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

Pharmacokinetics (**Part 2**): Sparse PK blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011) in approximately 300 (40%) of 750 subjects. Sotatercept (ACE-011) doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8 and Table 9, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening period tumor assessments may be performed up to six weeks prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Following randomization, tumor assessments will be performed at a maximum of every 9 weeks (± 7 days) or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments, FACIT Fatigue Scale (Version 4) and LCSS questionnaire, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins an every 3 week platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days following Day 1 of a platinum-based chemotherapy cycle**. **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.
Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.
If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

[r]Every 3-week platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

[s]Pemetrexed or erlotinib maintenance therapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose corresponds to the end of Treatment Period. Subjects who discontinue the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo Treatment Period early will continue to the Post Treatment Follow-Up Period and be followed for up to 6 months after their last dose of sotatercept (ACE-011)/placebo.

[u]Study Discontinuation visit should occur 12 months after starting treatment with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[v]Survival data will be collected monthly, via telephone contact, following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

Scheduled Time	Time relative to Sotatercept (ACE-011)	Part 1[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days
PT[f] Follow up, 1 month	72 days after final dose	X	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	± 1 week

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first sotatercept (ACE-011) dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first sotatercept (ACE-011) dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 30 subjects (approximately 10 subjects in each dose group).

[d] To be collected in other subjects.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

[f] PT = Post Treatment

Table 9: Schedule of Pharmacokinetic Assessments (Part 2)

Scheduled Time	Time relative to Sotatercept (ACE-011)/placebo dose	Sparse PK[a,b,c]	Collection Window[d]
Dose 1, D1	pre-Dose 1	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	±1 hour
Dose 1, D8	7 days after Dose 1	X	± 3 day
Dose 1, D15	14 days after Dose 1	X	± 3 day
Dose 1, D29	28 days after Dose 1	X	± 3 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	± 3 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	± 3 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	± 3 days
Dose 4, D43 (Dose 5, D1)	pre-Dose 5	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6	X	± 3 days
PT[e] Follow up, 3 month	132 days after final dose	X	± 1 week
PT Follow up, 5 month	192 days after final dose	X	± 1 week

[a] For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

[d] Except for Day 1 (Dose 1, D1), the collection window will be the same as the visit window defined in Table 7.

[e] PT = Post Treatment

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed within 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed within 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac, renal and thromboembolic events
- NSCLC history, including date of original diagnosis, histopathology, clinical stage at screening, date of metastatic stage and site involvement
- Prior ESA treatment history starting from initial diagnosis of NSCLC
- RBC transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up two months prior to randomization
- 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, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration
- Serum chemistry, hematology, absolute reticulocyte count to be assessed within 14 days of randomization
- Creatinine clearance (per Cockroft-Gault formula) within 14 days prior to study treatment administration
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and RBC folate levels
- Serum erythropoietin

- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Estrogen and estradiol – females only
- TSH
- Bone imaging – DXA scan
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks prior to randomization to this study. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized by a single-blind procedure utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

- In **Part 2**, subjects meeting all inclusion and exclusion criteria will enter into the Treatment Period and be randomized by a double-blind procedure utilizing IVRS to receive sotatercept (ACE-011) or placebo (1:1 ratio).
- A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days during the Treatment Period, as specified in the Table of Events (see Section 5).

In **Part 1**, the Treatment Period will last approximately 6 months, where subjects randomized to sotatercept (ACE-011) will receive treatment on Day 1 every 42 days for a planned 4 doses.

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional two doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration.
- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses collected at 7, 14 days and 28 days post-dose.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 43 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and 43 days after last dose of study treatment
- Serum erythropoietin
- Urinalysis

- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (**pre-dose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre- dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in archival tumor tissue
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week or per standard of care at the study site, starting from the previous [screening] tumor assessment) and following the chemotherapy schedule
- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Evaluation and all AE/SAE reporting (regardless causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or maintenance therapy
- Administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo at: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will enter the Post Treatment Follow-Up Period and be followed for 6 months after their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Upon completion of the Post Treatment Follow-Up Period, subjects will have a discontinuation visit and be followed for survival for up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

Following completion or early discontinuation from the Treatment Period, subjects will enter the Post Treatment Follow-Up Period and continue to be followed for 6 months after their last dose

of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every month. The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)
- Vitamin B12 and RBC folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH (at 2 month end of treatment follow-up visit)
- Serum for sotatercept (ACE-011) drug antibody test (pre-sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Bone imaging – DXA scan (at 3 month end of treatment follow-up visit)
- Activin A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood at 1 month end of treatment follow-up visit)
- Pharmacokinetics
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week or per standard of care at the study site, and following the chemotherapy schedule
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs

assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.

- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Study Discontinuation

Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects.

Subjects who discontinue from treatment early will enter the Post Treatment Follow-Up Period and be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Follow-up for twelve months for TTP and PFS will be performed from the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/Placebo. Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) – if Study Discontinuation date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Estrogen and estradiol – females only
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1) (PFS at 12 months)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire
- Reporting of adverse events (only AE/SAE assessed related to study treatment are to be reported)

- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Survival Follow-Up Period:

Monthly collection of survival data will begin following the Study Discontinuation Visit and continue for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Additional Procedure Descriptions:

Central ECG

Part 1 – ECGs will be performed and read per Central ECG vendor.

Part 2 – ECGs will be performed locally and read per Central ECG vendor.

Please refer to vendor manual for procedures.

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone) will be performed by a central laboratory.

Please refer to vendor manual for procedures.

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

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in the NSCLC population in a subset of subjects.

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin will be evaluated in all subjects.

Pharmacokinetics

- Part 1 - Full PK blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers

(approximately 10 subjects for each sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

- Part 2- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

Detailed PK sampling schedule is presented in Table 8 and Table 9: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

Bone Biomarkers

Bone biomarkers will be evaluated in all subjects. The serum and urine bone biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

Bone Imaging

DXA scan to evaluate overall bone health will be performed on approximately 200 subjects at select site(s).

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Independent External Radiology Review (Part 2 Only)

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC) (Part 2 Only)

The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each subject. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

7. STUDY POPULATION

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

7.1. Number of Subjects

This NSCLC platinum-based CIA study will enroll approximately 840 subjects in **Part 1** and **Part 2**.

In **Part 1**, up to 90 subjects will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC
- Sotatercept (ACE-011) 45.0 mg SC

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)

In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in Part 1, or placebo at a ratio of 1:1. Subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
4. ECOG Performance Status 0-1 vs. 2

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. Histologically confirmed (cytology or biopsy) non-small cell carcinoma of the lung.
3. Documented metastatic (Stage IV) disease, (including pleural or pericardial effusion involvement)
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L)
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function (creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin concomitantly administered)
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤5 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL), previous hypercalcemia treatment is allowed
6. Subjects may have received up to 3 cycles of their first regimen of first line platinum-based chemotherapy treatment for metastatic NSCLC. Allowed regimens are:
   - gemcitabine plus cisplatin or carboplatin ± bevacizumab
   - pemetrexed plus cisplatin or carboplatin ± bevacizumab
   - paclitaxel plus carboplatin ± bevacizumab
   - docetaxel plus cisplatin ± bevacizumab

   At randomization subjects are expected to be eligible to continue to receive at least two additional platinum-based chemotherapy cycles while on study. .
7. ≥ 28 days must have elapsed since previous treatment with ESA
8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 30 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)
10. If currently receiving bisphosphonate or denosumab (XGEVA™) therapy for bone metastases, must be on a stable dose for ≥ 2 months before Day 1 (ongoing bisphosphonate or denosumab therapy is allowed during study provided it is kept at a stable level). Bisphosphonate or denosumab therapy may not be started on study. Bisphosphonate therapy may be started on study for the treatment of hypercalcemia.

Subjects not currently on bisphosphonates or denosumab must not have received bisphosphonates or denosumab within 2 months prior to Day 1.

11. 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 at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).

12. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, even if he has undergone a successful vasectomy.
13. Life expectancy of ≥ 3 months.
14. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.
15. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C] at the time of screening, including Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g., asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non- hematological events (e.g., nausea, vomiting, fatigue, or muscle or bone/joint pain), occurring during the chemotherapy period and resolving.

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 subject participation in the study, at the discretion of the Investigator.
3. History of prior regimen(s) of platinum-based chemotherapy for metastatic NSCLC.
4. CNS metastases (exception: subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks prior to randomization).
5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying NSCLC.
6. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).
7. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.
8. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
9. 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).
10. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
11. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (SBP) must be < 150 mmHg or diastolic blood pressure (DBP) must be < 100 mmHg.
12. Known infection with human immunodeficiency virus (HIV).
13. Known active hepatitis B or C antibody defined by positive serology.
14. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.
15. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
16. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.
17. Urine protein / creatinine ratio > 1.0.
18. 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.
19. Any prior use of sotatercept (ACE-011).

20. Pregnant or lactating females or females planning to become pregnant.
21. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).
22. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

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

Note: Subjects receiving Process IIa clinical drug product will begin to receive Process III clinical drug product as soon as it becomes available at the study site.

Process IIa Clinical Drug Product – Frozen Liquid Formulation:

The clinical drug product consists of sotatercept (ACE-011) in phosphate buffered saline (PBS), pH 7.5. It is supplied as a 1 mL solution of 50 mg/mL sotatercept (ACE-011) in labeled, rubber stoppered, 2 mL vials providing 50 mg per vial. The recommended storage temperature for sotatercept (ACE-011) Process IIa frozen liquid drug product is ≤ -65˚C (colder than -65˚C) until thawed for administration. Vials of sotatercept (ACE-011) frozen liquid must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.

Process III Clinical Drug Product- Lyophilized Powder:

The clinical drug product consists of sotatercept (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 sotatercept (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 sotatercept (ACE-011). The reconstituted sotatercept (ACE-011), in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.

Placebo (Part 2 Only):

In **Part 2**, the sotatercept (ACE-011) placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Sterile, normal saline will be supplied by the investigational site's pharmacy. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

8.2. Treatment Administration and Schedule

Sotatercept (ACE-011) or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization all subjects must be receiving their first-line regimen of platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects will be randomized to this study during the time period in which they are receiving Cycle 1 to Cycle 3 of their first regimen of first-line platinum-based chemotherapy. Subjects must not have received any prior regimens of platinum-based chemotherapy for metastatic NSCLC.

Allowed concomitant platinum-based chemotherapy regimens are:

- gemcitabine plus cisplatin or carboplatin ± bevacizumab
- pemetrexed plus cisplatin or carboplatin ± bevacizumab
- paclitaxel plus carboplatin ± bevacizumab
- docetaxel plus cisplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Subjects may receive 4-6 cycles of the allowed platinum-based regimen selected by the Investigator. Up to 2 additional cycles (8 total cycles) of platinum-based chemotherapy may be given as determined by cancer response. The platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

While on treatment subjects will be allowed to receive maintenance therapy with a pemetrexed or erlotinib-containing regimen when indicated.

Subjects must be given sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to chemotherapy administration on the dose administration days.

In **Part 1** and **Part 2**, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb. Dose delays of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

In **Part 1**, subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC
- Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:
- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions

and/or ESAs. In order to determine the optimal dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) dose 1/day 1 through and including dose 2/day 43 (prior to dose 3).

- In addition to the hematopoietic response, safety profile, dose modifications and extent of exposure will be taken into account for dose level selection for Part 2.

Hematopoietic response will be determined by laboratory analysis.

In **Part 2**, subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo.

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo starting on Day 1 (one SC dose every 42 days) and continuing during the six-month (Part 1) or nine-month (Part 2) Treatment Period, as outlined in the Table of Events (see Section 5).

In **Part 1**, subjects will be randomized to receive one of three dose levels of sotatercept (ACE-011), with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive sotatercept (ACE-011) or placebo at a ratio of 1:1.

Each subject will return to the site on each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days of administration of a platinum-based chemotherapy cycle**. **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their NSCLC, whichever comes first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of NSCLC that requires the initiation of another treatment.

Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

8.2.3. Discontinuation

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100mm Hg) confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.
- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo Dose Modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL
  - In **Part 2:** > 3 dose reductions and/or delays
- Disease Progression of NSCLC
- Withdrawal of consent

- Death
- Lost to follow-up
- Protocol violation

The reason for treatment discontinuation should be recorded in the eCRF 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 (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- 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)
- Disease progression of NSCLC
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF 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.

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to 4 doses of sotatercept (ACE-011) in Part 1. In Part 2, subjects will be randomized at a ratio of 1:1 and receive up to 4 doses of study treatment and may receive 2 additional doses of sotatercept (ACE-011)/placebo, if clinically indicated, at the discretion of the Investigator. A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

8.4. Packaging and Labeling

The label(s) for investigational product (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 sotatercept (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 secured location. The investigational site must maintain accurate records demonstrating dates and amounts of sotatercept (ACE-011) received, to whom it was administered (subject-by-subject accounting), and accounts of any sotatercept (ACE-011) accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of sotatercept (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 sotatercept (ACE-011) to the Sponsor at the end of the study, or the sotatercept (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 investigational medicinal product.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF 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

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 and 7.3 Inclusion Criteria and 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 eCRF throughout the course of the study.

Concomitant therapies considered as supportive care are acceptable while participating in this study including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting and palliative radiation and bisphosphonates (Refer to Inclusion Criterion, Section 7.2) for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

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.

Iron supplementation

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

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study sponsor and Medical Monitor, as well as to the unblinded clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur. Subjects will not be unblinded.** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

In **Part 1**, all subjects who receive an ESA will be discontinued from the study treatment period and continue to the post treatment follow-up period. In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study treatment period and continue to the post treatment follow-up period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the treatment period. **The unblinded pharmacist will ensure that**

subjects randomized to receive treatment with sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo.

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered no sooner than 7 days from the date of the RBC transfusion.

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate therapy (see Section 7.2), other than for the treatment of hypercalcemia, must not be started on study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. In **Part 1**, subjects will be randomized to one of three doses of sotatercept (ACE-011) plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected sotatercept (ACE-011) dose determined from Part 1 plus platinum-based chemotherapy. Data from Part 1 will not be combined with data from Part 2 in all safety and efficacy analyses.

A DMC will be used to monitor the study conduct.

10.2. Study Population Definitions

- Three study populations will be used for analyses.
- The Intent-to-Treat (ITT) Population – All randomized subjects.
- Safety Population – All subjects who take at least one dose of study medication.
- Efficacy Evaluable (EE) Population – All ITT subjects who take at least one dose of study medication and have baseline and at least one post-baseline efficacy assessment without major protocol deviation.

10.3. Sample Size and Power Considerations

In **Part 1**, up to 90 subjects will be randomized among three dosing groups. This sample size is for the purpose of hypothesis generation. However, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a two-sided significance level (alpha) of 0.05.

In **Part 2**, subjects will be enrolled in two stages. In the first stage, approximately 180 subjects will be randomized in a 1:1 ratio to the selected sotatercept (ACE-011) dose group or placebo group. An interim analysis of transfusion rate will be performed after these 180 subjects have received at least two doses of sotatercept (ACE-011)/placebo, and have been followed for at least 4 months from randomization. A Data Monitoring Committee will review the results and provide recommendations on continuing or stopping the study. Based on the results of the futility analysis, further enrollment in the second stage of Part 2 of the study could be continued.

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in Part 2 (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept

[ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics by treatment arm, 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 by treatment arm. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

In **Part 1**, the primary endpoint will be the hematopoietic response defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the date of randomization. It will be estimated based on Kaplan-Meier method for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects who have documented RBC transfusion(s) from randomization until the last dose of concomitant platinum-based chemotherapy plus 30 days or from the initiation date of non-platinum-based chemotherapy, whichever is earlier, will be considered as having the event on the date of first RBC transfusion. Subjects who are discontinued from study treatment due to reasons other than disease progression or death will be considered as having the event on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Subjects who discontinue from study treatment due to disease progression or death will be censored on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Otherwise subjects will be censored on the date of last contact, or on the date of last dose of concomitant platinum-based chemotherapy plus 30 days or on the initiation date of non-platinum-based chemotherapy, whichever is earliest. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test, and the associated hazard ratio and 95% confidence interval will be provided using Cox proportional hazard model. The proportion of subjects receiving a transfusion based on Kaplan-Meier estimates at specific time points will also be provided by treatment arms.

As secondary endpoints for Part 2 of the study, time to progression, progression free survival and overall survival will be analyzed based on the ITT population.

Time to progression (TTP) is defined as the time between the randomization date and date of disease progression. **Disease progression is based on the IRC reviewed progression date.** If a subject dies due to reasons other than disease progression, the subject will be censored at the death date. If a subject does not have disease progression, then the subject will be censored at the last tumor assessment (prior to or on the first day of the first subsequent antitumor therapy).

Progression free survival (PFS) is defined as the time between the randomization and disease progression or death. **Disease progression is based on the IRC reviewed progression date.** Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the subject is censored at the time of last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. The date of progression is taken as the earliest date of: Date of PD as evaluation of response, date of new lesion on tumor measurements page, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who did not progress nor died (lost to follow-up or still being treated without documented disease progression or started subsequent antitumor therapy) will be censored at the date of the last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. PFS based on investigators' assessment will also be analyzed.

Overall survival (OS) is defined as the time between the randomization and death. A subject who dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the distribution function, six-month and one-year survival rates, as well as the medians and 95% confidence intervals will be provided. The stratified log rank test will be used to compare the distributions of TTP, PFS and OS respectively. The stratification factors are described in Section 4.1 . The associated hazard ratios and confidence intervals will be provided using stratified Cox proportional hazard model respectively for each endpoint.

Sensitivity analyses will be performed on TTP, PFS, and efficacy analyses will also be performed using EE population. Data listings will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.

10.7. Safety Analysis

All safety subjects will be used for safety analyses. Sotatercept (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 study part and treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized.

Safety information obtained during the Post Treatment Follow-Up Period during each segment will be incorporated into these analyses.

10.8. Interim Analysis

There are two interim analyses planned for this study. At the first interim analysis, the transfusion rate result will be used for go/no go decision, and overall survival will also be analyzed. At the second interim analysis, only the overall survival will be analyzed.

The first interim analysis on transfusion rate will be conducted after the first 180 eligible subjects randomized in Part 2 of the study (stage 1) who have received at least two doses of sotatercept (ACE-011)/placebo, have been followed for at least 4 months from randomization. This sample size would allow at least 90% power to detect a 15% difference between two arms (sotatercept [ACE-011] arm 15% vs. placebo 30%) in 4 month transfusion rates at two-sided 5% significance level based on the stratified log rank test and the assumption of exponential distribution for time to RBC transfusion. If the p-value at the interim analysis does exceed significance level of 0.05, the result will be considered as lack of efficacy. If the p-value is less than or equal to 0.05, additional subjects will be enrolled and the study will move on to the Part 2; however, the futility analysis result based on RBC transfusion rate may be up to DMC evaluation. For superiority, Type I error 0.0001 will be spent at this interim for transfusion rate, and the remaining 0.0499 will be spent at the final analysis after 750 subjects being enrolled.

Overall survival will also be analyzed at this interim, Type I error spending will be based on O'Brien and Fleming Boundary.

The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. Type I error spending will be based on O'Brien and Fleming boundary.

The final analysis will be performed when approximately 536 deaths are observed in Part 2.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of Part 1. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC_{42}, CL/F, Vz/F, and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

In exploratory population PK analysis, covariates to be tested may include type of chemotherapy, the presence of anti-sotatercept (ACE-011) antibodies, demographics (age, race, gender, and body weight), markers for hepatic and renal function, and other factors as deemed appropriate. Both full and sparse PK data will be included for population PK analyses.

The relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) will be explored.

10.10. Data Monitoring Committee (DMC)

A DMC will review safety and efficacy data to ensure the protection of study subjects. The DMC will receive periodic updates of all serious treatment-related toxicities and SAEs leading to deaths from all causes. The first planned review by the DMC will be conducted following the randomization and treatment of twenty subjects. The DMC will continue to monitor safety on an ongoing basis including recommendation of sotatercept (ACE-011) dose selection for Part 2. The first interim analysis will be conducted after the first 180 eligible subjects in Part 2 of the study (stage 1) have been followed for at least 4 months for RBC transfusion rate. The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. The final analysis will be performed when approximately 536 deaths are observed in Part 2.

Ad hoc meetings will be scheduled as needed.

The DMC will have a consultative role with respect to the Sponsor. The Sponsor will make the final decision regarding the recommendation proposed by the committee. A separate DMC charter will detail the activities of this committee.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately (i.e., 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. Seriousness

An 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of 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 (delay) 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 an SAE.

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

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

The female subject should be referred to an 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 investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Immediate 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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (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 sotatercept (ACE-011) based on the Investigator Brochure.

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

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

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (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

Please refer to Section 8.2.3.

Stopping Rules

In addition to Celgene routine pharmacovigilance surveillance, a DMC will review unblinded data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

In both Part 1 and Part 2 the blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.

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 eCRFs 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via an electronic data capture (EDC) system rather than paper. Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. The Clinical team and investigational site personnel will be alerted of discrepant data by the functionality of the system. 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMEA, 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 reulatory 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

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. Submitted 2008.

Chen Y-G, Lui HM, Lin S-L, Lee JM, and Ying S-Y. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. *Exp Biol Med* 2002; 227: 75-87.

Dang TP, Carbone DP: Cancer of the Lung, in DeVita, VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 8th edition, Philadelphia, PA. Lippincott Williams & Wilkens, 2008, 887-971.

Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F Version 4. *http://www.facit.org/qview/qlist.aspx*, last accessed 21Jul2010.

Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *Journal of the National Cancer Institute* 1999, 91, 1616-1634.

Hollen PJ, Gralla RJ, Kris MG 'Lung Cancer Symptom Scale (LCSS)', *Administration, Scoring and Procedures Manual*, (1995) Ver.1.1.

Hong WK, Tsao AS, in Lung Carcinoma: Tumors of the Lungs: Merck Manuals Online Medical Library for Healthcare Professionals, 2008.
http://www.merck.com/mmpe/print/sec05/ch062/ch062b.html

Lotinun S, Fajardo RJ, Pearsall RS, Bouxsein ML, and Baron R. A soluble activin receptor type IIA fusion protein, ACE-011, increases bone mass by stimulating bone formation and inhibiting bone resorption in cynomolgus monkeys. ASBMR 30th annual meeting, 2008.

Mathews LS. Activin receptors and cellular signaling by the receptor serine kinase family. *Endocr Rev* 1994; 15: 310-25.

Murata M, Onomichi K, Eto Y, Shibai H, and Muramatsu M. Expression of erythroid differentiation factor (EDF) in Chinese hamster ovary cells. *Biochem Biophys Res Commun* 1988; 151: 230-5.

Nakao K, Kosaka M and Saito S. Effects of erythroid differentiation factor (EDF) on proliferation and differentiation of human hematopoietic progenitors. *Exp Hematol* 1991; 19: 1090-5.

National Heart, Lung, and Blood Institute, National Institutes of Health. New York Heart Association Classification. 2008.

NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, V.2. 2010 http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf; 2009.

Non-small Cell Lung cancer Collaborative Group 'Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials', *British Medical Journal* 1995 vol. 311, no.7010, 899-909.

Oken, MM., Creech, R.H., Tormey, D.C., et. al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982; 5:649-655.

Parker SL, Tong T, Bolden S, et. al. Cancer statistics, 1997. *CA Cancer J Clin*, 1997, 47, no. 1, 5-27.

Pearsall RS, Canalis E, Cornwall-Brady M, Underwood KW, Haigis B, Ucran J, Kumar R, Pobre E, Grinberg A, Werner ED, Glatt V, Stadmeyer L, Smith D, Seehra J, and Bouxsein ML. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. Proc Natl Acad Sci USA 2008, 105: 7082-7.

Perrien DS, Akel NS, Edwards PK, et. al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology* 2007; 148: 1654-65.

Rivier J, Spiess J, McClintock R, Vaughan J and Vale W. Purification and partial characterization of inhibin from porcine follicular fluid. *Biochem Biophys Res Commun* 1985; 133: 120-7.

Rossi A, Maione P, Gridelli C Cetuximab in advanced non-small cell lung cancer. *Critical Reviews in Oncology/Hematology*, 2006 59, 139-149.

Ruckle J, Jacobs M, Kramer W, et. al. A single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res* 2009; 24 (4): 744-52.

Sandler A, Gray R, Perry M, et al Paclitaxel-Carboplatin alone or with Bevacizumab for Non Small Cell Lung Cancer, *NEJM*, 2006 vol.355, no.24, 2542-50.

Scagliotti G, Parikh P, von Pawel J, et al Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve patients With Advanced-Stage Non-Small-Cell Lung Cancer, JCO, 2008, 26 (21): 3543-51.

Schiller J, Harrington D, Belani C, et al Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Seder C, Hartojo W, Lin L, et al Upregulated INHBA Expression May Promote Cell Proliferation and Is Associated with Poor Survival in Lung Adenocarcinoma, Neoplasia, 2009, 11: 388-396.

Shedden K, Taylor J, Enkemann S, et al Gene Expression-Based Survival prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validation Study: Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Nat Med, 2008, 14 (8): 822-827.

Shiozaki M, Sakai R, Tabuchi M, et. al. Evidence for the participation of endogenous activin A/erythroid differentiation factor in the regulation of erythropoiesis. *Proc Natl Acad Sci USA* 1992; 89: 1553-6.

Shiozaki M, Sakai R, Tabuchi M, et. al. In vivo treatment with erythroid differentiation factor (EDF/activin A) increases erythroid precursors (CFU-E and BFU-E) in mice. *Biochem Biophys Res Commun* 1989; 165: 1155-61.

Vansteenkiste J, Pirker R, Massuti B, et. al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute, 2002, 94: 16: 1211-1220.

Woodruff TK. Regulation of cellular and system function by activin. *Biochem Pharmacol* 1998; 55: 953-63.

Ying S-Y. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine Rev* 1988; 9: 267-93.

19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Terms	**Definition**
Measurable disease	The presence of at least one measurable lesion by CT or MRI. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions	Lesions that can be accurately measured in least one dimension by CT scan with longest diameter $\geq$ 10 mm (CT scan thickness no greater than 5 mm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Non-measurable lesion	All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

RECIST Criteria-Response Evaluation

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
***Partial Response (PR)*:**	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
***Stable Disease (SD)*:**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
***Progressive Disease (PD)*:**	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

RECIST Criteria-Response Evaluation (continued)

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of best overall response	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (2009). European Journal of Cancer 45, 228-247.

Appendix B: 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 10: 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 C: 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 D: New York Heart Association - Classification of Heart Failure

Table 11: 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

– SUMMARY OF CHANGES –

AMENDMENT NO. 2

A RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH SELECTED METASTATIC SOLID TUMOR TYPES TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
ORIGINAL DATE:	22 MARCH 2011
AMENDMENT No. 2 DATE:	27 JUNE 2011
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

Contact Information:	
PPD	

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

28 June 2011

Signature of Celgene Therapeutic Area Head **dd mmm yyyy**

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below. These changes were based on feedback obtained from investigators/sites, key opinion leaders and internal discussions:

In Part 1-

1. Modified to expand eligible tumor types to include the following metastatic solid tumor types where the standard of care is platinum-based chemotherapy-
    - metastatic non-small cell lung cancer (NSCLC)
    - metastatic small cell lung cancer
    - metastatic bladder cancer
    - metastatic head and neck cancer
    - metastatic endometrial/cervical cancer
2. Modified to remove single-blind and add open-label of ACE-011 (sotatercept) dose levels.
3. Modified to allow for sparse PK in a subset of subjects not participating in the full PK analysis.
4. Modified to remove archival tumor tissue analysis.
5. Modified to allow any platinum-based regimen approved for the specific metastatic solid tumor type.

In Part 1 and Part 2

6. Modified to add Medical Monitor mobile phone number.
7. Revised screening period for tumor assessment from 6 weeks to 'as per standard of care at the study site '.
8. Clarification of data collection history of prior use of erythropoietic stimulating agents and red blood cell transfusion.
9. Removal of trailing zero's from sotatercept (ACE-011) doses (i.e., 15.0 mg replaced with 15 mg, etc.).
10. Further clarification of criteria to be met to determine addition of sotatercept (ACE-011) 45 mg dose level in Part 1 - the analysis of safety data following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completion of a 12 week follow-up period from the first dose and the subsequent decision to add a third dose level of 45 mg to the randomization schema.
11. Modified to include that concentration of sotatercept (ACE-011) may be determined in anti-drug (sotatercept) antibody samples.
12. Modified to describe PK parameters to be measured.

13. Discontinuation of study treatment- Clarification of definition of lack of sotatercept (ACE-011) therapeutic effect in Part 1 and Part 2 of the study and timeframe in which assessment should be performed.
14. Clarification of QoL Assessments to specify that all subjects will complete the FACIT Fatigue Scale [Version 4] and only subjects with NSCLC will complete the LCSS.
15. Modified to allow first dose of ACE-011 to be administered at any time during chemotherapy cycle versus +/- seven days.
16. Modified to allow bisphosphonate and denosumab therapy.
17. Objectives -

    Revised to include specific metastatic solid tumor types in Part 1 and only metastatic NSCLC in Part 2 of the study.
18. Additional clarification to describe the primary objective of transfusion rate following initiation of sotatercept (ACE-011)/placebo in Part 2.
19. Introduction- Revised to include:
    a. Additional selected solid metastatic tumors in Part 1.
    b. Detailed description of Part 2.
    c. Additional detail in Chemotherapy Induced Anemia, Treatment of Chemotherapy Induced Anemia and Sotatercept (ACE-011) Chemotherapy Induced Anemia Sections
20. Revision of Sotatercept (ACE-011) and Pharmacology sections to add and clarify preclinical data.
21. Potential Risks for Human Use-
    a. Clarification that liver enzymes will be monitored in this study
    b. Correction of typographical error- *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/kg*** *SC were generally well-tolerated in healthy postmenopausal women.*
22. Endpoints
    a. Clarification that hematopoietic response will be assessed by laboratory analysis of hemoglobin.
    b. Revised to include additional Lung Cancer Symptom Scale references.
    c. Clarification that archival tumor tissue analysis will occur only in Part 2 of the study.
23. Study Design- Clarification of treatment period timeframe for up to 4 doses of sotatercept (ACE-011) in Part 1 and up to 6 doses of sotatercept (ACE-011)/placebo in Part 2 of the study.
24. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules-

Confirmed sotatercept (ACE-011) dose 'delay' as > 4 days and correction of typographical error: *A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose administered **> 4 days** from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension **> SBP 150 mmHg and > DBP 100 mmHg** and/or sotatercept (ACE-011) related toxicity.*

25. Clarification of study design rationale describing clinical and nonclinical experience.
26. Revision of Schedule of Assessments
    a. Revised screening period for tumor assessment from 6 weeks to 'as per standard of care at the study site '.
    b. Modified collection of 'NSCLC history' to 'cancer history'.
    c. Clarification that Activin A and other proteins/biomarkers will be assessed in serum.
    d. Modified archival tumor tissue collection to optional.
    e. Clarification that dual energy X-ray Absorptiometry (DXA) scan includes lumbar spine and hip.
    f. Modified for sparse PK blood collection in a subset of subjects not participating in full PK in Part 1.
    g. Modified to allow first dose of ACE-011 to be administered at any time during a chemotherapy cycle versus +/- seven days.
    h. Clarification of QoL Assessments to specify that all subjects will complete the FACIT Fatigue Scale [Version 4] and only subjects with NSCLC will complete the LCSS.
27. Revision of Inclusion Criteria:
    a. Revised to include selected metastatic solid tumor types treated with platinum-based chemotherapy in Part 1.
    b. Modified to allow up to 4 prior cycles of first line platinum-based chemotherapy at randomization.
    c. Part 1- Modified to allow any platinum-based regimen approved for the specific metastatic solid tumor type.
    d. Part 2- Modified to include the following allowed regimens for the treatment of NSCLC:
        i. gemcitabine plus cisplatin or carboplatin ± bevacizumab
        ii. pemetrexed plus cisplatin or carboplatin ± bevacizumab
        iii. taxanes plus cisplatin or carboplatin ± bevacizumab
    e. Modified to allow prior and concurrent bisphosphonate or denosumab (XGEVA™) therapy for bone metastases.
28. Revision of Exclusion Criteria:

a. Revised to include selected metastatic solid tumor types treated with platinum-based chemotherapy in Part 1.

b. Revised to clarify acceptable history of prior platinum-based chemotherapy.

29. Clarification that subjects may receive maintenance therapy while on study treatment.

30. Modified to clarify role of unblinded pharmacist based on removal of single-blind in Part 1 of the study.

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

2. ITEMIZED CHANGES

2.1. Title Page (page 1)

Original Text:

A SINGLE-BLIND, RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) THERAPY FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

Revised Text:

~~A SINGLE-BLIND,~~AN OPEN-LABEL, RANDOMIZED, PHASE 2A, DOSE- RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) ~~THERAPY~~FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH SELECTED METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

Rationale:

Modified to expand study population in Part 1 of the study to include selected metastatic solid tumor types treated with first-line platinum-based chemotherapy.

2.2. Section: MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION, (page 2)

Original Text:

Contact Information:	
PPD	

Revised Text:

Contact Information:	
PPD	

Rationale:

Revised to add Celgene medical monitor's mobile telephone number.

2.3. Section: Protocol Summary (pages 6-12)

Original Text:

Protocol Summary

Study Title

A single-blind, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Metastatic Non-Small Cell Lung Cancer (NSCLC).

Objectives

The primary objectives are:

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011)/placebo treatment.

The secondary objectives are:

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in metastatic NSCLC subjects with CIA.
- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment in metastatic NSCLC subjects with CIA.
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects with metastatic NSCLC receiving platinum-based chemotherapy.

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- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

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The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.

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- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue.

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Study Design

This is a single-blind, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for CIA subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Part 2 is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages.

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Study Population

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles and must be randomized prior to receiving Cycle 4 of this current first-line platinum-based regimen to be eligible for the study. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

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Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days of randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks prior to randomization.

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Prior erythropoietic stimulating agent (ESA) treatment history starting from initial diagnosis of NSCLC and red blood cell (RBC) transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up to two months prior to randomization will be collected.

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Treatment Period (up to 6-9 months):

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In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

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Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the optimal dose for Part 2.

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In **Part 2**, a total of 750 subjects will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:

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In **Part 1**, full PK blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

In **Part 2**, the sparse PK assessment will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

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Subjects will be discontinued from Study Treatment due to the following:

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- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

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- Disease progression of NSCLC

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Post Treatment Follow-Up Period (monthly visits for up to 6 months)

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

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- Disease progression of NSCLC

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Overview of Safety Assessments

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- QoL Assessment (FACIT Fatigue Scale [Version 4]) and Lung Cancer Symptom Scale (LCSS) questionnaire.

Revised Text:

Study Title

An open-label, ~~single-blind,~~ randomized, phase 2a, dose- ranging study (**Part 1**) of sotatercept (ACE-~~–~~011) ~~therapy~~for chemotherapy-induced anemia in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Metastatic ~~Non-Small Cell Lung Cancer~~ Solid Tumors

Part 1 – Solid tumors, including metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy. No solid tumors other than those tumor types listed above should be considered for this study.

Part 2 - Metastatic NSCLC.

Objectives

The primary objectives are:

- **Part 1**: To determine ~~an effective~~a dose of sotatercept (ACE-011) ~~showing~~ that results in a hematopoietic response ~~in~~ for the treatment of CIA in ~~metastatic NSCLC~~ subjects~~.~~ with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens.

- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011~~)/placebo treatment~~) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

The secondary objectives are:

- **Part 1 and Part 2:**
  - To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS~~) in metastatic NSCLC subjects with CIA.~~).
  - To evaluate the safety and tolerability of sotatercept (ACE-011~~) treatment in metastatic NSCLC subjects with CIA.~~).
  - To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects~~ with metastatic NSCLC~~ receiving platinum-based chemotherapy.

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  - To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL~~) of NSCLC subjects with CIA.~~).

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The exploratory objectives are:

- **Part 1 and Part 2:**
  - To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism ~~in NSCLC subjects with CIA.~~

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  - To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (Part 2 only).

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Study Design

This is an open-label, ~~single blind,~~ randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine a~~n effective~~ dose of sotatercept (ACE-011) that results in~~showing~~ a hematopoietic response in the treatment of CIA in subjects with metastatic ~~NSCLC subjects.~~solid tumors treated with

platinum-based chemotherapy. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Part 2 is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

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Study Population

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-~~containing~~ based chemotherapy , given every three weeks, for the treatment of one of the selected metastatic ~~NSCLC.~~ solid tumor types which include: metastatic non-small cell lung cancer (NSCLC~~)~~, metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer , and metastatic endometrial/cervical cancer. Subjects may have already received up to ~~3~~4 cycles of this current platinum-based regimen and must be randomized prior to receiving Cycle ~~4 of this current first-line platinum-based regimen to be eligible for the study.~~5.. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other platinum containing regimens of chemotherapy for the first-line ~~platinum containing~~ treatment of a metastatic ~~NSCLC~~solid tumor prior to the regimen they are receiving at the time of randomization.

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Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to ~~of~~ randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks or as per standard care at the study site prior to randomization.

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Prior erythropoietic stimulating agent (ESA) treatment history starting from initial diagnosis of ~~NSCLC~~selected solid tumor types and red blood cell (RBC) transfusion history starting from diagnosis of metastatic ~~NSCLC~~disease, at a minimum of up to two months prior to randomization will be collected.

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Treatment Period (up to 6-9 months):

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In **Part 1** (the dose-ranging portion of the study), subjects with selected metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15~~.0~~ mg SC
- Sotatercept (ACE-011) 30~~.0~~ mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15~~.0~~ mg dose level and 10 subjects at the 30~~.0~~ mg dose level, with each subject having received ~~at least~~a minimum of one dose of sotatercept (ACE-011~~), plus~~) and completed a 12-week follow-up period from the first dose. ~~Following this analysis, the addition of a third dose level:~~

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45~~.0~~ mg SC

to the randomization schema will be determined.

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Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the ~~optimal~~sotatercept (ACE-011) dose for Part 2.

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In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:

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In **Part 1**, ~~full PK~~ blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment ~~will~~may participate in the sparse PK assessment. In **Part 2**, blood samples will be collected for the sparse PK assessment that will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either Part 1 full or sparse PK assessments or Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

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Subjects will be discontinued from Study Treatment due to the following:

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- ~~Lack~~In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb

from baseline following two doses of sotatercept (ACE-011~~) or sotatercept (ACE-011~~)/placebo~~.~~ (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).

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- Disease progression ~~of NSCLC~~

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Post Treatment Follow-Up Period (monthly visits for up to 6 months)

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

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- Disease progression ~~of NSCLC~~

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Overview of Safety Assessments

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- QoL Assessment (FACIT Fatigue Scale [Version 4]) ~~and~~ – all subjects
- Lung Cancer Symptom Scale (LCSS) questionnaire~~.~~ – subjects with NSCLC

Rationale:

Modified to:

- Include subjects with selected metastatic solid tumor types in Part 1 and specify metastatic NSCLC subjects in Part 2 of the study
- Provide clarification of primary objective of Part 2 of the study
- Modified to increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 and allow subjects with selected metastatic solid tumor types in Part 1 of the study
- Expand acceptable time period for screening tumor assessment to align with standard of care per site
- Clarification of criteria for analysis of safety data from the 15 and 30 mg sotatercept (ACE-011) dose levels to determine the addition of the 45 mg sotatercept (ACE-011) dose level
- Delete term ‘optimal’ to describe sotatercept dose determined in Part 1 to be administered in Part 2
- Clarify that sparse PK in Part 1 is optional
- Include that concentration of sotatercept (ACE-011) may be determined in anti-drug (sotatercept) antibody samples.

- Clarify assessment of sotatercept (ACE-011) therapeutic effect in Part 1 and Part 2 of the study and provide the timeframe in which assessment should be performed
- Clarify FACIT Fatigue Scale to be performed on all subjects
- Clarify LCSS questionnaire to be performed only on subjects with NSCLC

2.4. Section 1: Introduction (pages 18-33)

Original Text:

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to define the recommended sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 2 will be performed in two stages. In the first stage approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

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Treatment of Chemotherapy-Induced Anemia

Chemotherapy-induced anemia is an area of unmet medical need. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these patients, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002).

The current treatment options for CIA include blood transfusion and ESAs. However, the blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients in chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. In the pivotal Aranesp study for CIA in NSCLC, 27 % of patients were transfused with Packed Red Blood Cells (PRBC's) at 4 months vs. 52% in the placebo arm. In a subsequent recent Phase III study of pemetrexed (Alimta®) plus cisplatin vs. gemcitabine plus cisplatin where all first-line NSCLC patients with anemia or not

were enrolled, 16.1% vs 27.3% of patients respectively were transfused with PRBC's during that study (Scagliotti, 2008).

Chemotherapy-induced anemia is a significant problem for patients with cancer, causing fatigue and reducing quality-of-life (QoL). Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two Phase 1 studies in healthy volunteers, as well as in a Phase 2a study for multiple myeloma (MM). The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

Activin Biology

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

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Sotatercept (ACE-011)

(text not previously present)

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Pharmacology Studies

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

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The effect of this activin antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in 5T2MM murine myeloma cells isolated from the bone marrow of disease bearing animals.

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In addition, the RAP-011 was highly effective in restoring bone mineral density (BMD) when administered therapeutically in a murine model of postmenopausal osteoporosis. RAP-011 has also been shown to increase trabecular bone density in normal mice.

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In addition, in the MCF-7 model, a 60% reduction in tumor weight was observed in the RAP-011 treated mice.

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Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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Potential Risks for Human Use

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The most significant toxicity findings are listed below:

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- 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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, these endpoints will continue to be monitored in the clinic.

Revised Text:

This is an open-label, ~~single-blind,~~ randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects with selected metastatic solid tumor types treated with platinum-based chemotherapy will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to determine the ~~recommended~~ sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

~~**Part 2** will be performed in two stages.~~ **Part 2** will include only subjects with metastatic NSCLC and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility

assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period. Based on the results of the futility analysis and upon recommendation to continue the study, ~~with~~ up to an additional 570 subjects will be randomized in the second stage of **Part 2**, to achieve full study accrual.

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Chemotherapy-Induced Anemia

Chemotherapy-induced anemia (CIA) is an area of unmet medical need. It is a significant problem for patients with cancer, causing fatigue and reducing quality-of-life (QoL).

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002). The incidence and severity of chemotherapy-induced anemia (CIA) is further dependent on a variety of factors, such as the type, schedule, and intensity of chemotherapy administered, and whether the patient has received prior myelosuppressive chemotherapy and/or radiation therapy (Groopman, 1999). Platinum-based treatments (eg, cisplatin and carboplatin), commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity. Antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan) are also considered particularly myelosuppressive (Groopman, 1999). Dose intensity, the increasingly widespread practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression

The association between uncorrected anemia before or during chemotherapy and poorer patients' outcomes has been reported in several studies (Grogan, 1999; Laurie, 2006; MacRae, 2002; Obermair, 2003). Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and may also have an adverse impact on co-morbid conditions, such as cardiac and pulmonary disease. The most common patient complaints are dyspnea on exertion and chronic fatigue, which may interfere with a patient's ability to perform normal daily activities (Groopman, 1999). A key differentiating characteristic of cancer-related fatigue versus fatigue in healthy individuals is its likelihood of persistence at rest (National Comprehensive Cancer Network, 2008) In various published surveys, fatigue has been represented as a symptom that has affected patients' everyday life the most and has been linked to changes in employment status among patients and even caregivers (Schwartz, 2007). The association between Hgb levels and fatigue is well documented, with one analysis of 5 randomized trials linking an increase in Hgb concentrations of at least 2 g/dL with an improvement in fatigue, and consequently, in energy, ability to perform usual activities, and overall health (Cella, 2004).

In looking at the impact of CIA on survival, a meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer and anemia compared with patients without anemia (Carlos, 2001). The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that also is supported by other retrospective studies. Tumor hypoxia, resulting from the reduced oxygen-

carrying capacity of blood in patients with anemia, has been hypothesized to be a major contributor to reduced survival. Several studies have shown that tumor hypoxia also reduces the effectiveness of radiotherapy and chemotherapy, and is associated with tumor progression (Aapro, 2006).

Treatment of Chemotherapy-Induced Anemia

The current treatment options for CIA include blood transfusion and erythropoiesis-stimulating agents (ESAs). However, blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients receiving chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. However, the past five years has seen a major change in the use of ESAs for cancer related and chemotherapy induced anemia. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. Retrospective statistical analysis in one study in head and neck cancer patients, and two studies with adjuvant breast cancer revealed substantial safety concerns of increased thromboembolic events, and decreased PFS and overall survival.

Sotatercept (ACE-011) Treatment of Chemotherapy-Induced Anemia

Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two phase 1 studies in healthy volunteers, as well as in a phase 2a study in multiple myeloma (MM) subjects. The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

In a phase 1 single-dose and multiple-dose studies of sotatercept in postmenopausal women (Studies A011-01 and A011-02, respectively), and in a phase 2 study in subjects with osteolytic lesions associated with MM that examined concurrent administration of sotatercept with melphalan, prednisolone, and thalidomide (MPT) anti-myeloma therapy, increases in Hgb, RBC count and HCT were observed following sotatercept treatment, and these increases remained detectable throughout the course of study. The observed Hgb, RBC count, and HCT effects of sotatercept were dose-dependent and time-dependent. These phase 1 and phase 2 clinical data are consistent with the increased hematologic parameters observed in nonclinical studies, The results from the three completed clinical studies A011-01, A011-02, and A011-04 are summarized in **Summary of Clinical Experience**.

The mechanism of action of sotatercept with regards to increased RBC counts is not known; however, the mechanism of action for the hematopoietic effect of sotatercept may be different than that of ESAs, as some level of erythrocyte stimulatory effect was observed in the presence

of anti-EPO antibodies in one nonclinical study. As such, sotatercept may provide a unique clinical profile with a favorable benefit-risk profile in the chemotherapy-induced anemia patient population, thereby addressing some of the unmet medical needs in chemotherapy-induced anemia treatment.

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~~**Treatment of Chemotherapy-Induced Anemia**~~

~~Chemotherapy-induced anemia is an area of unmet medical need. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these patients, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.~~

~~Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002).~~

~~The current treatment options for CIA include blood transfusion and ESAs. However, the blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients in chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.~~

~~Erythropoiesis-stimulating agents have been approved for treating CIA. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.~~ In the pivotal Aranesp (darbepoetin alfa) study for CIA in NSCLC, 27 % of patients were transfused with ~~Packed Red Blood Cells~~packed red blood cells (PRBC's) at 4 months ~~vs.~~versus 52% in the placebo arm. ~~In a subsequent recent Phase III study of pemetrexed (Alimta®) plus cisplatin vs. gemcitabine plus cisplatin where all first-line NSCLC patients with anemia or not were enrolled, 16.1% vs 27.3% of patients respectively were transfused with PRBC's during that study (Scagliotti, 2008).~~

~~Chemotherapy-induced anemia is a significant problem for patients with cancer, causing fatigue and reducing quality-of-life (QoL). Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two Phase 1 studies in healthy volunteers, as well as in a Phase 2a study for multiple myeloma (MM). The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.~~

Activin Biology

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

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Sotatercept (ACE-011)

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Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

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Pharmacology Studies

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

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~~The effect of this activin antagonist on the inhibition of bone formation and osteoblast function in myeloma bone disease was investigated in 5T2MM murine myeloma cells isolated from the bone marrow of disease bearing animals.~~.

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~~In addition, the RAP-011 was highly effective in restoring bone mineral density (BMD) when administered therapeutically in a murine model of postmenopausal osteoporosis. RAP-011 has also been shown to increase trabecular bone density in normal mice.~~

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~~In addition, in the MCF-7 model, a 60% reduction in tumor weight was observed in the RAP-011 treated mice.~~

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Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	0.1 mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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Potential Risks for Human Use

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The most significant toxicity findings are listed below:

- 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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, ~~these endpoints~~ liver enzymes will continue to be monitored in ~~the clinic.~~this study.

Rationale:

Modified to:

- Include subjects with specific metastatic solid tumor types in Part 1 and clarify the two stages in Part 2 of the study.
- Revise and add Chemotherapy-Induced Anemia, Treatment of Chemotherapy-Induced Anemia and Sotatercept (ACE-011) Treatment of Chemotherapy-Induced Anemia sections to provide additional solid tumor type and chemotherapy-induced anemia background data.
- Provide additional description of Sotatercept (ACE-011) and Activin Biology.
- Clarify results of pharmacology studies.
- Include missing dose level in Table 4.
- Clarify the continued monitoring of liver enzymes.

2.5. Section 2.1: Primary Objective (page 34)

Original Text:

- **Part 1**: To determine an effective dose of sotatercept (ACE-011) showing a hematopoietic response in the treatment of CIA in metastatic NSCLC subjects.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment.

Revised Text:

- **Part 1**: To determine ~~an effective~~a dose of sotatercept (ACE-011) ~~showing~~ that results in a hematopoietic response ~~in~~ for the treatment of CIA in ~~metastatic NSCLC~~ subjects~~.~~ with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment~~.~~ versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

Rationale:

Modified to include subjects with selected metastatic solid tumor types in Part 1 and specify metastatic NSCLC subjects in Part 2 of the study.

2.6. Section 2.2: Secondary Objectives (page 34)

Original Text:

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) in metastatic NSCLC subjects with CIA.
- To evaluate the safety and tolerability of sotatercept (ACE-011) treatment in metastatic NSCLC subjects with CIA.
- To determine the PK of sotatercept (ACE-011) in subjects with metastatic NSCLC receiving platinum-based chemotherapy.

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- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL) of NSCLC subjects with CIA.

Revised Text:

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS~~) in metastatic NSCLC subjects with CIA.~~
- To evaluate the safety and tolerability of sotatercept (ACE-011~~) treatment in metastatic NSCLC subjects with CIA.~~
- To determine the PK of sotatercept (ACE-011) in subjects ~~with metastatic NSCLC~~ receiving platinum-based chemotherapy.

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- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL~~) of NSCLC subjects with CIA.~~

Rationale:

Modified to not specify subjects with metastatic NSCLC only.

2.7. Section 2.3: Exploratory Objectives (page 34)

Original Text:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism in NSCLC subjects with CIA.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue.

Revised Text:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism ~~in NSCLC subjects with CIA.~~
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (Part 2 only).

Rationale:

Modified to:

Remove subjects with metastatic NSCLC only.

Clarify that archival tumor tissue analysis will occur only in Part 2 of the study.

2.8. Section 3.1: Primary Endpoint(s) (page 35)

Original Text:

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- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the optimal dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).

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Hematopoietic response will be determined by laboratory analysis.

Revised Text:

– – – – – – – – – –

- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the ~~optimal~~ dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).

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Hematopoietic response will be determined by laboratory analysis~~.~~ of hemoglobin levels.

Rationale:

Modified to:

Delete term ‘optimal’ to describe sotatercept dose determined in Part 1 to be administered in Part 2.

Clarify how hematopoietic response will be determined.

2.9. Section 3.2: Secondary Endpoint(s) (page 35)

Original Text:

- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1995)

Revised Text:

- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1993 ; Hollen, 1994a ; Hollen, 1994b; Hollen, 1995)

Rationale:

Modified to include additional Lung Cancer Symptom Scale references.

2.10. Section 3.3: Exploratory Endpoint(s) (page 36)

Original Text:

- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in the NSCLC population.

Revised Text:

- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue ~~in the NSCLC population~~(Part 2 only).

Rationale:

Modified to provide clarification that archival tumor tissue analysis will occur only in Part 2 of the study.

2.11. Section 4.1: Study Design (pages 37-39)

Original Text:

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to define the recommended sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

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Part 1 is planned to be conducted at selected US sites. The study will be extended to additional global sites for the conduct of Part 2.

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Three starting sotatercept (ACE-011) dose levels, 15.0, 30.0, and 45.0 mg, were selected for Part 1 of the study. Up to approximately 90 subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for four doses.

In **Part 2**, a total of 750 subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo, at a ratio of 1:1:

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The Treatment Period for Part 1 is up to approximately six months and for Part 2 up to nine months. Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first.

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At the time of randomization all subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects may have already received up to 3 cycles of this first-line platinum-based regimen to be eligible for the study. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment prior to initiating any maintenance chemotherapy for the treatment of metastatic NSCLC.

Revised Text:

This is an open-label, ~~single-blind,~~ randomized, phase 2a, dose-ranging study (Part 1) of sotatercept (ACE-011) therapy in subjects with selected metastatic solid tumor~~s~~ types treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects with selected metastatic solid tumor types will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to determine the ~~recommended~~ sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study~~.~~ in subjects with metastatic NSCLC.

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Part 1 is planned to be conducted at selected ~~US~~ sites and~~. The study~~ will be extended to additional global sites for the conduct of **Part 2.**

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Three starting sotatercept (ACE-011) dose levels, 15~~.0~~, 30~~.0~~, and 45~~.0~~ mg, were selected for Part 1 of the study. Up to approximately 90 subjects with selected metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15~~.0~~ mg SC
- Sotatercept (ACE-011) 30~~.0~~ mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15~~.0~~ mg dose level and 10 subjects at the 30~~.0~~ mg dose level, with each subject having received ~~at least~~a minimum of one dose of sotatercept (ACE-011~~), plus~~) and completed a 12-week follow-up period from the first dose. ~~Following this analysis, the addition of a third dose level:~~

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45~~.0~~ mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for a total of four doses.

In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo, at a ratio of 1:1:

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The Treatment Period for Part 1 is ~~up to~~ approximately six months, which includes up to 4 doses of sotatercept (ACE-011) and for Part 2 ~~up to~~ approximately nine months~~.~~, which includes up to 6 doses of sotatercept (ACE-011/placebo). Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their ~~NSCLC~~metastatic disease, whichever comes first.

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At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-~~containing~~ based chemotherapy, given every three weeks, for the treatment of a metastatic ~~NSCLC~~.solid tumor. Subjects may have already received up to ~~3~~4 cycles of this ~~first-~~

~~line~~current platinum-based regimen ~~to~~and must be ~~eligible for the study. Subjects are~~ randomized prior to receiving Cycle 5. It is expected ~~to~~ that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment ~~prior to initiating any maintenance~~.

Subjects must not have received any other platinum containing regimens of chemotherapy for the first-line treatment of a metastatic ~~NSCLC.~~solid tumor prior to the regimen they are receiving at the time of randomization.

Rationale:

Modified to:

- Include subjects with selected metastatic solid tumor types in Part 1 of the study
- Delete participation of US sites only in Part 1 of the study.
- Clarify the criteria for analysis of safety data from the 15 and 30 mg sotatercept (ACE-011) dose levels to determine the addition of the 45 mg sotatercept (ACE-011) dose level.
- Increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 and allow subjects with metastatic tumors in Part 1 of the study.

2.12. Section 4.1.1: Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules (pages 40-43)

Original Text:

[3]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg.. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose not administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension < SBP 150mm Hg and < DBP 100 mm Hg and/or sotatercept (ACE-011) related toxicity).

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Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels

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Dose Schedule Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days- 45.0 mg	38.0 mg	33.0 mg	28.0 mg
Every 42 days- 30.0 mg	26.0 mg	22.0 mg	18.0 mg
Every 42 days- 15.0 mg	13.0 mg	11.0 mg	9.0 mg

*Note: Any Hgb increase of ≥3.0 g/dL will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

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Dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. In Part 2, subjects in the placebo group who are designated by their treating physician to undergo dose reduction will continue to receive placebo.

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Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only)

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45.0 mg	50.0 mg	55.0 mg	61.0 mg
Every 42 days-30.0 mg	33.0 mg	36.0 mg	40.0 mg
Every 42 days-15.0 mg	17.0 mg	20.0 mg	23.0 mg

Dose increase steps and the subsequent administration of the increased dose(s) of sotatercept (ACE-011) will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject.

Revised Text:

[3]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg~~.~~. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose ~~not~~ administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension ~~<~~> SBP 150 mmHg and ~~<~~> DBP 100 mmHg and/or sotatercept (ACE-011) related toxicity).

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Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels

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Dose Schedule Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days-45~~.0~~ mg	38~~.0~~ mg	33~~.0~~ mg	28~~.0~~ mg
Every 42 days-30~~.0~~ mg	26~~.0~~ mg	~~22.0 mg~~22mg	18~~.0~~ mg
Every 42 days-15~~.0~~ mg	13~~.0~~ mg	11~~.0~~ mg	9~~.0~~ mg

*Note: Any Hgb increase of ≥3.0 g/dL sustained for a 28 day period since last doing day will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

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~~Dose~~In **Part 2**, dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011~~) or sotatercept (ACE-011~~)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. ~~In Part 2,~~S subjects in the placebo group who are designated ~~by their treating physician~~ to undergo dose reduction will continue to receive placebo.

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Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only)

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45~~.0~~ mg	50~~.0~~ mg	55~~.0~~ mg	61~~.0~~ mg
Every 42 days-30~~.0~~ mg	33~~.0~~ mg	36~~.0~~ mg	40~~.0~~ mg
Every 42 days-15~~.0~~ mg	17~~.0~~ mg	20~~.0~~ mg	23~~.0~~ mg

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~~Dose increase steps and the subsequent administration of the increased dose(s) of sotatercept (ACE-011) will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject.~~

Rationale:

Modified to:

- Correct typographical error – blood pressure measurements.
- Remove sotatercept (ACE-011) trailing zeros.
- Remove references to single-blind in Part 1.

2.13. Section 4.2: Study Design Rationale (page 43)

Original Text:

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a significant 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 sotatercept (ACE-011), suggests an entirely novel mechanism of RBC production.

Revised Text:

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a ~~significant increase~~rapid, sustained and dose-dependent increases in hematopoietic parameters, ~~beginning rapidly and sooner~~(Hgb, HCT and RBC counts) which occurred earlier than would be expected from a stimulation of ~~the erythropoietic effect~~ erythropoiesis by an ESA. This ~~fact, as well as the fairly rapid and persistent elevation~~ observation, couple with nonclinical data demonstrating some level of erythrocyte stimulatory effect in the ~~relative Hgb, HCT, and RBC counts of the majority~~presence of ~~subjects from each dose~~anti-erthyropoietin (EPO) antibodies, suggests that the hematopoieitc effect of sotatercept ~~(ACE-011), suggests an entirely novel mechanism~~is different from that of ~~RBC production.~~ ESAs.

Rationale:

Revised to clarify prior clinical and non-clinical findings in support of study design rationale.

2.14. Section 4.3: Study Duration (page 46)

Original Text:

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects in Part 1 and 750 subjects in Part 2 will be randomized prior to receiving the fourth cycle of platinum-based chemotherapy for metastatic NSCLC. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Revised Text:

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects with selected metastatic solid tumor types in Part 1 and 750 subjects with metastatic NSCLC in Part 2 will be randomized prior to receiving the ~~four~~fifth cycle of platinum-based chemotherapy~~ for metastatic NSCLC.~~.. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their ~~NSCLC~~metastatic disease, whichever comes first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Rationale:

Modified to:

- Include subjects with selected metastatic solid tumor types in Part 1 of the study.
- Modified to increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 cycles.

2.15. Section 5: Table Of Events (pages 47-52)

Original Text:

Table 7: Sotatercept (ACE-011) NSCLC Schedule of Assessments

		Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
	Screening Period	Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Activin A and other proteins/biomarkers in Blood (pre-dose study treatment in a subset of subjects)		X	X				X					X						
Activin and other proteins/biomarkers in archival tumor tissue	X																	
Tumor Assessments[o]	X	≤ Every 9 weeks ± 1 week or per standard of care at study site																

[a]Include NSCLC history, date of original diagnosis, clinical stage at Screening and date of metastases and metastatic site involvement. Record prior ESA history, starting at diagnosis of NSCLC. Record RBC transfusion history, starting from diagnosis of metastatic NSCLC, at a minimum of two months prior to randomization.

[m]Dual Energy X-ray Absorptiometry (DXA) scan to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15.0, 30.0 and 45.0 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.

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[o]Tumor assessments: Screening period tumor assessments may be performed up to six weeks prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Following randomization, tumor assessments will be performed at a maximum of every 9 weeks (± 7 days) or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments, FACIT Fatigue Scale (Version 4) and LCSS questionnaire, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins an every 3 week platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days following Day 1 of a platinum-based chemotherapy cycle**. **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

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If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

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[r]Every 3-week platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

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[d]To be collected in other subjects.

Revised Text:

Table 7: Sotatercept (ACE-011) ~~NSCLC~~ Schedule of Assessments

		Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
	Screening Period	Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Activin A and other proteins/biomarkers in blood (serum) (pre-dose study treatment in a subset of subjects)		X	X				X					X						
Activin and other proteins/biomarkers in archival tumor tissue (Part 2 only - optional)	X																	
Tumor Assessments[o]	~~X~~X[o]	≤ Every 9 weeks ~~± 1 week~~ or as per standard of care at study site																

[a]Include ~~NSCLC~~cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and metastatic site involvement. Record prior ESA history, starting at selected solid tumor diagnosis ~~of NSCLC~~. Record RBC transfusion history, starting from diagnosis of metastatic ~~NSCLC~~disease, at a minimum of two months prior to randomization.

[m]Dual Energy X-ray Absorptiometry (DXA) ~~scan~~of lumbar spine and hip to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15~~.0~~, 30~~.0~~ and 45~~.0~~ mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment ~~will~~may participate in the sparse PK assessment.

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[o]Tumor assessments: Screening period tumor assessments may be performed ~~up to~~ within six weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Following randomization, tumor assessments will be performed ~~at a maximum of~~≤ every 9 weeks ~~(± 7 days)~~ or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments, FACIT Fatigue Scale (Version 4) – all subjects and LCSS questionnaire – only subjects with NSCLC, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins an every 3 week, platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo ~~should~~**may be given** ~~**within 7 days prior to or within 7 days**~~**at any time following** ~~**Day 1**~~**the first dose of** ~~**a**~~**first-line platinum-based chemotherapy** ~~**cycle**~~**.** **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

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~~If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.~~

~~[r]Every 3-week platinum~~

[r] Platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded. ~~If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.~~

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

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[d]To be collected in ~~other~~ subjects~~.~~ participating in sparse PK sampling and not participating in full PK sampling.

Rationale:

Modified to:

- Clarify that archival tumor tissue analysis will occur only in Part 2 of the study and will be optional.
- Include subjects with selected metastatic solid tumor types in Part 1 of the study.
- Clarify sites of DXA scan.
- Clarify that sparse PK in Part 1 is optional.
- Expand acceptable time period for screening tumor assessment to align with standard of care per site.
- Clarify FACIT Fatigue Scale to be performed on all subjects..
- Clarify LCSS questionnaire to be performed only on subjects with NSCLC.
- Allow administration of the first dose of sotatercept (ACE-011) at any time during a chemotherapy cycle dependent upon hemoglobin level.
- Allow administration of sotatercept (ACE-011) before or after chemotherapy administration.
- Clarify sparse PK sampling in Part 1.

2.16. Section 6: Procedures (pages 55-62)

Original Text:

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed within 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed within 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – –

- NSCLC history, including date of original diagnosis, histopathology, clinical stage at screening, date of metastatic stage and site involvement
- Prior ESA treatment history starting from initial diagnosis of NSCLC
- RBC transfusion history starting from diagnosis of metastatic NSCLC at a minimum of up two months prior to randomization

– – – – – – – – – –

- Bone imaging – DXA scan
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks prior to randomization to this study. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire

– – – – – – – – – –

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized by a single-blind procedure utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15.0 mg SC
- Sotatercept (ACE-011) 30.0 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with each subject having received at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose. Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45.0 mg SC

to the randomization schema will be determined.

– – – – – – – – – –

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional two doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

– – – – – – – – – –

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

– – – – – – – – – –

- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre- dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in archival tumor tissue

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- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week **or per standard of care at the study site,** starting from the previous [screening] tumor assessment) and following the chemotherapy schedule

– – – – – – – – – –

- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire

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Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

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The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – –

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≥ every 9 weeks ± one week **or per standard of care at the study site,** and following the chemotherapy schedule
- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire

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Study Discontinuation

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The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

- QoL Assessment (FACIT Fatigue Scale (Version 4)) and LCSS questionnaire

– – – – – – – – – –

- Reporting of adverse events (only AE/SAE assessed related to study treatment are to be reported)

– – – – – – – – – –

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in the NSCLC population in a subset of subjects.

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Pharmacokinetics

- Part 1 - Full PK blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment will participate in the sparse PK assessment.
- Part 2- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

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Bone Imaging

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Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS

consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Revised Text:

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed ~~within~~≤ 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization~~.~~ or as per study site standard of care. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed ~~within~~≤ 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – –

- ~~NSCLC~~Cancer history, including date of original diagnosis, histopathology, clinical stage at screening, date of metastatic stage and site involvement
- Prior ESA treatment history starting from initial diagnosis of ~~NSCLC~~one-of the selected solid tumors
- RBC transfusion history starting from diagnosis of metastatic ~~NSCLC~~disease at a minimum of up two months prior to randomization

– – – – – – – – – –

- Bone imaging – DXA scan (optional at selected sites)
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks or as per study site standard of care prior to randomization~~ to this study.~~. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) ~~and~~ – all subjects
- LCSS questionnaire – only subjects with NSCLC

– – – – – – – – – –

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized ~~by a single-blind procedure~~ utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15~~.0~~ mg SC
- Sotatercept (ACE-011) 30~~.0~~ mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15~~.0~~ mg dose level and 10 subjects at the 30~~.0~~ mg dose level, with each subject having received ~~at least~~a minimum of one dose of sotatercept (ACE-011~~), plus~~) and completed a 12-week follow-up period from the first dose. ~~Following this analysis, the addition of a third dose level:~~

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45~~.0~~ mg SC

to the randomization schema will be determined.

– – – – – – – – – –

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional ~~two~~2 doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

– – – – – – – – – –

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

– – – – – – – – – –

- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre- dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in archival tumor tissue (Part 2 only)

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- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ~~≥~~≤ every 9 weeks ~~± one week~~ **or per standard of care at the study site,** starting from the previous [screening] tumor assessment) and following the chemotherapy schedule

– – – – – – – – – –

- QoL Assessment (FACIT Fatigue Scale ~~(~~[Version 4~~)) and LCSS questionnaire~~]) – all subjects
- LCSS questionnaire – only subjects with NSCLC

– – – – – – – – – –

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

– – – – – – – – – –

The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ~~≥~~≤ every 9 weeks ~~± one week~~ **or as per standard of care at the study site,** and following the chemotherapy schedule
- QoL Assessment (FACIT Fatigue Scale (Version 4)) ~~and LCSS questionnaire~~ – all subjects
- LCSS questionnaire – subjects with NSCLC

– – – – – – – – – –

Study Discontinuation

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The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – –

- QoL Assessment (FACIT Fatigue Scale (Version 4)) ~~and~~ – all subjects
- LCSS questionnaire – only subjects with NSCLC

– – – – – – – – – –

- ~~Reporting of adverse events (only AE/SAE assessed related to study treatment are to be reported)~~
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.

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Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in ~~the NSCLC population in~~ a subset of subjects~~.~~ (Part 2 only).

– – – – – – – – – –

Pharmacokinetics

- Part 1 -~~ Full PK blood~~Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment ~~will~~may participate in the sparse PK assessment.
- Part 2- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either Part 1 full or sparse PK assessments or in Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

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Bone Imaging - optional

– – – – – – – – – –

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) will be completed by all subjects and LCSS questionnaire will be completed for subjects with NSCLC. Each assessment will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Rationale:

Modified to:

- Clarify screening period.
- Expand acceptable time period for screening tumor assessment to align with standard of care per site.
- Include subjects with selected metastatic solid tumor types in Part 1 of the study.
- Clarify collection of RBC transfusion data.
- Clarify DXA scanning is optional.
- Clarify FACIT Fatigue Scale will be performed on all subjects.
- Clarify LCSS questionnaire to be performed only for subjects with NSCLC.
- Clarify collection of adverse event data at study discontinuation visit.
- Clarify criteria for analysis of safety data from the 15 and 30 mg sotatercept (ACE-011) dose levels to determine the addition of the 45 mg sotatercept (ACE-011) dose level.
- Add editorial revision – ‘two’ to ‘2’.

- Clarify that archival tumor tissue analysis will occur only in Part 2 of the study.
- Deleted redundant wording – ‘ Full PK blood’.
- Clarify that sparse PK in Part 1 is optional.
- Clarify that concentration of sotatercept (ACE-011) may be determined in anti-drug (sotatercept) antibody samples.

2.17. Section 7: Study Population (page 63)

Original Text:

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC at the time of randomization. Subjects must be randomized prior to receiving Cycle 4 of this current first-line platinum-based chemotherapy regimen. Subjects are expected to be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of chemotherapy for the first-line platinum containing treatment of metastatic NSCLC prior to the regimen at the time of randomization.

Revised Text:

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy , given every three weeks, for the treatment of a selected metastatic ~~NSCLC~~solid tumor at the time of randomization: metastatic NSCLC, metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy. Subjects may have already received up to 4 cycles of this current platinum-based regimen and must be randomized prior to receiving Cycle ~~4 of this current first-line platinum-based chemotherapy regimen. Subjects are~~5. It is expected ~~to~~ that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of platinum containing chemotherapy for the first-line ~~platinum-containing~~ treatment of metastatic ~~NSCLC~~solid tumors prior to the regimen they are receiving at the time of randomization.

Rationale:

Modified to increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 and allow subjects with selected metastatic solid tumor types in Part 1 of the study.

2.18. Section 7.1: Number of Subjects (page 63)

Original Text:

This NSCLC platinum-based CIA study will enroll approximately 840 subjects in **Part 1** and **Part 2**.

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In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in Part 1, or placebo at a ratio of 1:1. Subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:

Revised Text:

This ~~NSCLC~~ platinum-based CIA study will enroll approximately 840 subjects, approximately 90 subjects with selected metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**.

– – – – – – – – – –

In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in Part 1, or placebo at a ratio of 1:1. ~~Subjects will be randomized to receive either sotatercept (ACE-011) or placebo and~~Subjects will be stratified by:

Rationale:

Modified to:

- Include subjects with selected metastatic solid tumor types in Part 1.
- Delete redundant wording.

2.19. Section 7.2: Inclusion Criteria (page 64)

Original Text:

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

– – – – – – – – – –

2. Histologically confirmed (cytology or biopsy) non-small cell carcinoma of the lung.
3. Documented metastatic (Stage IV) disease, (including pleural or pericardial effusion involvement)

– – – – – – – – – –

5. All of the following laboratory values:

– – – – – – – – – –

- Hepatic function (bilirubin $\leq$ 1.5 x ULN; AST and ALT $\leq$ 3.0 x ULN and $\leq$5 ULN for subjects with liver metastases)

– – – – – – – – – –

6. Subjects may have received up to 3 cycles of their first regimen of first line platinum-based chemotherapy treatment for metastatic NSCLC. Allowed regimens are:
   - gemcitabine plus cisplatin or carboplatin ± bevacizumab
   - pemetrexed plus cisplatin or carboplatin ± bevacizumab
   - paclitaxel plus carboplatin ± bevacizumab
   - docetaxel plus cisplatin ± bevacizumab

   At randomization subjects are expected to be eligible to continue to receive at least two additional platinum-based chemotherapy cycles while on study. .

– – – – – – – – – –

10. If currently receiving bisphosphonate or denosumab (XGEVA™) therapy for bone metastases, must be on a stable dose for $\geq$ 2 months before Day 1 (ongoing bisphosphonate or denosumab therapy is allowed during study provided it is kept at a stable level). Bisphosphonate or denosumab therapy may not be started on study. Bisphosphonate therapy may be started on study for the treatment of hypercalcemia. Subjects not currently on bisphosphonates or denosumab must not have received bisphosphonates or denosumab within 2 months prior to Day 1.

Revised Text:

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

– – – – – – – –

2. **Part 1 -** Histologically confirmed (cytology or biopsy) solid tumor malignancy, including metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer,

metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer , where the standard of care is platinum-based chemotherapy.

Part 2 - Histologically confirmed (cytology or biopsy) non-small cell lung cancer. ~~carcinoma of the lung.~~

3. Documented metastatic ~~(Stage IV)~~ disease~~, (including pleural or pericardial effusion involvement)~~

– – – – – – – – – –

5. All of the following laboratory values:

– – – – – – – – – –

- Hepatic function (bilirubin $\leq$ 1.5 x ULN; AST and ALT $\leq$ 3.0 x ULN and $\leq$ 5.0 ULN for subjects with liver metastases)

– – – – – – – – – –

6. Subjects may have received up to ~~3~~4 cycles of their first regimen of first line platinum-based chemotherapy treatment.

- For Part 1- any platinum-based regimen approved for the specific indication
- For Part 2 -allowed regimens for the treatment of metastatic NSCLC ~~. Allowed regimens~~ are:
  - ~~•~~○ gemcitabine plus cisplatin or carboplatin ± bevacizumab
  - ~~•~~○ pemetrexed plus cisplatin or carboplatin ± bevacizumab
  - ~~• paclitaxel~~○taxanes plus cisplatin or carboplatin ± bevacizumab
- ~~• docetaxel plus cisplatin ± bevacizumab~~

At randomization, subjects are expected to be eligible to continue to receive at least two additional platinum-based chemotherapy cycles while on study. .

– – – – – – – – – –

~~10. If currently receiving bisphosphonate or denosumab (XGEVA™) therapy for bone metastases, must be on a stable dose for $\geq$ 2 months before Day 1 (ongoing bisphosphonate or denosumab therapy is allowed during study provided it is kept at a stable level). Bisphosphonate or denosumab therapy may not be started on study. Bisphosphonate therapy may be started on study for the treatment of hypercalcemia. Subjects not currently on bisphosphonates or denosumab must not have received bisphosphonates or denosumab within 2 months prior to Day 1.~~

Rationale:

Modified to:

- Include subjects with selected metastatic solid tumor types in Part 1 of the study.

- Correction of hepatic function typographical error.
- Increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 cycles.
- Expand the type of platinum-based regimens allowed in Part 1 of the study.
- Clarify the types of platinum-based regimens allowed in Part 2 of the study.
- Include use of bisphosphonates and denosumab for bone metastases to be consistent with standard of care and treatment practices.

2.20. Section 7.3: Exclusion Criteria (pages 65-67)

Original Text:

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

– – – – – – – – – –

3. History of prior regimen(s) of platinum-based chemotherapy for metastatic NSCLC.

– – – – – – – – – –

5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying NSCLC.

Revised Text:

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

– – – – – – – – – –

3. History of prior regimen(s) of platinum-based chemotherapy for metastatic ~~NSCLC.~~ disease and/or history of adjuvant platinum-based chemotherapy with last dose received less than six months prior to the start of current first-line platinum-based chemotherapy for metastatic disease.

– – – – – – – – – –

5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying ~~NSCLC~~malignancy.

Rationale: Modified to include selected metastatic solid tumor types in Part 1 of the study and clarify acceptable history of prior adjuvant platinum-based chemotherapy.

2.21. Section 8.2: Treatment Administration and Schedule (pages 68-69)

Original Text:

At the time of randomization all subjects must be receiving their first-line regimen of platinum-containing chemotherapy, given every three weeks, for the treatment of metastatic NSCLC. Subjects will be randomized to this study during the time period in which they are receiving Cycle 1 to Cycle 3 of their first regimen of first-line platinum-based chemotherapy. Subjects must not have received any prior regimens of platinum-based chemotherapy for metastatic NSCLC.

Allowed concomitant platinum-based chemotherapy regimens are:

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- paclitaxel plus carboplatin ± bevacizumab
- docetaxel plus cisplatin ± bevacizumab

– – – – – – – – – –

The platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

While on treatment subjects will be allowed to receive maintenance therapy with a pemetrexed or erlotinib-containing regimen when indicated.

Subjects must be given sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to chemotherapy administration on the dose administration days.

Revised Text:

At the time of randomization all subjects must be receiving their first-line regimen of platinum-containing chemotherapy, given every three weeks, for the treatment of a metastatic ~~NSCLC.~~solid tumor. Subjects will be randomized to this study during the time period in which they are receiving Cycle 1 ~~to~~through Cycle ~~3~~4 of ~~their first~~ this regimen~~ of first-line platinum-based chemotherapy.~~. Subjects must not have received any prior regimens of first line platinum-based chemotherapy for a metastatic ~~NSCLC.~~solid tumor..

Allowed concomitant platinum-based chemotherapy regimens are:

- For Part 1- any platinum-based regimen approved for the specific indication
- For Part 2 -allowed regimens for the treatment of metastatic NSCLC are:

– – – – – – – – – –

- ~~paclitaxel~~○taxanes plus cisplatin or carboplatin ± bevacizumab
- ~~docetaxel plus cisplatin ± bevacizumab~~

– – – – – – – – – –

~~The platinum~~ P*latinum*-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

While on study treatment subjects will be allowed to receive maintenance therapy with a pemetrexed or erlotinib-containing regimen when indicated.

~~Subjects must be given sotatercept (ACE-011) or sotatercept (ACE-011)/placebo prior to chemotherapy administration on the dose administration days.~~

Rationale:

Modified to:

- Include selected metastatic solid tumor types in Part 1 of the study.
- Increase the number of allowed prior cycles of first-line platinum-based chemotherapy to 4 cycles.
- Expand the type of platinum-based regimens allowed in Part 1 of the study.
- Clarify the types of platinum-based regimens allowed in Part 2 of the study.
- Make editorial correction.
- Clarify that maintenance therapy is allowed while subject is on study treatment.

2.22. Section 8.2.1: Selection of Dose for the Study (pages 69-70)

Original Text:

– – – – – – – – – –

- Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15.0 mg dose level and 10 subjects at the 30.0 mg dose level, with at least of one dose of sotatercept (ACE-011), plus a 12-week follow-up period from first dose.

– – – – – – – – – –

- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the optimal dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).

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Hematopoietic response will be determined by laboratory analysis.

Revised Text:

– – – – – – – – – –

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15~~.0~~ mg dose level and 10 subjects at the 30~~.0~~ mg dose level, with ~~at least~~each subject having received a minimum of one dose of sotatercept (ACE-011~~), plus~~) and completed a 12-week follow-up period from the first dose.

– – – – – – – – – –

- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the~~ optimal~~ dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).

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Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

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Rationale:

Modified to:

Clarify criteria for analysis of safety data from the 15 and 30 mg sotatercept (ACE-011) dose levels to determine the addition of the 45 mg sotatercept (ACE-011) dose level.

Delete term ‘optimal’ to describe sotatercept dose determined in Part 1 to be administered in Part 2.

Clarify how hematopoietic response will be determined.

2.23. Section 8.2.2: Selection and Timing of Dosing for Each Subject (pages 70-71)

Original Text:

– – – – – – – – – –

The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **within 7 days prior to or within 7 days <u>of administration</u> of a platinum-based chemotherapy cycle**. **Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

– – – – – – – – – –

If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their NSCLC, whichever comes first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of NSCLC that requires the initiation of another treatment.

Revised Text:

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The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo ~~should~~can be administered ~~given **within 7 days prior to or within 7 days**~~ **<u>of</u> at any time after the first cycle and prior to the fifth cycle of first-line platinum-based chemotherapy~~ cycle~~. Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

– – – – – – – – – –

~~If sotatercept (ACE-011) or sotatercept (ACE-011)/placebo is administered on the same day as chemotherapy, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be given **prior** to chemotherapy administration.~~

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their ~~NSCLC~~metastatic disease, whichever comes first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of ~~NSCLC~~metastatic disease that requires the initiation of another treatment.

Rationale:

Modified to:

- Allow administration of the first dose of sotatercept (ACE-011) at any time during a chemotherapy cycle dependent upon hemoglobin level.
- Allow administration of sotatercept (ACE-011) before or after chemotherapy administration.
- Include metastatic solid tumor progression as a reason for Study Treatment Discontinuation.

2.24. Section 8.2.3: Discontinuation (pages 71-72)

Original Text:

Treatment Discontinuation

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Subjects will be discontinued from Study Treatment due to the following:

– – – – – – – – – –

- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb following two doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo

– – – – – – – – – –

- Disease Progression of NSCLC

– – – – – – – – – –

Study Discontinuation:

– – – – – – – – – –

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

– – – – – – – – – –

- Disease progression of NSCLC

Revised Text:

Treatment Discontinuation

– – – – – – – – – –

Subjects will be discontinued from Study Treatment due to the following:

– – – – – – – – – –

- ~~Lack~~In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011~~) or sotatercept (ACE-011~~)/placebo~~.~~ (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).

– – – – – – – – – –

- Disease Progression ~~of NSCLC~~

– – – – – – – – – –

Study Discontinuation:

– – – – – – – – – –

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

– – – – – – – – – –

- Disease progression ~~of NSCLC~~

Rationale:

Modified to:

- Clarify assessment of sotatercept (ACE-011) therapeutic effect in Part 1 and Part 2 of the study and provide the timeframe in which assessment should be performed.
- Include metastatic solid tumor progression in rules for Study Treatment and Study Discontinuation.

2.25. Section 9.1: Permitted Concomitant Medications and Procedures (pages 74-75)

Original Text:

General concomitant medication usage

– – – – – – – – – –

Concomitant therapies considered as supportive care are acceptable while participating in this study including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting and palliative radiation and bisphosphonates (Refer to Inclusion Criterion, Section 7.2) for bone metastases.

– – – – – – – – – –

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study sponsor and Medical Monitor, as well as to the unblinded clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur. Subjects will not be unblinded.**

– – – – – – – – – –

In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study treatment period and continue to the post treatment follow-up period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the treatment period. **The unblinded pharmacist will ensure that subjects randomized to receive treatment with sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo.**

RBC transfusions

– – – – – – – – – –

If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered no sooner than 7 days from the date of the RBC transfusion.

Revised Text:

General concomitant medication usage

– – – – – – – – – –

Concomitant therapies considered as supportive care are acceptable while participating in this study including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting and palliative radiation ~~and~~ , bisphosphonates and denosumab (Refer to Inclusion Criterion, Section 7.2) for bone metastases.

– – – – – – – – – –

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study sponsor and Medical Monitor, as well as to the ~~unblinded~~ clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur~~. Subjects will not be unblinded.~~**

– – – – – – – – – –

In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study treatment period and continue to the post treatment follow-up period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the treatment period~~.~~ as follows: **The unblinded pharmacist will ensure that subjects randomized to receive treatment with sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo. The investigator, site personnel and subject will remain blinded.**

RBC transfusions

– – – – – – – – – –

If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered ~~no sooner than~~ >7 days from the date of the RBC transfusion.

Rationale:

Modified to:

- Include use of bisphosphonates and denosumab for bone metastases to be consistent with standard of care and treatment practices.
- Clarify blinding procedures in Part 2 following treatment with ESAs.
- Clarify allowed timing of sotatercept (ACE-011) dosing following RBC transfusion.

2.26. Section 10.1: Overview (page 76)

Original Text:

This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

Revised Text:

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with selected metastatic solid tumor types treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. ~~This is a single-blind, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.~~

Rationale:

Modified to include selected metastatic solid tumor types, remove single-blind and add open-label in Part 1 of the study.

2.27. Section 10.9: Other Topics (page 80)

Original Text

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of Part 1. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC_{42}, CL/F, Vz/F, and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

Revised Text:

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of Part 1. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC_{42}, ~~CL/F, Vz/F,~~ and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality

will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

Rationale:

Revision of PK parameters to be measured.

2.28. Section 11.1: Monitoring, Recording, and Reporting of Adverse Events (page 81)

2.29.

Original Text:

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately (i.e., 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

Revised Text:

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately ~~(i.e.,~~ 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

Rationale:

Updated in alignment with current protocol template.

2.30. Section 11.5: Immediate Reporting of Serious Adverse Events Adverse Events (page 85)

Original Text:

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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately (i.e., 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.

Revised Text:

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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately ~~(i.e.,~~ 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.

Rationale:

Updated in alignment with current protocol template.

2.31. Section 18: References (pages 96-98)

Original Text:

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. Submitted 2008.

Revised Text:

Aapro M, Vaupel P. Erythropoietin: effects on life expectancy in patients with cancer-related anemia. *Curr Med Res Opin.* 2006; 22(suppl 4):5-13.

Carlos JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer.* 2001; 91:2214-2221.

Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue, and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol.* 2004; 15:979-986.

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. J Bone Miner Res- 2010; 25 (12), 2633-46,~~1.~~ Erroatum in J Bone Miner Res 2011; 26 (2), 439~~ Submitted 2008.~~

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Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer.* 1999; 86:1528-1536.

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Hollen, PJ, Gralla, RJ, Kris, MG, and Potanovich, LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). European Journal of Cancer, 1993; 29A, S51-S58.

Hollen, PJ, Gralla, RJ, Kris, MG, & Cox, C. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1994a; 2, 213-222.

Hollen, PJ, Gralla, RJ, Kris, MG, Cox, C, Belani, CP, Grunberg, SM, Crawford, J, and Neidhart, JA. Measurement of quality of life in patients with lung cancer in multicenter trials of new

therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer, 1994b; 73, 2087-98.

Hollen, PJ, Gralla, RJ, Kris, MG, Eberly, SW, and Cox, C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1999; 7, 140-148.

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Laurie SA, Jeyabalan N, Nicholas G, Dahrouge S. Association between anemia arising during therapy and outcomes of chemoradiation for limited small-cell lung cancer. *J Thorac Oncol.* 2006;146-151.

– – – – – – – – – –

MacRae R, Shyr Y, Jonson D, Choy H. Declining hemoglobin Turing chemoradiotherapy for locally advanced non-small cell lung cancer is significant. *Radiother Oncol.* 2002;64:37-40.

– – – – – – – – – –

Obermair A, Cheuk R, Horwood K, et al. Anemia before and during concurrent chemoradiotherapy in patients with cervical carcinoma: effect on progression-free survival. *Int J Gynecol Cancer.* 2003; 13:633-639.

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Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. *Am J Health Syst Pharm.* 2007; 64 (suppl 2):S5-S13.

Rationale:

References added provide additional information for:

- Addition of selected metastatic solid tumor types in Part 1 of the study.
- Chemotherapy-induced anemia.
- QoL- Lung Cancer Symptom Scale Assessment.

Reference updated to include publishing details.

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH SELECTED METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
AMENDMENT 1.0 FINAL:	22 MARCH 2011
AMENDMENT 2.0 FINAL:	27 JUNE 2011
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

MEDICAL MONITOR / **EMERGENCY CONTACT INFORMATION**

Contact Information:	
PPD	

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:	PPD

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

Signature of Celgene Therapeutic Area Head

PPD 28 June 2011

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:_____** By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

An open-label randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Metastatic Solid Tumors

Part 1 – Solid tumors, including metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy. No solid tumors other than those tumor types listed above should be considered for this study.

Part 2 - Metastatic NSCLC.

Objectives

The primary objectives are:

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

The secondary objectives are:

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS).
- To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (Part 2 only).
- To assess renal function biomarkers

Study Design

This is an open-label, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy for CIA in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine a dose of sotatercept (ACE-011) that results in a hematopoietic response in the treatment of CIA in subjects with selected metastatic solid tumors treated with platinum-based chemotherapy. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Part 2 is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During **Part 2** (first and second stage) overall survival will be assessed. The total sample size of 750 subjects will allow observation of at least 536 deaths and thus, at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Study Population

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-based chemotherapy, given every three weeks, for the treatment of one of the selected metastatic solid tumor types, which include: metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer. Subjects may have already received up to 4 cycles of this current platinum-based regimen and must be randomized prior to receiving Cycle 5. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other platinum containing regimens of chemotherapy for the first-line treatment of a metastatic solid tumor prior to the regimen they are receiving at the time of randomization.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening, Treatment Period, Post Treatment Follow-Up Period, and Survival Follow-Up Period. Study treatment is defined as sotatercept (ACE-011) in Part 1 and sotatercept (ACE-011)/placebo in Part 2.

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks or as per standard care at the study site prior to randomization. **Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected and used for assessment of tumor response.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from initial diagnosis of selected solid tumor types and red blood cell (RBC) transfusion history starting from diagnosis of metastatic disease, at a minimum of up to two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the Screening Period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Treatment Period (up to 6-9 months):

The Treatment Period is approximately six months (four doses of study treatment given on Day 1, every 42 days), two additional sotatercept (ACE-011)/placebo doses may be given only in **Part 2**, at the discretion of the Investigator.

In **Part 1** (the dose-ranging portion of the study), subjects with selected metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The effective dose of sotatercept (ACE-011) is defined as follows:

> An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks during the first two doses of sotatercept (ACE-011) (Dose 1/Day 1 through and including Dose 2/Day 43 [prior to Dose 3]), in approximately 70% of subjects, in at least one or more treatment arms (in the absence of RBC transfusions and/or ESAs).

Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the sotatercept (ACE-011) dose for Part 2.

In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses. Up to two additional doses (in Part 2 only) may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011) (at the dose determined from Part 1) or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered > 7 days from the date of the RBC transfusion.

In **Part 1**, blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment. In **Part 2**, blood samples will be collected for the sparse PK assessment that will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either Part 1 full or sparse PK assessments or Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100mmHg), confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy. Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months of sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.

- In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥ 3.0 g/dL following a two-level dose reduction due to a Hgb increase ≥ 3.0 g/dL
  - In **Part 2**: > 3 dose reductions and/or delays
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

Post Treatment Follow-Up Period (monthly visits for up to 6 months)

Subjects who enter the Post Treatment Follow-Up Period will be followed monthly for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to one year from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their NSCLC, whichever comes first.

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

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

- Adverse event(s)

- Disease progression
- Protocol violation

Survival Follow-up Period (monthly for up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo)

In both **Part 1** and **Part 2**, survival data will be collected monthly via telephone contact for up to 24 months following the subject's first dose of sotatercept (ACE-011) (Part 1) or sotatercept (ACE-011)/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit.

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Overview of Efficacy Assessments

- Serum hematology, absolute reticulocyte counts
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Tumor Assessments
- Documentation of concomitant RBC transfusions

Overview of Safety Assessments

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac and thromboembolic events
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- AE(s)
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy testing
- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone).
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- Lung Cancer Symptom Scale (LCSS) questionnaire – subjects with NSCLC
- Documentation of concomitant medications / procedures.

Overview of Exploratory Assessments

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- DXA scan
- Renal function biomarkers

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 19
2. STUDY OBJECTIVES 36
2.1. Primary Objective 36
2.2. Secondary Objectives 36
2.3. Exploratory Objectives 36
3. STUDY ENDPOINTS 37
3.1. Primary Endpoint(s) 37
3.2. Secondary Endpoint(s) 37
3.3. Exploratory Endpoint(s) 38
4. OVERALL STUDY DESIGN 39
4.1. Study Design 39
4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules 43
4.2. Study Design Rationale 46
4.2.1. Fixed Dose 46
4.2.2. Dosing Schedule 47
4.2.3. Starting Dose Levels in Part 1 47
4.2.4. Evaluation of Dosing Schema via Modeling/Simulation 48
4.3. Study Duration 49
5. TABLE OF EVENTS 50
6. PROCEDURES 58
7. STUDY POPULATION 67
7.1. Number of Subjects 67
7.2. Inclusion Criteria 68
7.3. Exclusion Criteria 69
8. DESCRIPTION OF STUDY TREATMENTS 72
8.1. Description of Investigational Product(s) 72
8.2. Treatment Administration and Schedule 72
8.2.1. Selection of Dose for the Study 73
8.2.2. Selection and Timing of Dosing for Each Subject 74

8.2.3. Discontinuation 75
8.3. Method of Treatment Assignment 76
8.4. Packaging and Labeling 76
8.5. Investigational Product Accountability And Disposal 77
8.6. Investigational Product Compliance 77
9. CONCOMITANT MEDICATIONS AND PROCEDURES 78
9.1. Permitted Concomitant Medications and Procedures 78
9.2. Prohibited Concomitant Medications and Procedures 79
9.3. Required Concomitant Medications and Procedures 79
10. STATISTICAL ANALYSES 80
10.1. Overview 80
10.2. Study Population Definitions 80
10.3. Sample Size and Power Considerations 80
10.4. Background and Demographic Characteristics 81
10.5. Subject Disposition 81
10.6. Efficacy Analysis 81
10.7. Safety Analysis 82
10.8. Interim Analysis 83
10.9. Other Topics 83
10.10. Data Monitoring Committee (DMC) 84
11. ADVERSE EVENTS 85
11.1. Monitoring, Recording and Reporting of Adverse Events 85
11.2. Evaluation of Adverse Events 85
11.2.1. Seriousness 85
11.2.2. Severity / Intensity 86
11.2.3. Causality 87
11.2.4. Duration 87
11.2.5. Action Taken 88
11.2.6. Outcome 88
11.3. Abnormal Laboratory Values 88
11.4. Pregnancy 88
11.4.1. Females of Childbearing Potential 88
11.4.2. Male Subjects 89

11.5. Immediate Reporting of Serious Adverse Events 89
11.6. Safety Queries 89
11.7 Expedited Reporting of Adverse Events 89
12. DISCONTINUATIONS 91
13. EMERGENCY PROCEDURES 92
13.1. Emergency Contact 92
13.2. Emergency Identification of Investigational Products 92
14. REGULATORY CONSIDERATIONS 93
14.1. Good Clinical Practice 93
14.2. Investigator Responsibilities 93
14.3. Subject Information and Informed Consent 93
14.4. Confidentiality 94
14.5. Protocol Amendments 94
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 94
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 95
14.8. Closure of the Study 95
15. DATA HANDLING AND RECORDKEEPING 96
15.1. Data/Documents 96
15.2. Data Management 96
15.3. Record Retention 96
16. QUALITY CONTROL AND QUALITY ASSURANCE 98
16.1. Study Monitoring and Source Data Verification 98
16.2. Audits and Inspections 98
17. PUBLICATIONS 99
18. REFERENCES 100
19. APPENDICES 103
Appendix A: Response Evaluation Criteria in Solid Tumors 103
Appendix B: ECOG Performance Status Scale 105
Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 106
Appendix D: New York Heart Association - Classification of Heart Failure 107

LIST OF TABLES

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation 28
Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall 31
Table 3: Summary of SAEs Reported 32
Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days 32
Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels 45
Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only) 46
Table 7: Sotatercept (ACE-011) Schedule of Assessments 50
Table 8: Schedule of Pharmacokinetic Assessments (Part 1) 56
Table 9: Schedule of Pharmacokinetic Assessments (Part 2) 57
Table 10: ECOG Performance Status Scale 105
Table 11: Classification of Heart Failure 107

LIST OF FIGURES

Figure 1: Study Design 42
Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population 48

1. INTRODUCTION

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects with selected metastatic solid tumor types treated with platinum-based chemotherapy will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 2 will include only subjects with metastatic NSCLC and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period. Based on the results of the futility analysis and upon recommendation to continue the study, up to an additional 570 subjects will be randomized in the second stage of **Part 2**, to achieve full study accrual.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The chemical structure of sotatercept (ACE-011) is composed of a disulfide-linked, glycosylated, dimeric protein. Sotatercept (ACE-011) competes with the activin receptor IIA and binds a number of TGF-β superfamily ligands including activin, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

In both a single and a multiple dose phase 1 study of sotatercept (ACE-011) in healthy volunteer, postmenopausal women, a dose and time dependent increase in hemoglobin (Hgb) and hematocrit (HCT), and red blood cell (RBC) levels were observed following sotatercept (ACE-011) treatment and remained elevated over the course of study.

Although the mechanism(s) underlying the stimulation effect of sotatercept (ACE-011) on erythropoiesis are not yet fully understood, the result of clinical experience showed a rapid and sustainable increase in mature erythrocytes released into circulation. The sotatercept (ACE-011) proposed mechanism of action may be different than that of known erythropoiesis-stimulating agents (ESAs) and may provide a different clinical profile in the treatment of CIA.

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

Chemotherapy-Induced Anemia

Chemotherapy-induced anemia (CIA) is an area of unmet medical need. It is a significant problem for patients with cancer, causing fatigue and reducing quality of life (QoL).

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002). The incidence and severity of chemotherapy-induced anemia (CIA) is further dependent on a variety of factors, such as the type, schedule, and intensity of chemotherapy administered, and whether the patient has received prior myelosuppressive chemotherapy and/or radiation therapy (Groopman, 1999). Platinum-based treatments (eg, cisplatin and carboplatin), commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity. Antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan) are also considered particularly myelosuppressive (Groopman, 1999). Dose intensity, the increasingly widespread practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression

The association between uncorrected anemia before or during chemotherapy and poorer patients' outcomes has been reported in several studies (Grogan, 1999; Laurie, 2006; MacRae, 2002; Obermair, 2003). Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and may also have an adverse impact on co-morbid conditions, such as cardiac and pulmonary disease. The most common patient complaints are dyspnea on exertion and chronic fatigue, which may interfere with a patient's ability to perform normal daily activities (Groopman, 1999). A key differentiating characteristic of cancer-related fatigue versus fatigue in healthy individuals is its likelihood of persistence at rest (National Comprehensive Cancer Network, 2008) In various published surveys, fatigue has been represented as a symptom that has affected patients' everyday life the most and has been linked to changes in employment status among patients and even caregivers (Schwartz, 2007). The association between Hgb levels and fatigue is well documented, with one analysis of 5 randomized trials linking an increase in Hgb concentrations of at least 2 g/dL with an improvement in fatigue, and consequently, in energy, ability to perform usual activities, and overall health (Cella, 2004).

In looking at the impact of CIA on survival, a meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer and anemia compared with patients without anemia (Carlos, 2001). The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that also is supported by other retrospective studies. Tumor hypoxia, resulting from the reduced oxygen-carrying capacity of blood in patients with anemia, has been hypothesized to be a major contributor to reduced survival. Several studies have shown that tumor hypoxia also reduces the effectiveness of radiotherapy and chemotherapy, and is associated with tumor progression (Aapro, 2006).

Treatment of Chemotherapy-Induced Anemia

The current treatment options for CIA include blood transfusion and erythropoiesis-stimulating agents (ESAs). However, blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients receiving chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. However, the past five years has seen a major change in the use of ESAs for cancer related and chemotherapy induced anemia. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. Retrospective statistical analysis in one study in head and neck cancer patients, and two studies with adjuvant breast cancer revealed substantial safety concerns of increased thromboembolic events, and decreased PFS and overall survival.

Sotatercept (ACE-011) Treatment of Chemotherapy-Induced Anemia

Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two phase 1 studies in healthy volunteers, as well as in a phase 2a study in multiple myeloma (MM) subjects. The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

In a phase 1 single-dose and multiple-dose studies of sotatercept in postmenopausal women (Studies A011-01 and A011-02, respectively), and in a phase 2 study in subjects with osteolytic lesions associated with MM that examined concurrent administration of sotatercept with melphalan, prednisolone, and thalidomide (MPT) anti-myeloma therapy, increases in Hgb, RBC count and HCT were observed following sotatercept treatment, and these increases remained detectable throughout the course of study. The observed Hgb, RBC count, and HCT effects of sotatercept were dose-dependent and time-dependent. These phase 1 and phase 2 clinical data are consistent with the increased hematologic parameters observed in nonclinical studies, The results from the three completed clinical studies A011-01, A011-02, and A011-04 are summarized in Summary of Clinical Experience

.

The mechanism of action of sotatercept with regards to increased RBC counts is not known; however, the mechanism of action for the hematopoietic effect of sotatercept may be different than that of ESAs, as some level of erythrocyte stimulatory effect was observed in the presence of anti-EPO antibodies in one nonclinical study. As such, sotatercept may provide a unique clinical profile with a favorable benefit-risk profile in the chemotherapy-induced anemia patient population, thereby addressing some of the unmet medical needs in chemotherapy-induced anemia treatment.

Non-Small Cell Lung Cancer Current Therapy Status

Lung cancer is the leading cause of cancer death in the world, accounting for 32% of cancer deaths in males and 25% in females, affecting approximately 171,000 people annually in the US (Parker, 1997; Sandler, 2006) and more than 200,000 people in Europe (Rossi, 2006). Of these patients, approximately 85% have NSCLC, including squamous carcinoma, adenocarcinoma and large cell carcinoma (Rossi, 2006; Sandler, 2006). These histologies are typically classified together because the approaches to diagnosis, staging and prognosis, and treatment are similar.

Patients are often diagnosed with an advanced stage of disease. Studies of advanced NSCLC patients treated with platinum-based chemotherapy report a one year survival rate that ranges from 30% to 43% and a median survival that ranges from seven to ten months (Dang, 2008). The 5-year survival rate of patients with NSCLC varies by stage, from 60% to 70% for patients with stage I disease to < 1% for patients with stage IV disease (Hong, 2008). Patients having stage IIIb/IV NSCLC are not considered to be candidates for curative resection surgery or radiation, and radiation therapy is primarily used as palliative treatment in advanced stages of NSCLC.

The role of chemotherapy is now well established as the recommended treatment of advanced NSCLC (Non-small Cell Lung Cancer Collaborative, Group 1995). The current globally accepted standard of treatment for NSCLC is platinum-based combination therapy. In advanced-stage (stage IIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine (Gemzar®), vinorelbine, taxanes (paclitaxel or docetaxel) or pemetrexed are reference regimens. When compared head-to-head in phase 3 studies, these doublets have shown comparable efficacy, in regards to overall survival (Schiller, 2002) with differences in toxicity profiles (Schiller, 2002). When administered in a 3-week schedule, cisplatin plus gemcitabine, or cisplatin plus pemetrexed are effective and are widely used regimens for first-line treatment of NSCLC. A recent phase 3 study in NSCLC compared cisplatin plus gemcitabine with cisplatin plus pemetrexed (Scagliotti, 2008). Both had similar efficacy, with cisplatin plus pemetrexed having better tolerability and more convenient administration than cisplatin/gemcitabine. This study was also the first prospective phase 3 study in NSCLC to show a survival difference based on histologic type (non-squamous benefited from pemetrexed plus cisplatin). Drug-related grade (G) 3 or 4 anemia was at the rate of 6% for cisplatin/pemetrexed versus 10% for cisplatin/gemcitabine. The incidence of RBC transfusion was 16.1% versus 27.3% and administration of erythropoietic agents 10.4% versus 18.1% respectively. There was no significant difference between treatment arms in the incidence of or reason for deaths (7%).

In the pivotal Aranesp (darbepoetin alfa) study for CIA in NSCLC, 27 % of patients were transfused with packed red blood cells (PRBC's) at 4 months versus 52% in the placebo arm.

Activin Biology

The activins (A-E) are a group of proteins that form dimers and heterodimers. All are part of the TGF-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 A was also 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).

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

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

In a retrospective study (Seder, 2009) activin immunoreactivity was found in 78% of lung adenocarcinomas surveyed (n=164). Expression ranged from moderate in the majority of individuals to high in approximately 19.7% of samples evaluated. Gene expression analysis was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples. An average of three-fold more activin transcript was detected in diseased tissue relative to normal samples and particularly high levels of overexpression were associated with worse overall survival in stage I patients with NSCLC.

Additionally, in the NIH “directors challenge” study for NSCLC adenocarcinoma (Shedden, 2008), 3 of the 12 molecular subgroups, including the subgroup with the worst survival prognosis, demonstrated overexpression of Activin A. Thus, overexpression of activin may play a role in NSCLC tumor progression.

Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below. Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

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 (IP) twice per week for 3 months resulted in a 16-26% increase in RBC counts compared to control animals. Rats treated with sotatercept (ACE-011) at 0.3, 3 and 30 mg/kg once per week for 3 months showed RBC count increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of sotatercept (ACE-011) twice per month for 3 months, there was a 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 sotatercept (ACE-011).

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

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

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

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

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model demonstrated that RAP-011 could prevent the development of osteolytic bone disease in a preventative setting.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

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

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

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

Toxicology

Sotatercept (ACE-011) has been evaluated for toxicological effects in two species, Sprague-Dawley rats and cynomolgus monkeys. The dose levels ranged from 0.3 to 30 mg/kg in rats and

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

Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-sotatercept (ACE-011) antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats. However, high plasma concentrations of sotatercept (ACE-011) in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (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, the NOAEL from the 6 month monkey study is < 10 mg/kg. A 9-month monkey study to evaluate the effects of lower concentrations of sotatercept (ACE-011) has been completed (refer to Potential Risks for Human Use).

Summary of Clinical Experience

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

Sotatercept (ACE-011) was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal females (Ruckle, 2009). Sotatercept (ACE-011) was diluted in normal saline administered as an IV infusion (over approximately 1 hour) or as a SC injection on Day 1. Dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg IV and 0.03 and 0.1 mg/kg SC. A total of 48 subjects were enrolled; 5 active and 1 placebo at each of the IV and SC dose levels. All subjects were followed for 4 months following a single dose administration.

The pharmacokinetics (PK) of sotatercept (ACE-011) was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (CL) ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half life in serum ($t_{1/2,}$ z) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, sotatercept (ACE-011) was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs was mild in severity and were judged to be unrelated to

sotatercept (ACE-011). No deaths, serious AEs (SAEs), or AEs leading to discontinuation were reported. Changes in RBCs, Hgb, reticulocytes, liver function tests, glucose, uric acid, amylase and lipase occurred in some subjects. Mild, transient elevations in pancreas enzymes, liver enzymes, or glucose were reported as AEs in five subjects.

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

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

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

Sotatercept (ACE-011) was studied in a phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalating study to evaluate the safety, tolerability and pharmacodynamics of sotatercept (ACE-011) in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following dose levels: 0.1, 0.3, 1.0, and 2.0 mg/kg administered SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of sotatercept (ACE-011) or placebo every 28 days for a total of 4 doses. All subjects were to be followed for 12 weeks after the last dose.

The treatment phase of the study was terminated early after a dose-limiting pharmacodynamic effect was observed. While on study, one subject in the 1.0 mg/kg cohort experienced an SAE of progressive and persistent hypertension that was attributed to a rapid and significant rise in Hgb levels, up to 20 g/dL and HCT levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting pharmacodynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and treated. Dose levels of sotatercept (ACE-011) administered included 0.1, 0.3, and 1.0 mg/kg (Cohorts 1, 2, and 3 respectively). All subjects randomized to active treatment in Cohort 1 received all 4 planned doses of sotatercept (ACE-011). Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of sotatercept (ACE-011), and subjects randomized to active treatment in Cohort 3 received 2 doses of sotatercept (ACE-011). Subjects randomized to placebo treatment received between 1 and 4 doses of study treatment.

In the analysis of the data, after the administration of the first dose, a dose and time dependent increase in Hgb, 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]	**Sotatercept (ACE-011) 0.1 mg/kg N=8**	**Sotatercept (ACE-011) 0.3 mg/kg N=8**	**Sotatercept (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

Other than the serious case of Hgb increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the

subjects in the 1.0 mg/kg group with elevated Hgb levels underwent phlebotomies and all Hgb elevations were resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups.

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

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

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

The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ((apparent) volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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

Study A011-04 is a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety, tolerability and efficacy of sotatercept (ACE-011) in subjects with osteolytic lesions of multiple myeloma (MM).

In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of sotatercept (ACE-011) (0.1, 0.3 and 0.5 mg/kg) or placebo, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept (ACE-011) was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg sotatercept (ACE-011), 8 subjects received 0.3 mg/kg sotatercept (ACE-011), and 8 subjects received 0.5 mg/kg sotatercept (ACE-011). Twenty six (86.7%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

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

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

Fourteen out of 24 subjects (58%) who received study treatment (sotatercept [ACE-011]) did receive 3 doses or more (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level).

Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (i.e., those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept (ACE-011) or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg sotatercept (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to sotatercept (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups and Table 3 is a summary of SAEs reported.

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

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

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

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug (sotatercept (ACE-011) or placebo).

Table 3: Summary of SAEs Reported

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

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

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

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hgb values were observed within 28 days after administration of the first dose of sotatercept (ACE-011)/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	0.1 mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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

Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies

were as a result of the expected biologic activity of 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 sotatercept (ACE-011) treatment and is being targeted as a therapeutic intervention for conditions associated with anemia.
- In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~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 sotatercept (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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, liver enzymes will continue to be monitored in this study.

- Pregnancy and Lactation
  - 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 lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg (~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 sotatercept (ACE-011) is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all sotatercept (ACE-011) protocols describe pregnancy prevention requiring females of child-bearing potential to use highly effective methods of birth control. In addition, since it is unknown if sotatercept (ACE-011) is found in breast milk, breast feeding is prohibited in all protocols.
- Fertility
  - In male rats, sperm granulomas and testicular degeneration were observed histologically. In addition, sperm analysis revealed a reduction in sperm counts and motility as well as sperm fragmentation in isolated animals (2/10 males) at doses of 30 mg/kg IV. Sperm fragmentation was also noted in 2/5 males administered 10 mg/kg IV at the end of the recovery period. Overall, there was some evidence of recovery (motility similar to controls) at the end of the 4-week recovery period. There was no evidence of a treatment-related impact on reproductive organs (testes, ovary, uterus) of monkeys in the toxicity studies; however, the monkeys on these studies, were too immature to fully assess the potential impact on reproductive organs. The NOAEL for reproductive effects (testicular or ovarian) was 1 mg/kg IV. Serum exposure (AUC_{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 sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) is targeted toward patient groups for whom the potential benefits outweigh the perceived risks.

Because of the potential risks sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) was first studied in healthy postmenopausal in two completed phase 1 clinical trials. In addition, due to the potential for effects on hormones in the pituitary, levels of growth hormone, ACTH, and thyroid stimulating hormone (TSH) were monitored closely in the phase 1 studies.

Completed studies in humans carried out in postmenopausal females showed a dose-dependent decrease in circulating levels of FSH, with mean levels in the multi-dose study in the two higher dose groups remaining below baseline at study end. FSH will continue to be evaluated in ongoing studies. No abnormal effects of sotatercept (ACE-011) on growth hormone, ACTH, and TSH and kidney toxicities were observed.

Based on the safety data from the two completed phase 1 studies, single doses of sotatercept (ACE-011) up to 3.0 mg/kg IV and multiple doses of sotatercept (ACE-011) up to 0.3 mg/kg 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 sotatercept (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 sotatercept (ACE-011).

2. STUDY OBJECTIVES

2.1. Primary Objective

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with selected metastatic solid tumors treated with platinum-based chemotherapeutic regimens.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

2.2. Secondary Objectives

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS). To evaluate the safety and tolerability of sotatercept (ACE-011). To determine the PK of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

2.3. Exploratory Objectives

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (Part 2 only).
- To assess renal function biomarkers

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Part 1: Dose Finding

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).
- In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in Part 2.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following the date of randomization to sotatercept (ACE-011)/placebo treatment

3.2. Secondary Endpoint(s)

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- TTP
- PFS (including at 6 and 12 months)
- OS (at 12 months and up to 24 months)
- ORR
- Duration of hematopoietic response
- Sotatercept (ACE-011) concentration in serum
- Non-compartmental PK parameters for sotatercept (ACE-011) (**Part 1** only)
- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1993 ; Hollen, 1994a ; Hollen, 1994b; Hollen, 1995)

3.3. Exploratory Endpoint(s)

- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or sotatercept (ACE-011) mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- A population PK model for sotatercept (ACE-011)
- A population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics
- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue (Part 2 only).
- Change in renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an open-label randomized, phase 2a, dose-ranging study (Part 1) of sotatercept (ACE-011) therapy in subjects with selected metastatic solid tumor types treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects with selected metastatic solid tumor types will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of Part 1 data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study in subjects with metastatic NSCLC.

A DMC will monitor the conduct of the study.

Part 1 is planned to be conducted at selected sites and will be extended to additional global sites for the conduct of **Part 2.**

Study treatment is defined as sotatercept (ACE-011) in Part 1 and sotatercept (ACE-011)/placebo in Part 2.

Three starting sotatercept (ACE-011) dose levels, 15, 30, and 45 mg, were selected for Part 1 of the study. Up to approximately 90 subjects with selected metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for a total of four doses.

In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in Part 1)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses; two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from Part 1, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

The Treatment Period for Part 1 is approximately six months, which includes up to 4 doses of sotatercept (ACE-011) and for Part 2 approximately nine months, which includes up to 6 doses of sotatercept (ACE-011/placebo). Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their metastatic disease, whichever comes first.

Survival data will be collected monthly for up to 24 months following the subject's first dose of sotatercept (ACE-011) in Part 1 or sotatercept (ACE-011)/placebo in Part 2.

At the time of randomization, all subjects must be receiving their first regimen of first-line platinum-based chemotherapy, given every three weeks, for the treatment of a selected metastatic solid tumor. Subjects may have already received up to 4 cycles of this current platinum-based regimen and must be randomized prior to receiving Cycle 5. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

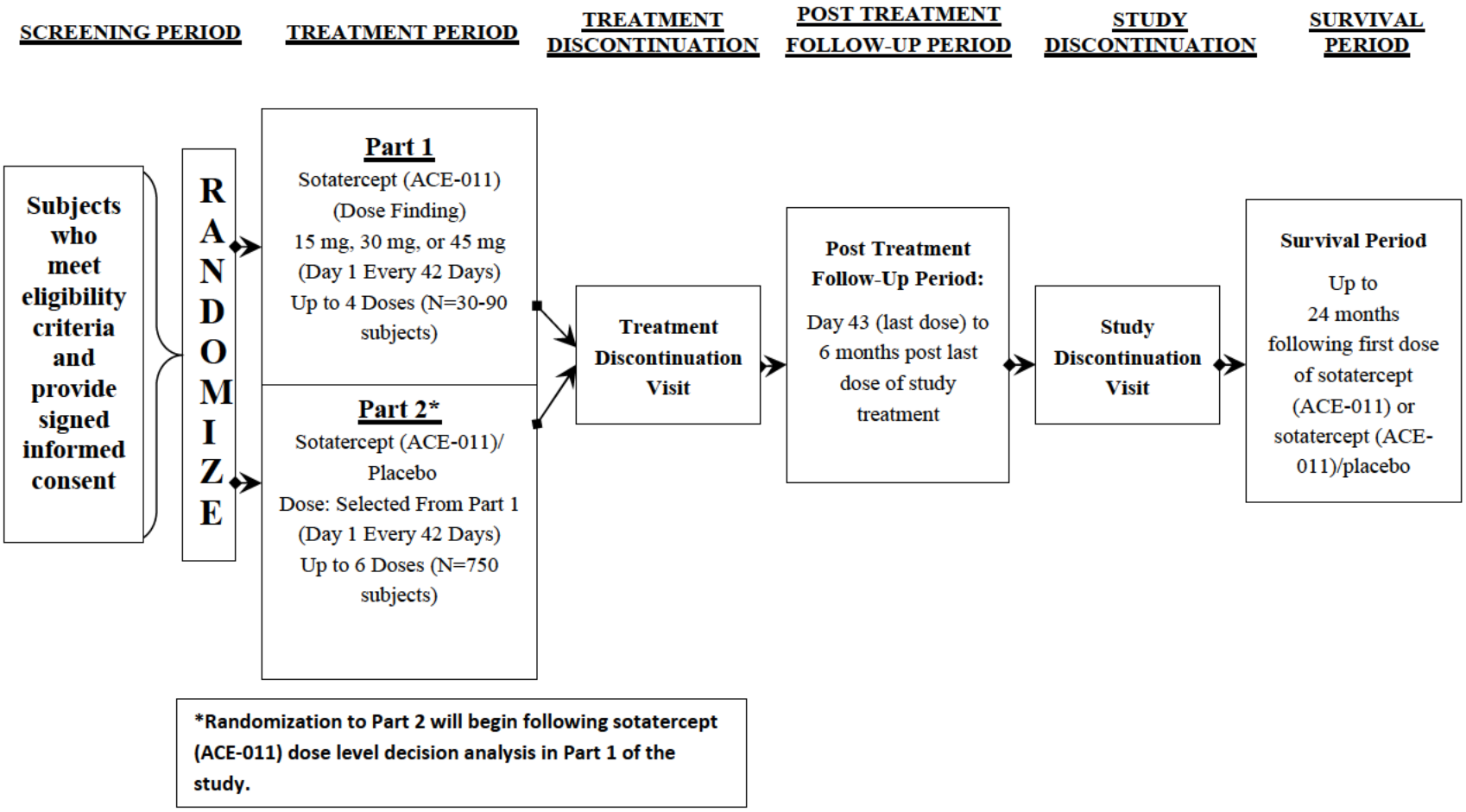
Subjects must not have received any other platinum containing regimens of chemotherapy for the first-line treatment of a metastatic solid tumor prior to the regimen they are receiving at the time of randomization.

Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

- In **Part 1**, subjects will be randomized to one of three sotatercept (ACE-011) dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
- In **Part 2** subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL

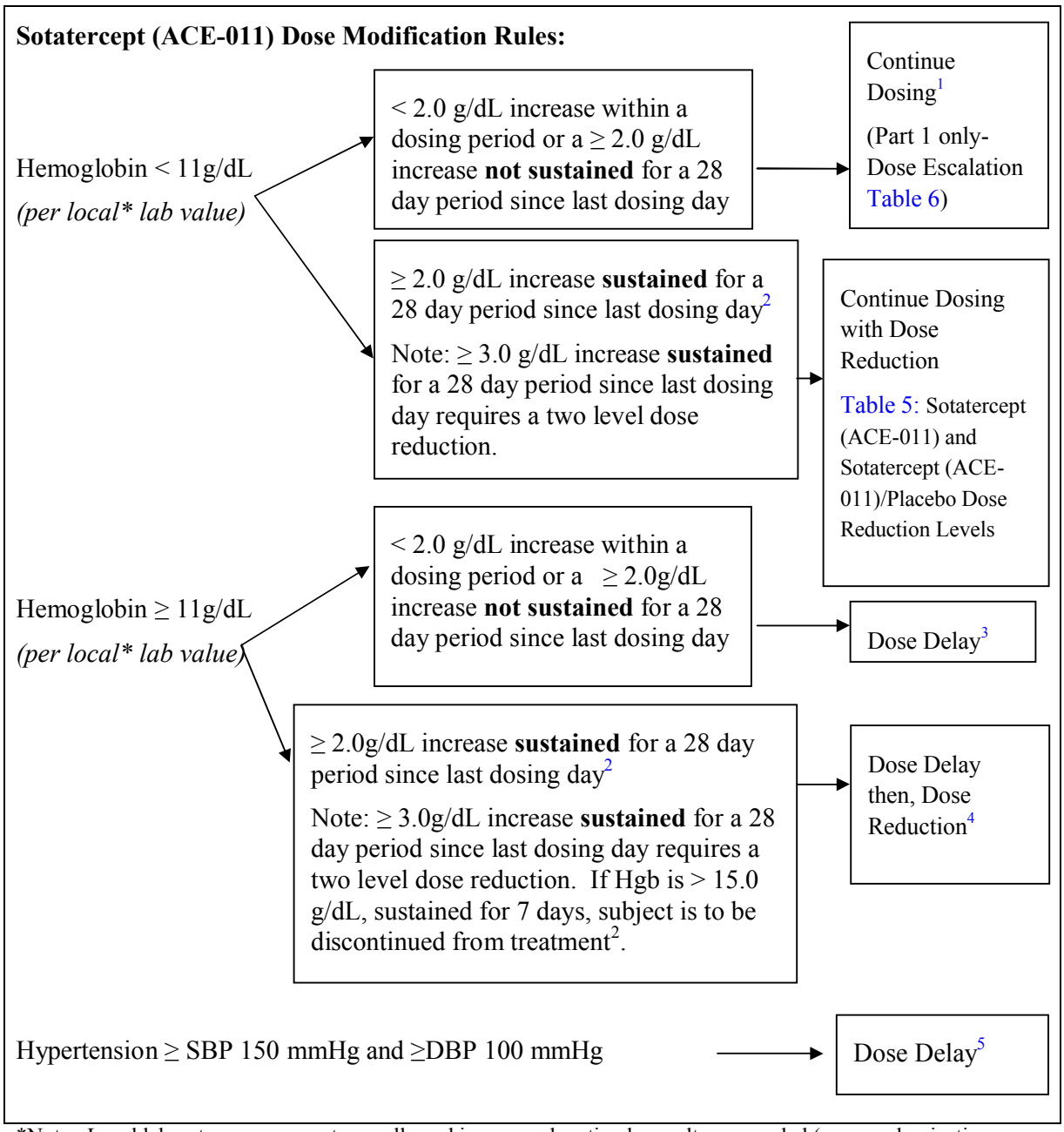
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
4. ECOG Performance Status 0-1 vs. 2

Figure 1: Study Design



4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) or sotatercept (ACE-011)/placebo for the subject's **second** dose of study treatment and beyond.



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

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011) should not be administered ≤ 7 days post RBC transfusion.

For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** sotatercept (ACE-011)/placebo dose if the transfusion was given greater than 7 days from the previous dose of sotatercept (ACE-011)/placebo AND the Hgb level is < 11 g/dL AND hypertension is < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011)/placebo should not be administered ≤ 7 days post RBC transfusion.

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , 22 (after first dose of study treatment) and 28 days after dosing, and reviewed in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels (Refer to sotatercept (ACE-011) and sotatercept (ACE-011)/Placebo Dose Reduction Levels (Table 5). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > SBP 150 mmHg and > DBP 100 mmHg and/or sotatercept (ACE-011) related toxicity).

[4]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be held until hypertension resolves to < SBP 150mmHg and < DBP 100 mmHg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels

When required, per dose modification rules above, sotatercept (ACE-011) dose(s) in **Part 1** and sotatercept (ACE-011)/placebo dose(s) in **Part 2** should be reduced as follows:

Dose Schedule Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days- 45 mg	38 mg	33 mg	28 mg
Every 42 days- 30 mg	26 mg	22 mg	18 mg
Every 42 days- 15 mg	13 mg	11 mg	9 mg

*Note: Any Hgb increase of ≥3.0 g/dL sustained for a 28 day period since last doing day will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for four doses. An additional two doses (total of 6 doses) may be given only during **Part 2** at the discretion of the Investigator.

Blood pressure (confirmed by two measurements obtained five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

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. A dose level may not be increased following a dose reduction.

In **Part 2**, dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. Subjects in the placebo group who are designated to undergo dose reduction will continue to receive placebo.

Placebo will be administered at the same volume as the corresponding sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction.

Sotatercept (ACE-011) Dose Escalation Levels:

The following dose escalation rules apply for sotatercept (ACE-011) dose(s) in **Part 1** only. Dose escalations are not allowed in **Part 2**:

- Less than 1.0 g/dL increase in Hgb in response to prior sotatercept (ACE-011) dose
- Hgb level must be < 11.0 g/dL and hypertension < SBP 150mmHg and < DBP 100 mmHg
- Dose escalation to begin at next treatment visit

- Sotatercept (ACE-011) should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of Sotatercept (ACE-011) at the subsequent visit per the escalation table below.

Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only)

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45 mg	50 mg	55 mg	61 mg
Every 42 days-30 mg	33 mg	36 mg	40 mg
Every 42 days-15 mg	17 mg	20 mg	23 mg

Blood pressure (confirmed by two measurements obtained five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

4.2. Study Design Rationale

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a rapid, sustained and dose-dependent increases in hematopoietic parameters, (Hgb, HCT and RBC counts) which occurred earlier than would be expected from a stimulation of erythropoiesis by an ESA. This observation, couple with nonclinical data demonstrating some level of erythrocyte stimulatory effect in the presence of anti-erthyropoietin (EPO) antibodies, suggests that the hematopoietic effect of sotatercept is different from that of ESAs. Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Guidelines, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

4.2.1. Fixed Dose

Sotatercept (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 sotatercept (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 sotatercept (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 sotatercept (ACE-011) exposure. Because the Hgb response is dependent on sotatercept (ACE-011) exposure and because body weight is not a major source for the intersubject variability of sotatercept (ACE-011) exposure, a fixed dosing approach is considered to be appropriate for the current study.

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 by taking into consideration the rapid and prolonged Hgb response to sotatercept (ACE-011) as well as the dosing schedule for the platinum-based chemotherapies. The Hgb-increasing effect of sotatercept (ACE-011) was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks. In addition, as platinum-based chemotherapy is often administered once every 3 weeks, a once every 6 weeks dosing schedule allows administration of sotatercept (ACE-011) at the same visit for the chemotherapy, which is convenient to both subjects and study sites.

4.2.3. Starting Dose Levels in Part 1

Three starting dose levels, 15, 30, and 45 mg, were chosen for Part 1 of the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of sotatercept (ACE-011) at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, sotatercept (ACE-011) had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal sotatercept (ACE-011) concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The three starting dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg, 31.5 mg, and 52.5 mg, respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three sotatercept (ACE-011) doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to sotatercept (ACE-011). In this study, the starting dose level of 45 mg (during the dose finding Part 1) will be implemented only after at least 10 subjects at each lower dose level (10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level) have been evaluated as well as following DMC review of safety data and assessment of dose effects on Hgb levels.

In addition, in this study, during the first 6-week treatment period for a 70 kg subject receiving the starting dose at 45 mg, the sotatercept (ACE-011) exposure ($C_{max,\ day\ 1\text{-}43}$ and $AUC_{1\text{-}43}$) is projected to be approximately 10% lower than the exposure for the dose regimen of 0.5 mg/kg once every 4 weeks. Afterwards, safety measures (Hgb and blood pressure) will be used to guide the adjustment of the second dose and beyond. Thus, the use of the 45 mg starting dose in the current study is not anticipated to significantly compromise subject safety.

In this study, the 45 mg group will have the highest starting dose, and it may be titrated up to 61.0 mg for the last dose (Dose 4). Assuming a 70 kg subject who receives the maximal amount of dose during the entire study (i.e., starting at 45 mg followed by dose escalation every 6 weeks to 50.0, 55.0, and 61.0 mg for Doses 2, 3, and 4, respectively), the projected cumulative AUC during the treatment period (168 days) would be approximately 60% of the steady state AUC cumulated during the same period at the NOAEL level of 1 mg/kg (given every 4 weeks for a

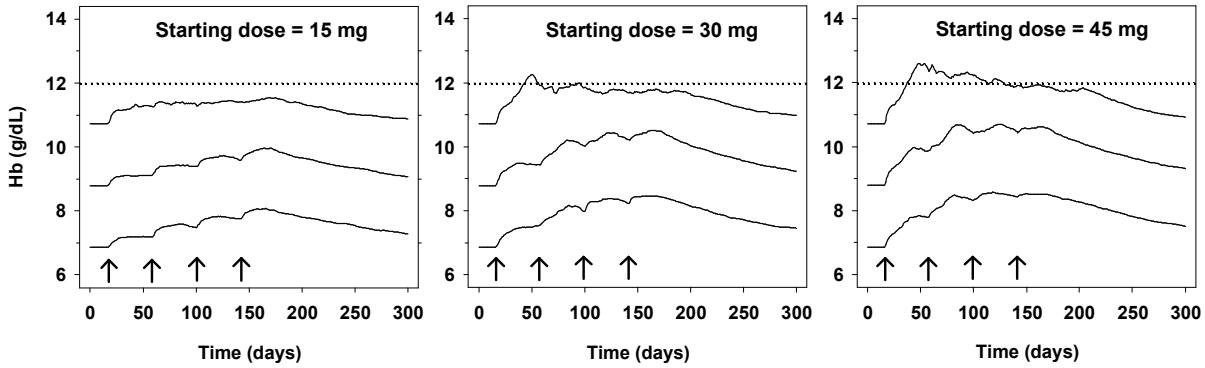
total of 6 doses) as reported in the 9-month, repeat-dose toxicity study in monkeys. The projected highest C_{max} for the current study would be less than 50% of the steady state C_{max} in the monkey study.

4.2.4. Evaluation of Dosing Schema via Modeling/Simulation

The performance of the proposed dosing schema (three fixed starting dose levels, 6-week dosing interval, and dose adjustment rules [see Section 4.1.1 for details]) for this study was evaluated via PK/pharmacodynamic modeling/simulation. A tentative mechanistic PK/pharmacodynamic model for Hgb was developed using PK and Hgb data from healthy postmenopausal women and the model was extended to include MM subjects as a sub-population. The model was required to appropriately reproduce the observed PK and Hgb profiles in MM subjects. Monte Carlo simulations of the Hgb response to sotatercept (ACE-011) in a hypothetical anemic population (6.5 ≤ baseline Hgb < 11 g/dL; body weight 47 – 108 kg) were performed using the model parameterized with preliminary PK and pharmacodynamic parameters from MM subjects. In this simulation analysis, efficacy refers to an Hgb increase > 1 g/dL from the baseline for 28 consecutive days while safety refers to both the absolute Hgb levels and the rate of Hgb increase.

The simulation predicts that the desired efficacy would be achieved 6 weeks after the second dose in approximately 70% subjects of the 45 mg group and 6 weeks after the last dose in >70% subjects of the 30 mg group. Further, the simulation predicts the Hgb level would be maintained under 12 g/dL in 90% subjects and under 13 g/dL in 95% of subjects during the course of the study (Figure 2). No subjects are predicted to have a Hgb level above the upper limit of the normal range for Hgb (16 g/dL). Approximately 6% subjects are predicted to have an Hgb rise > 2 g/dL within 28 days of the first dose, mostly from the 45 mg group (4%); however, the fraction of subjects with an Hgb rise > 3 g/dL per 28 days is predicted to be similar between the three dose groups (approximately 2.5% for each group).

Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population



The middle solid lines represent the median Hgb level. The top and bottom solid lines represent the Hgb level at 5% and 95% percentile, respectively. The area between 5% and 95% percentiles represents 90% prediction interval. The straight dot lines represent the Hgb level of 12 g/dL. The arrows indicate the dosing time of sotatercept (ACE-011). The two level dose reductions upon ≥ 3 g/dL increase sustained for 28 days of a dose (Table 5) was not included in the simulation.

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects with selected metastatic solid tumor types in Part 1 and 750 subjects with metastatic NSCLC in Part 2 will be randomized prior to receiving the fifth cycle of platinum-based chemotherapy.. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their metastatic disease, whichever comes first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

5. TABLE OF EVENTS

Table 7: Sotatercept (ACE-011) Schedule of Assessments

	Screening Period	Treatment Period									Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)										
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Complete Medical History	X																	
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X			X		X		X	X	X	X	X	X	X	
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X		X	X	X	X	X	
12-Lead Electrocardiogram (ECG) – **Part 1**[c]	X	X	X				X				X							
12-Lead Electrocardiogram (ECG) – **Part 2**[c]	X	X									X							
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[f]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X							
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X		X					
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X	X	X	X	X	X	X	
FSH and LH – Males and Females	X	X	X				X		X		X			X			X	
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X			X			X	
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X			X			X	
TSH[k]	X	X					X[k]						X					

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Sotatercept (ACE-011) drug antibody test (pre-dose)		X		X			X				X			X		X		
Bone Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[l] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X			X				
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X													X				
Activin A and other proteins/biomarkers in blood (serum) (pre-dose study treatment in a subset of subjects)		X	X				X					X						
Activin and other proteins/biomarkers in archival tumor tissue (Part 2 only - optional)	X																	
Pharmacokinetics– **Part 1** and **Part 2**)[n]		Refer to Table 8 and Table 9 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X[o]	≤ Every 9 weeks or as per standard of care at study site																
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose only AEs assessed as related to study treatment are to be reported																
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X		X			X	X	

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Concomitant Procedures	X	X		X			X		X		X		X			X	X	
Hospitalizations (Record)	X	X		X			X		X		X		X			X	X	
Randomization		X																
Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X											
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice																
Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[v]																		X
Post Treatment Anti-Neoplastic Therapy											X	X	X	X	X	X	X	X

[a]Include cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and metastatic site involvement. Record prior ESA history, starting at selected solid tumor diagnosis . Record RBC transfusion history, starting from diagnosis of metastatic disease, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) or sotatercept (ACE-011)/ placebo dose, at Treatment Discontinuation, and at Study Discontinuation. Blood pressure should be confirmed by two measurements obtained five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: For **Part 1**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011) dose, Day 8 post dose 1, every sotatercept (ACE-011) dosing Visit (post-dose) and at end of study treatment (day 43 post last dose).

For **Part 2**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011)/placebo dose and at end of study treatment (day 43 post last dose).

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days **prior** to the start of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo during the Treatment Period. Subjects must agree to use highly effective birth control measures (e.g., oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo to ensure levels are within normal limits and that sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (Part 1).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the Treatment Period, every month (except month 1) during the Post Treatment Follow-Up Period and at study discontinuation .

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and end of study treatment (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. For full PK assessment, weekly after first dose of sotatercept (ACE-011).

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at 2 month post-treatment follow-up visit.

[l]Bone Biomarkers- Collected for **full** PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. For all other subjects collected prior to dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan of lumbar spine and hip to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15, 30 and 45 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.

Pharmacokinetics (**Part 2**): Sparse PK blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011) in approximately 300 (40%) of 750 subjects. Sotatercept (ACE-011) doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8 and Table 9, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening Period tumor assessments may be performed within six weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected. Following randomization, tumor assessments will be performed ≤ every 9 weeks or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments, FACIT Fatigue Scale (Version 4) – all subjects and LCSS questionnaire – only subjects with NSCLC, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins an every 3 week platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo **may be given at any time following the first dose of first-line platinum-based chemotherapy. Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

[r]Platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded.

[s]Pemetrexed or erlotinib maintenance therapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose corresponds to the end of Treatment Period. Subjects who discontinue the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo Treatment Period early will continue to the Post Treatment Follow-Up Period and be followed for up to 6 months after their last dose of sotatercept (ACE-011)/placebo.

[u]Study Discontinuation visit should occur 12 months after starting treatment with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[v]Survival data will be collected monthly, via telephone contact, following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

Scheduled Time	Time relative to Sotatercept (ACE-011)	Part 1[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days
PT[f] Follow up, 1 month	72 days after final dose	X	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	± 1 week

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first sotatercept (ACE-011) dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first sotatercept (ACE-011) dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 30 subjects (approximately 10 subjects in each dose group).

[d] To be collected in subjects participating in sparse PK sampling and not participating in full PK sampling.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

[f] PT = Post Treatment

Table 9: Schedule of Pharmacokinetic Assessments (Part 2)

Scheduled Time	Time relative to Sotatercept (ACE-011)/placebo dose	Sparse PK[a,b,c]	Collection Window[d]
Dose 1, D1	pre-Dose 1	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	±1 hour
Dose 1, D8	7 days after Dose 1	X	± 3 day
Dose 1, D15	14 days after Dose 1	X	± 3 day
Dose 1, D29	28 days after Dose 1	X	± 3 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	± 3 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	± 3 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	± 3 days
Dose 4, D43 (Dose 5, D1)	pre-Dose 5	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6	X	± 3 days
PT[e] Follow up, 3 month	132 days after final dose	X	± 1 week
PT Follow up, 5 month	192 days after final dose	X	± 1 week

[a] For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

[d] Except for Day 1 (Dose 1, D1), the collection window will be the same as the visit window defined in Table 7.

[e] PT = Post Treatment

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed ≤ 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization or as per study site standard of care. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed ≤ 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac, renal and thromboembolic events
- Cancer history, including date of original diagnosis, histopathology, clinical stage at screening, date of metastatic stage and site involvement
- Prior ESA treatment history starting from initial diagnosis of one of the selected solid tumors
- RBC transfusion history starting from diagnosis of metastatic disease at a minimum of up two months prior to randomization
- 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, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration
- Serum chemistry, hematology, absolute reticulocyte count to be assessed within 14 days of randomization
- Creatinine clearance (per Cockroft-Gault formula) within 14 days prior to study treatment administration
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and RBC folate levels

- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Estrogen and estradiol – females only
- TSH
- Bone imaging – DXA scan (optional at selected sites)
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

- In **Part 2**, subjects meeting all inclusion and exclusion criteria will enter into the Treatment Period and be randomized by a double-blind procedure utilizing IVRS to receive sotatercept (ACE-011) or placebo (1:1 ratio).
- A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days during the Treatment Period, as specified in the Table of Events (see Section 5).

In **Part 1**, the Treatment Period will last approximately 6 months, where subjects randomized to sotatercept (ACE-011) will receive treatment on Day 1 every 42 days for a planned 4 doses.

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional 2 doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration.
- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses collected at 7, 14 days and 28 days post-dose.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 43 days after last dose of study treatment

- Vitamin B12 and RBC folate levels at last dose and 43 days after last dose of study treatment
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (**pre-dose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre- dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in archival tumor tissue (Part 2 only)
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or per standard of care at the study site, starting from the previous [screening] tumor assessment) and following the chemotherapy schedule
- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and all AE/SAE reporting (regardless of causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or maintenance therapy
- Administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo at: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will enter the Post Treatment Follow-Up Period and be followed for 6 months after their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Upon completion of the Post Treatment Follow-Up Period,

subjects will have a discontinuation visit and be followed for survival for up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

Following completion or early discontinuation from the Treatment Period, subjects will enter the Post Treatment Follow-Up Period and continue to be followed for 6 months after their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every month. The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)
- Vitamin B12 and RBC folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH (at 2 month end of treatment follow-up visit)
- Serum for sotatercept (ACE-011) drug antibody test (pre-sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Bone imaging – DXA scan (optional at selected sites-performed at 3 month end of treatment follow-up visit)
- Activin A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood at 1 month end of treatment follow-up visit)
- Pharmacokinetics

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or as per standard of care at the study site, and following the chemotherapy schedule
- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Study Discontinuation

Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects.

Subjects who discontinue from treatment early will enter the Post Treatment Follow-Up Period and be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Follow-up for twelve months for TTP and PFS will be performed from the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/Placebo. Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) – if Study Discontinuation date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Estrogen and estradiol – females only

- Dihyroepiandosterone and Testosterone (free and total) – males only
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1) (PFS at 12 months)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Survival Follow-Up Period:

Monthly collection of survival data will begin following the Study Discontinuation Visit and continue for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Additional Procedure Descriptions:

Central ECG

Part 1 – ECGs will be performed and read per Central ECG vendor.

Part 2 – ECGs will be performed locally and read per Central ECG vendor.

Please refer to vendor manual for procedures.

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone) will be performed by a central laboratory.

Please refer to vendor manual for procedures.

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

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in a subset of subjects (Part 2 only).

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin will be evaluated in all subjects.

Pharmacokinetics

- Part 1 -Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.
- Part 2- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either Part 1 full or sparse PK assessments or in Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Detailed PK sampling schedule is presented in Table 8 and Table 9: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

Bone Biomarkers

Bone biomarkers will be evaluated in all subjects. The serum and urine bone biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

Bone Imaging - optional

DXA scan to evaluate overall bone health will be performed on approximately 200 subjects at select site(s).

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) will be completed by all subjects and LCSS questionnaire will be completed for subjects with NSCLC. Each assessment will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Independent External Radiology Review (Part 2 Only)

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC) (Part 2 Only)

The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each subject. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

7. STUDY POPULATION

Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given, every three weeks, for the treatment of a selected metastatic solid tumor at the time of randomization: metastatic NSCLC, metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy. Subjects may have already received up to 4 cycles of this current platinum-based regimen and must be randomized prior to receiving Cycle 5. It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.

Subjects must not have received any other regimens of platinum containing chemotherapy for the first-line treatment of metastatic solid tumors prior to the regimen they are receiving at the time of randomization.

7.1. Number of Subjects

This platinum-based CIA study will enroll approximately 840 subjects, approximately 90 subjects with selected metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**.

In **Part 1**, up to 90 subjects will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC
- Sotatercept (ACE-011) 45 mg SC

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)

In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in Part 1, or placebo at a ratio of 1:1. Subjects will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
4. ECOG Performance Status 0-1 vs. 2

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. **Part 1** - Histologically confirmed (cytology or biopsy) solid tumor malignancy, including metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy.

   Part 2 - Histologically confirmed (cytology or biopsy) non-small cell lung cancer.
3. Documented metastatic disease
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L)
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function (creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin concomitantly administered)
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤ 5.0 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL), previous hypercalcemia treatment is allowed
6. Subjects may have received up to 4 cycles of their first regimen of first line platinum-based chemotherapy treatment.
   - For Part 1- any platinum-based regimen approved for the specific indication
   - For Part 2 -allowed regimens for the treatment of metastatic NSCLC are:
     - gemcitabine plus cisplatin or carboplatin ± bevacizumab
     - pemetrexed plus cisplatin or carboplatin ± bevacizumab
     - taxanes plus cisplatin or carboplatin ± bevacizumab

   At randomization, subjects are expected to be eligible to continue to receive at least two additional platinum-based chemotherapy cycles while on study.
7. ≥ 28 days must have elapsed since previous treatment with ESA
8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 30 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)

10. 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 at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).

11. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, even if he has undergone a successful vasectomy.
12. Life expectancy of ≥ 3 months.
13. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.
14. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C] at the time of screening, including Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g., asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non- hematological events (e.g., nausea, vomiting, fatigue, or muscle or bone/joint pain), occurring during the chemotherapy period and resolving.

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 subject participation in the study, at the discretion of the Investigator.
3. History of prior regimen(s) of platinum-based chemotherapy for metastatic disease and/or history of adjuvant platinum-based chemotherapy with last dose received less than six months prior to the start of current first-line platinum-based chemotherapy for metastatic disease.
4. CNS metastases (exception: subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks prior to randomization).
5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying malignancy.
6. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).
7. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.
8. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
9. 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).
10. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
11. Uncontrolled hypertension. If hypertension is considered clinically stable, systolic blood pressure (SBP) must be < 150 mmHg or diastolic blood pressure (DBP) must be < 100 mmHg.
12. Known infection with human immunodeficiency virus (HIV).
13. Known active hepatitis B or C antibody defined by positive serology.
14. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.
15. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
16. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.
17. Urine protein / creatinine ratio > 1.0.

18. 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.
19. Any prior use of sotatercept (ACE-011).
20. Pregnant or lactating females or females planning to become pregnant.
21. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).
22. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

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

Note: Subjects receiving Process IIa clinical drug product will begin to receive Process III clinical drug product as soon as it becomes available at the study site.

Process IIa Clinical Drug Product – Frozen Liquid Formulation:

The clinical drug product consists of sotatercept (ACE-011) in phosphate buffered saline (PBS), pH 7.5. It is supplied as a 1 mL solution of 50 mg/mL sotatercept (ACE-011) in labeled, rubber stoppered, 2 mL vials providing 50 mg per vial. The recommended storage temperature for sotatercept (ACE-011) Process IIa frozen liquid drug product is ≤ -65˚C (colder than -65˚C) until thawed for administration. Vials of sotatercept (ACE-011) frozen liquid must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.

Process III Clinical Drug Product- Lyophilized Powder:

The clinical drug product consists of sotatercept (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 sotatercept (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 sotatercept (ACE-011). The reconstituted sotatercept (ACE-011), in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.

Placebo (Part 2 Only):

In **Part 2**, the sotatercept (ACE-011) placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Sterile, normal saline will be supplied by the investigational site's pharmacy. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

8.2. Treatment Administration and Schedule

Sotatercept (ACE-011) or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization all subjects must be receiving their first-line regimen of platinum-containing chemotherapy, given every three weeks, for the treatment of a metastatic solid tumor. Subjects will be randomized to this study during the time period in which they are receiving Cycle 1 through Cycle 4 of this regimen. Subjects must not have received any prior regimens of first line platinum-based chemotherapy for a metastatic solid tumor.

Allowed concomitant platinum-based chemotherapy regimens are:

- For Part 1- any platinum-based regimen approved for the specific indication
- For Part 2 -allowed regimens for the treatment of metastatic NSCLC are:
  - gemcitabine plus cisplatin or carboplatin ± bevacizumab
  - pemetrexed plus cisplatin or carboplatin ± bevacizumab
  - taxanes plus cisplatin or carboplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Subjects may receive 4-6 cycles of the allowed platinum-based regimen selected by the Investigator. Up to 2 additional cycles (8 total cycles) of platinum-based chemotherapy may be given as determined by cancer response. Platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

While on study treatment subjects will be allowed to receive maintenance therapy with a pemetrexed or erlotinib-containing regimen when indicated.

In **Part 1** and **Part 2**, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb. Dose delays of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

In **Part 1**, subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The following are decision rules for dose determination in Part 1 in order to move forward to Part 2:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions

and/or ESAs. In order to determine the dose of sotatercept (ACE-011) to be used in Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) dose 1/day 1 through and including dose 2/day 43 (prior to dose 3).

- In addition to the hematopoietic response, safety profile, dose modifications and extent of exposure will be taken into account for dose level selection for Part 2.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

In **Part 2**, subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in Part 1) or placebo.

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo starting on Day 1 (one SC dose every 42 days) and continuing during the six-month (Part 1) or nine-month (Part 2) Treatment Period, as outlined in the Table of Events (see Section 5).

In **Part 1**, subjects will be randomized to receive one of three dose levels of sotatercept (ACE-011), with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive sotatercept (ACE-011) or placebo at a ratio of 1:1.

Each subject will return to the site on each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered **at any time after the first cycle and prior to the fifth cycle of first-line platinum-based chemotherapy. Subsequent doses** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their metastatic disease, whichever comes first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of metastatic disease that requires the initiation of another treatment.

Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

8.2.3. Discontinuation

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100mmHg) confirmed by two measurements obtained five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0 or > 2.0 (if bevacizumab [Avastin®] is concomitantly administered)
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.
- In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months from first dose of study treatment.
- Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo Dose Modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL
  - In **Part 2:** > 3 dose reductions and/or delays
- Disease Progression
- Withdrawal of consent

- Death
- Lost to follow-up
- Protocol violation

The reason for treatment discontinuation should be recorded in the eCRF 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 (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months from first dose of study treatment.
- 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)
- Disease progression
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF 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.

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to 4 doses of sotatercept (ACE-011) in Part 1. In Part 2, subjects will be randomized at a ratio of 1:1 and receive up to 4 doses of study treatment and may receive 2 additional doses of sotatercept (ACE-011)/placebo, if clinically indicated, at the discretion of the Investigator. A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

8.4. Packaging and Labeling

The label(s) for investigational product (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 sotatercept (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 secured location. The investigational site must maintain accurate records demonstrating dates and amounts of sotatercept (ACE-011) received, to whom it was administered (subject-by-subject accounting), and accounts of any sotatercept (ACE-011) accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of sotatercept (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 sotatercept (ACE-011) to the Sponsor at the end of the study, or the sotatercept (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 investigational medicinal product.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF 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

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 and 7.3 Inclusion Criteria and 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 eCRF throughout the course of the study.

Concomitant therapies considered as supportive care are acceptable while participating in this study including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting and palliative radiation, bisphosphonates and denosumab (Refer to Inclusion Criterion, Section 7.2) for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

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.

Iron supplementation

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

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study sponsor and Medical Monitor, as well as to the clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

In **Part 1**, all subjects who receive an ESA will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up Period. In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up Period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the Treatment Period as follows: **The unblinded pharmacist will ensure that subjects randomized to receive treatment with**

sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo. The investigator, site personnel and subject will remain blinded.

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered >7 days from the date of the RBC transfusion.

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate therapy (see Section 7.2), other than for the treatment of hypercalcemia, must not be started on study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with selected metastatic solid tumor types treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. In **Part 1**, subjects will be randomized to one of three doses of sotatercept (ACE-011) plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected sotatercept (ACE-011) dose determined from Part 1 plus platinum-based chemotherapy. Data from Part 1 will not be combined with data from Part 2 in all safety and efficacy analyses.

A DMC will be used to monitor the study conduct.

10.2. Study Population Definitions

- Three study populations will be used for analyses.
- The Intent-to-Treat (ITT) Population – All randomized subjects.
- Safety Population – All subjects who take at least one dose of study medication.
- Efficacy Evaluable (EE) Population – All ITT subjects who take at least one dose of study medication and have baseline and at least one post-baseline efficacy assessment without major protocol deviation.

10.3. Sample Size and Power Considerations

In **Part 1**, up to 90 subjects will be randomized among three dosing groups. This sample size is for the purpose of hypothesis generation. However, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a two-sided significance level (alpha) of 0.05.

In **Part 2**, subjects will be enrolled in two stages. In the first stage, approximately 180 subjects will be randomized in a 1:1 ratio to the selected sotatercept (ACE-011) dose group or placebo group. An interim analysis of transfusion rate will be performed after these 180 subjects have received at least two doses of sotatercept (ACE-011)/placebo, and have been followed for at least 4 months from randomization. A Data Monitoring Committee will review the results and provide recommendations on continuing or stopping the study. Based on the results of the futility analysis, further enrollment in the second stage of Part 2 of the study could be continued.

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in Part 2 (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude

more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics by treatment arm, 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 by treatment arm. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

In **Part 1**, the primary endpoint will be the hematopoietic response defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the date of randomization. It will be estimated based on Kaplan-Meier method for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects who have documented RBC transfusion(s) from randomization until the last dose of concomitant platinum-based chemotherapy plus 30 days or from the initiation date of non-platinum-based chemotherapy, whichever is earlier, will be considered as having the event on the date of first RBC transfusion. Subjects who are discontinued from study treatment due to reasons other than disease progression or death will be considered as having the event on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Subjects who discontinue from study treatment due to disease progression or death will be censored on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Otherwise subjects will be censored on the date of last contact, or on the date of last dose of concomitant platinum-based chemotherapy plus 30 days or on the initiation date of non-platinum-based chemotherapy, whichever is earliest. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test, and the associated hazard ratio and 95% confidence interval will be provided using Cox proportional hazard model. The proportion of subjects receiving a transfusion based on Kaplan-Meier estimates at specific time points will also be provided by treatment arms.

As secondary endpoints for Part 2 of the study, time to progression, progression free survival and overall survival will be analyzed based on the ITT population.

Time to progression (TTP) is defined as the time between the randomization date and date of disease progression. **Disease progression is based on the IRC reviewed progression date.** If a subject dies due to reasons other than disease progression, the subject will be censored at the death date. If a subject does not have disease progression, then the subject will be censored at the last tumor assessment (prior to or on the first day of the first subsequent antitumor therapy).

Progression free survival (PFS) is defined as the time between the randomization and disease progression or death. **Disease progression is based on the IRC reviewed progression date.** Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the subject is censored at the time of last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. The date of progression is taken as the earliest date of: Date of PD as evaluation of response, date of new lesion on tumor measurements page, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who did not progress nor died (lost to follow-up or still being treated without documented disease progression or started subsequent antitumor therapy) will be censored at the date of the last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. PFS based on investigators' assessment will also be analyzed.

Overall survival (OS) is defined as the time between the randomization and death. A subject who dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the distribution function, six-month and one-year survival rates, as well as the medians and 95% confidence intervals will be provided. The stratified log rank test will be used to compare the distributions of TTP, PFS and OS respectively. The stratification factors are described in Section 4.1 . The associated hazard ratios and confidence intervals will be provided using stratified Cox proportional hazard model respectively for each endpoint.

Sensitivity analyses will be performed on TTP, PFS, and efficacy analyses will also be performed using EE population. Data listings will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.

10.7. Safety Analysis

All safety subjects will be used for safety analyses. Sotatercept (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 study part and treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized.

Safety information obtained during the Post Treatment Follow-Up Period during each segment will be incorporated into these analyses.

10.8. Interim Analysis

There are two interim analyses planned for this study. At the first interim analysis, the transfusion rate result will be used for go/no go decision, and overall survival will also be analyzed. At the second interim analysis, only the overall survival will be analyzed.

The first interim analysis on transfusion rate will be conducted after the first 180 eligible subjects randomized in Part 2 of the study (stage 1) who have received at least two doses of sotatercept (ACE-011)/placebo, have been followed for at least 4 months from randomization. This sample size would allow at least 90% power to detect a 15% difference between two arms (sotatercept [ACE-011] arm 15% vs. placebo 30%) in 4 month transfusion rates at two-sided 5% significance level based on the stratified log rank test and the assumption of exponential distribution for time to RBC transfusion. If the p-value at the interim analysis does exceed significance level of 0.05, the result will be considered as lack of efficacy. If the p-value is less than or equal to 0.05, additional subjects will be enrolled and the study will move on to the Part 2; however, the futility analysis result based on RBC transfusion rate may be up to DMC evaluation. For superiority, Type I error 0.0001 will be spent at this interim for transfusion rate, and the remaining 0.0499 will be spent at the final analysis after 750 subjects being enrolled.

Overall survival will also be analyzed at this interim, Type I error spending will be based on O'Brien and Fleming Boundary.

The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. Type I error spending will be based on O'Brien and Fleming boundary.

The final analysis will be performed when approximately 536 deaths are observed in Part 2.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of Part 1. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC_{42}, and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

In exploratory population PK analysis, covariates to be tested may include type of chemotherapy, the presence of anti-sotatercept (ACE-011) antibodies, demographics (age, race, gender, and body weight), markers for hepatic and renal function, and other factors as deemed appropriate. Both full and sparse PK data will be included for population PK analyses.

The relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) will be explored.

10.10. Data Monitoring Committee (DMC)

A DMC will review safety and efficacy data to ensure the protection of study subjects. The DMC will receive periodic updates of all serious treatment-related toxicities and SAEs leading to deaths from all causes. The first planned review by the DMC will be conducted following the randomization and treatment of twenty subjects. The DMC will continue to monitor safety on an ongoing basis including recommendation of sotatercept (ACE-011) dose selection for Part 2. The first interim analysis will be conducted after the first 180 eligible subjects in Part 2 of the study (stage 1) have been followed for at least 4 months for RBC transfusion rate. The second interim analysis will be performed when approximately 265 deaths are observed in Part 2. The final analysis will be performed when approximately 536 deaths are observed in Part 2.

Ad hoc meetings will be scheduled as needed.

The DMC will have a consultative role with respect to the Sponsor. The Sponsor will make the final decision regarding the recommendation proposed by the committee. A separate DMC charter will detail the activities of this committee.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. Seriousness

An 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of 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 (delay) 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 an SAE.

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

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

The female subject should be referred to an 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 investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Immediate 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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (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.

11.6. 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.

11.7. Expedited Reporting of Adverse Events

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

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics

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

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (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

Please refer to Section 8.2.3.

Stopping Rules

In addition to Celgene routine pharmacovigilance surveillance, a DMC will review unblinded data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

In both Part 1 and Part 2 the blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.

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 eCRFs 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via an electronic data capture (EDC) system rather than paper. Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. The Clinical team and investigational site personnel will be alerted of discrepant data by the functionality of the system. 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMEA, 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

Aapro M, Vaupel P. Erythropoietin: effects on life expectancy in patients with cancer-related anemia. *Curr Med Res Opin.* 2006; 22(suppl 4):5-13.

Carlos JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer.* 2001; 91:2214-2221.

Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue, and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol.* 2004; 15:979-986.

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. J Bone Miner Res 2010; 25 (12), 2633-46, Erroatum in J Bone Miner Res 2011; 26 (2), 439

Chen Y-G, Lui HM, Lin S-L, Lee JM, and Ying S-Y. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. *Exp Biol Med* 2002; 227: 75-87.

Dang TP, Carbone DP: Cancer of the Lung, in DeVita, VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 8th edition, Philadelphia, PA. Lippincott Williams & Wilkens, 2008, 887-971.

Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F Version 4. *http://www.facit.org/qview/qlist.aspx*, last accessed 21Jul2010.

Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer.* 1999; 86:1528-1536.

Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *Journal of the National Cancer Institute* 1999, 91, 1616-1634.

Hollen, PJ, Gralla, RJ, Kris, MG, and Potanovich, LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). European Journal of Cancer, 1993; 29A, S51-S58.

Hollen, PJ, Gralla, RJ, Kris, MG, & Cox, C. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1994a; 2, 213-222.

Hollen, PJ, Gralla, RJ, Kris, MG, Cox, C, Belani, CP, Grunberg, SM, Crawford, J, and Neidhart, JA. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer, 1994b; 73, 2087-98.

Hollen PJ, Gralla RJ, Kris MG 'Lung Cancer Symptom Scale (LCSS)', *Administration, Scoring and Procedures Manual*, (1995) Ver.1.1.

Hollen, PJ, Gralla, RJ, Kris, MG, Eberly, SW, and Cox, C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1999; 7, 140-148.

Hong WK, Tsao AS, in Lung Carcinoma: Tumors of the Lungs: Merck Manuals Online Medical Library for Healthcare Professionals, 2008.
http://www.merck.com/mmpe/print/sec05/ch062/ch062b.html

Laurie SA, Jeyabalan N, Nicholas G, Dahrouge S. Association between anemia arising during therapy and outcomes of chemoradiation for limited small-cell lung cancer. *J Thorac Oncol.* 2006;146-151.

Lotinun S, Fajardo RJ, Pearsall RS, Bouxsein ML, and Baron R. A soluble activin receptor type IIA fusion protein, ACE-011, increases bone mass by stimulating bone formation and inhibiting bone resorption in cynomolgus monkeys. ASBMR 30th annual meeting, 2008.

MacRae R, Shyr Y, Jonson D, Choy H. Declining hemoglobin Turing chemoradiotherapy for locally advanced non-small cell lung cancer is significant. *Radiother Oncol.* 2002;64:37-40.

Mathews LS. Activin receptors and cellular signaling by the receptor serine kinase family. *Endocr Rev* 1994; 15: 310-25.

Murata M, Onomichi K, Eto Y, Shibai H, and Muramatsu M. Expression of erythroid differentiation factor (EDF) in Chinese hamster ovary cells. *Biochem Biophys Res Commun* 1988; 151: 230-5.

Nakao K, Kosaka M and Saito S. Effects of erythroid differentiation factor (EDF) on proliferation and differentiation of human hematopoietic progenitors. *Exp Hematol* 1991; 19: 1090-5.

National Heart, Lung, and Blood Institute, National Institutes of Health. New York Heart Association Classification. 2008.

NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, V.2. 2010 http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf; 2009.

Non-small Cell Lung cancer Collaborative Group 'Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials', *British Medical Journal* 1995 vol. 311, no.7010, 899-909.

Obermair A, Cheuk R, Horwood K, et al. Anemia before and during concurrent chemoradiotherapy in patients with cervical carcinoma: effect on progression-free survival. *Int J Gynecol Cancer.* 2003; 13:633-639.

Oken, MM., Creech, R.H., Tormey, D.C., et. al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982; 5:649-655.

Parker SL, Tong T, Bolden S, et. al. Cancer statistics, 1997. *CA Cancer J Clin*, 1997, 47, no. 1, 5-27.

Pearsall RS, Canalis E, Cornwall-Brady M, Underwood KW, Haigis B, Ucran J, Kumar R, Pobre E, Grinberg A, Werner ED, Glatt V, Stadmeyer L, Smith D, Seehra J, and Bouxsein ML. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. Proc Natl Acad Sci USA 2008, 105: 7082-7.

Perrien DS, Akel NS, Edwards PK, et. al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology* 2007; 148: 1654-65.

Rivier J, Spiess J, McClintock R, Vaughan J and Vale W. Purification and partial characterization of inhibin from porcine follicular fluid. *Biochem Biophys Res Commun* 1985; 133: 120-7.

Rossi A, Maione P, Gridelli C Cetuximab in advanced non-small cell lung cancer. *Critical Reviews in Oncology/Hematology*, 2006 59, 139-149.

Ruckle J, Jacobs M, Kramer W, et. al. A single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res* 2009; 24 (4): 744-52.

Sandler A, Gray R, Perry M, et al Paclitaxel-Carboplatin alone or with Bevacizumab for Non Small Cell Lung Cancer, *NEJM*, 2006 vol.355, no.24, 2542-50.

Scagliotti G, Parikh P, von Pawel J, et al Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve patients With Advanced-Stage Non-Small-Cell Lung Cancer, JCO, 2008, 26 (21): 3543-51.

Schiller J, Harrington D, Belani C, et al Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. *Am J Health Syst Pharm.* 2007; 64 (suppl 2):S5-S13.

Seder C, Hartojo W, Lin L, et al Upregulated INHBA Expression May Promote Cell Proliferation and Is Associated with Poor Survival in Lung Adenocarcinoma, Neoplasia, 2009, 11: 388-396.

Shedden K, Taylor J, Enkemann S, et al Gene Expression-Based Survival prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validation Study: Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Nat Med, 2008, 14 (8): 822-827.

Shiozaki M, Sakai R, Tabuchi M, et. al. In vivo treatment with erythroid differentiation factor (EDF/activin A) increases erythroid precursors (CFU-E and BFU-E) in mice. *Biochem Biophys Res Commun* 1989; 165: 1155-61.

Shiozaki M, Sakai R, Tabuchi M, et. al. Evidence for the participation of endogenous activin A/erythroid differentiation factor in the regulation of erythropoiesis. *Proc Natl Acad Sci USA* 1992; 89: 1553-6.

Vansteenkiste J, Pirker R, Massuti B, et. al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute, 2002, 94: 16: 1211-1220.

Woodruff TK. Regulation of cellular and system function by activin. *Biochem Pharmacol* 1998; 55: 953-63.

Ying S-Y. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine Rev* 1988; 9: 267-93.

19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Terms	**Definition**
Measurable disease	The presence of at least one measurable lesion by CT or MRI. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions	Lesions that can be accurately measured in least one dimension by CT scan with longest diameter $\geq$ 10 mm (CT scan thickness no greater than 5 mm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Non-measurable lesion	All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

RECIST Criteria-Response Evaluation

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
***Partial Response (PR)*:**	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
***Stable Disease (SD)*:**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
***Progressive Disease (PD)*:**	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

RECIST Criteria-Response Evaluation (continued)

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of best overall response	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (2009). European Journal of Cancer 45, 228-247.

Appendix B: 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 10: 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 C: 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 D: New York Heart Association - Classification of Heart Failure

Table 11: 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

– SUMMARY OF CHANGES –

AMENDMENT NO. 3

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
ORIGINAL DATE:	17 SEPTEMBER 2010
AMENDMENT No. 1 DATE:	22 MARCH 2011
AMENDMENT No. 2 DATE:	27 JUNE 2011
AMENDMENT No. 3 DATE:	01 NOVEMBER 2011
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

Contact Information:

PPD

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

02 NOV 2011

dd mmm yyyy

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below. These changes were based on feedback obtained from investigators/sites, key opinion leaders and internal discussions:

- Modified to expand eligible tumor types to include advanced or metastatic solid tumors treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent, in **Part 1** of the study.
- Modified to confirm only metastatic NSCLC subjects are eligible for **Part 2** of the study.
- Clarification that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals.
- Revised to allow subjects to be randomized while receiving maintenance therapy following completion of treatment with platinum-based chemotherapy.
- Modified to remove all reference to ACE-011 Process IIa Clinical Drug Product - Frozen Liquid Formulation. Only ACE-011 Process III Clinical Drug Product – Lyophilized Powder Formulation will be administered in this study.
- Expanded allowable concomitant and maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents) which are approved for a given tumor type, in addition to platinum-based chemotherapy.
- Clarification of data collection history of prior use of erythropoietic stimulating agents and red blood cell transfusion.
- Clarification of timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.
- Clarification that subject discontinuation from treatment and/or study due to protocol violation will be determined by the Sponsor.
- Clarification that monthly survival data can be collected via telephone contact.
- Addition of description of accrual and statistical analysis details in **Part 2** of the study in the Introduction Section.
- Clarification of description of sotatercept (ACE-011) as a recombinant human fusion protein.
- Toxicology and Potential Risks for Human Use – Revision of sections to provide updated non-clinical study data and revised safety multiples based on current human exposure data and/or projections.
- Correction of typographical error in hypertension measurement criteria determining sotatercept (ACE-011) dose delay.
- Correction of hemoglobin collection day 21 post first dose of sotatercept (ACE-011).

- Revision of Table 7: Schedule of Assessments:
    a. Footnote 'a' - modified to expand eligible tumor types to include advanced solid tumors and clarify data collection of prior use of erythropoietic stimulating agents and red blood cell transfusion.
    b. Footnote 'b' – clarification of timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.
    c. Footnote 'e', 'f', 'g' – clarification of screening period for hematology, absolute reticulocyte, serum chemistry and creatinine clearance assessments.
    d. Footnote 'q' – clarification that subjects must have received at least one cycle of platinum based chemotherapy.
    d. Footnote 's' – revised description of allowable concomitant and maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents).
    e. Footnote 'v' – clarification that monthly survival data can be collected via telephone contact.
- Revision of Inclusion Criteria:
    a. Modified to expand study population in Part 1 of the study to include advanced or metastatic solid tumor types treated with first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
    b. Clarification that hemoglobin levels ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L) must be attributed to chemotherapy-induced anemia.
    c. Consolidation of definition of adequate renal function in Inclusion Criteria to include urine protein / creatinine ratio.
    d. Expand allowable corrected calcium levels.
    e. Clarification that subjects must have received at least one cycle of platinum-based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals OR be receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Revision of Exclusion Criteria:
    a. Clarification of allowed prior type and setting of platinum-based chemotherapy in **Part 2** only.
    b. Deletion of exclusion of subjects with second malignancy within three years prior to randomization due to frequency of second malignancies in these patient populations.
    c. Correction of typographical error in blood pressure measurement exclusion.
    d. Deletion of urine protein / creatinine ratio exclusion criterion. Moved to define adequate renal function in Inclusion Criteria.
- Revision of Section 9 – Concomitant Medications and Procedures:

a. Deletion of reference to Section 7.2, not applicable following Amendment 2.

b. Further clarify when bisphosphonate and denosumab therapy for metastatic bone disease is allowed to begin.

Other administrative changes (e.g., correction of typographical errors, editorial changes, etc.) 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: Title Page (page 1)

Revised Text:

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ~~SELECTED~~ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

Rationale:

Modified to:

- Expand reference to study population to include advanced or metastatic solid tumor types treated with platinum-based chemotherapy.

2.2. Section: Protocol Summary (pages 6-12)

Revised Text:

Study Title

An open-label randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Advanced or Metastatic Solid Tumors

Part 1 – ~~Solid tumors, including~~Advanced or metastatic ~~non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is~~solid tumors treated with ≥ first~~-~~line platinum~~-~~based chemotherapy~~. No~~, excluding those solid tumors ~~other than those tumor types listed above should be considered for this study.~~ treated with curative intent.

Part 2 - Metastatic NSCLC~~.~~

Objectives

The primary objectives are:

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent.

– – – – – – – – – – –

Study Design

This is an open-label, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy for CIA in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine a dose of sotatercept (ACE-011) that results in a hematopoietic response in the treatment of CIA in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapy, excluding those solid tumors treated with curative intent. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to

detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

– – – – – – – – – – –

Study Population

At the time of randomization~~, all~~ in **Part 1** and **Part 2**, subjects must ~~be receiving their first regimen of first-line platinum-based chemotherapy, given every three weeks, for the treatment of one of the selected metastatic solid tumor types, which include: metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer. Subjects may~~ have already received:

- at least one cycle and up to 4 cycles (q3w schedule) of ~~this current~~ platinum-based ~~regimen~~chemotherapy and ~~must~~ be randomized prior to receiving Cycle 5~~.~~

OR

- at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.~~

~~Subjects~~In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing ~~regimens of~~ chemotherapy for ~~the~~ first-line treatment ~~of a metastatic solid tumor~~ prior to the regimen they are receiving at the time of randomization.

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents) which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

– – – – – – – – – – –

Screening Period (28 days):

– – – – – – – – – – –

Prior erythropoietic stimulating agent (ESA) treatment history starting from the initial ~~diagnosis of selected~~ solid tumor ~~types~~diagnosis and red blood cell (RBC) transfusion history starting from diagnosis of advanced or metastatic disease, at a minimum of up to two months prior to randomization will be collected.

Treatment Period (up to 6-9 months):

– – – – – – – – – – –

In **Part 1** (the dose-ranging portion of the study), subjects with ~~selected~~advanced or metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

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In **Part 1**, blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group~~.~~ investigated. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment. In **Part 2**, blood samples will be collected for the sparse PK assessment that will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either **Part 1** full or sparse PK assessments or Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100mmHg), confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.

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  - Urine protein / creatinine ratio > 1.0; or > 2.0 ~~(~~if bevacizumab ~~[~~(Avastin®~~]~~®) is concomitantly administered~~)~~

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- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months ~~from~~after first dose of study treatment.

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- Protocol violation - as determined by the Sponsor

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Post Treatment Follow-Up Period (monthly visits for up to 6 months)

Subjects who enter the Post Treatment Follow-Up Period will be followed monthly for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to one year from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their ~~NSCLC~~advanced or metastatic disease, whichever occurs first.

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months ~~from~~after first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse event(s)
- Disease progression
- Protocol violation

Survival Follow-up Period (monthly for up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo)

In both **Part 1** and **Part 2**, survival data will be collected monthly (can be via telephone contact) for up to 24 months following the subject's first dose of sotatercept (ACE-011) (**Part 1**) or sotatercept (ACE-011)/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit. Data to be collected will include:

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy, if any

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Confirm only metastatic NSCLC subjects are eligible for **Part 2** of the study.

- Clarify that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals.
- Allow subjects to be randomized while receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Expand allowable concomitant and maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents) which are approved for a given tumor type, in addition to platinum-based chemotherapy.
- Clarify prior ESA treatment and RBC transfusion history to be recorded at screening.
- Clarify data collection of prior use of erythropoietic stimulating agents and red blood cell transfusion history.
- Clarify timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.
- Clarify that subject discontinuation from treatment and study due to protocol violation will be determined by the Sponsor.
- Clarify that monthly survival data can be collected via telephone contact.
- Correct various grammatical and editorial errors in Introduction section.

2.3. Section 1: Introduction (pages 19-34)

Revised Text:

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects with ~~selected~~advanced or metastatic solid tumor types treated with platinum-based chemotherapy will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 2 will include only subjects with metastatic NSCLC and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage of **Part 2** approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period. Based on the results of the futility analysis and upon recommendation to continue the study, up to an additional 570 subjects will be randomized in the second stage of **Part 2**, to achieve full study accrual.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

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Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of

sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below. Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

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Toxicology

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Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-sotatercept (ACE-011) antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats as well as demonstration, by immunohistochemistry, of immunoglobulin and complement at the site of injury in monkeys, consistent with immune complex deposition. However, high plasma concentrations of sotatercept (ACE-011) in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (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, the NOAEL from the 6-month monkey study is < 10 mg/kg. A 9-month monkey study to evaluate the effects of lower concentrations of sotatercept (ACE-011) has been completed (refer to Potential Risks for Human Use).~~ in rats and monkeys were 3 (3-month study) and 1 mg/kg (9-month study), respectively.

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Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies were as a result of the expected biologic activity of ~~activin inhibition~~sotatercept 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).~~erythropoiesis.

The most significant toxicity findings are listed below:

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- In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~1.3~~4~~-fold greater than the projected serum exposure in humans at the maximum proposed human dose of 61 mg every 6 weeks~~.~~ in a 50 kg subject. Because sotatercept is a fully human molecule, immunogenicity and, by extension, kidney injury is not expected in humans. In the single- and multiple-dose studies in healthy postmenopausal women, there have been no changes in serum chemistry or urinalysis profiles suggestive of kidney injury. Subjects administered sotatercept (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. These changes were also considered related to the formation of anti-drug antibodies. Findings at 1 mg/kg were limited to mononuclear cell infiltrates and were not considered adverse.

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- 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 in rats at doses ≥ 15 mg/kg (~~15~~2.8-fold greater ~~on a mg/kg basis~~exposure than the projected exposure at the maximum proposed human dose of ~~60~~61 mg every 6 weeks ~~assuming~~in a ~~60~~50 kg ~~person~~subject). In addition, at 50 mg/kg (~~100~~4.7-fold the exposure at the maximum proposed human dose), there was an increase in late fetal death coupled with an overall increase in post implantation loss and a reduction in live litter size, as well as an increase in the incidence of developmental variations of supernumerary ribs with corresponding increases and decreases in thoracic and lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg ~~(~~(1.5-fold greater exposure than the exposure at the maximum proposed human dose of 6~~0~~1 mg every 6 weeks ~~assuming~~in a ~~60~~50 kg ~~person~~subject) based on reduced fetal weights and associated delays in ossification. ~~Although the risks for embryofetal~~

- In an embryo-fetal development ~~effects are considered relatively low given~~study in rabbits, post implantation loss was increased and average litter size and live fetuses were reduced at 15 and 50 mg/kg. In addition, fetal body weights were reduced in all sotatercept dosage groups. Abortions occurred in one rabbit in the ~~large safety margins, precautions~~5 mg/kg dosage group and two rabbits in the 50 mg/kg dosage group. Based on these findings, an NOAEL was not identified in this study and was therefore less than 5 mg/kg (<1.2-fold greater exposure than the exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject)
- Precautions should ~~still~~ be taken to protect females of childbearing potential. Nonclinical studies on breast milk have not been done.

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- 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 6~~0~~1 mg every 6 weeks (estimated AUC_{28d} ~ 4~~5~~248 µg·hr/mL in a 50 kg subject).

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Include additional description of accrual and statistical analysis details in **Part 2** of the study.
- Add description of sotatercept (ACE-011) as a recombinant human fusion protein.
- Incorporate updated toxicology and non-clinical study data and revised safety multiples based on current human exposure data and/or projections.

2.4. Section 2: Study Objectives (page 36)

Revised Text:

2.1. Primary Objective

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with ~~selected~~advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens~~.~~, excluding those solid tumors treated with curative intent,.

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.

2.5. Section 4: Overall Study Design (pages 39-40)

Revised Text:

4.1. Study Design

This is an open-label randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy in subjects with ~~selected~~advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects with ~~selected~~ advanced or metastatic solid tumor types will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study in subjects with metastatic NSCLC.

A DMC will monitor the conduct of the study.

Part 1 is planned to be conducted at selected sites and will be extended to additional global sites for the conduct of **Part 2.**

Study treatment is defined as sotatercept (ACE-011) in **Part 1** and sotatercept (ACE-011)/placebo in **Part 2**.

Three starting sotatercept (ACE-011) dose levels, 15, 30, and 45 mg, were selected for **Part 1** of the study. Up to approximately 90 subjects with ~~selected~~advanced or metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

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The Treatment Period for **Part 1** is approximately six months, which includes up to 4 doses of sotatercept (ACE-011) and for **Part 2** approximately nine months, which includes up to 6 doses of sotatercept (ACE-011/placebo). Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first.

Survival data will be collected monthly for up to 24 months following the subject's first dose of sotatercept (ACE-011) in **Part 1** or sotatercept (ACE-011)/placebo in **Part 2**.

At the time of randomization~~, all~~ in **Part 1** and **Part 2**, subjects must ~~be receiving their first regimen of first-line platinum-based chemotherapy, given every three weeks, for the treatment of a selected metastatic solid tumor. Subjects may~~ have already received:

- at least one cycle and up to 4 cycles (q3w schedule) of ~~this current~~ platinum-based ~~regimen~~chemotherapy and ~~must~~ be randomized prior to receiving Cycle 5~~.~~

OR

- at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.~~

~~Subjects~~In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing ~~regimens of~~ chemotherapy for ~~the~~ first-line treatment ~~of a metastatic solid tumor~~ prior to the regimen they are receiving at the time of randomization.

Rationale:

Modified to:

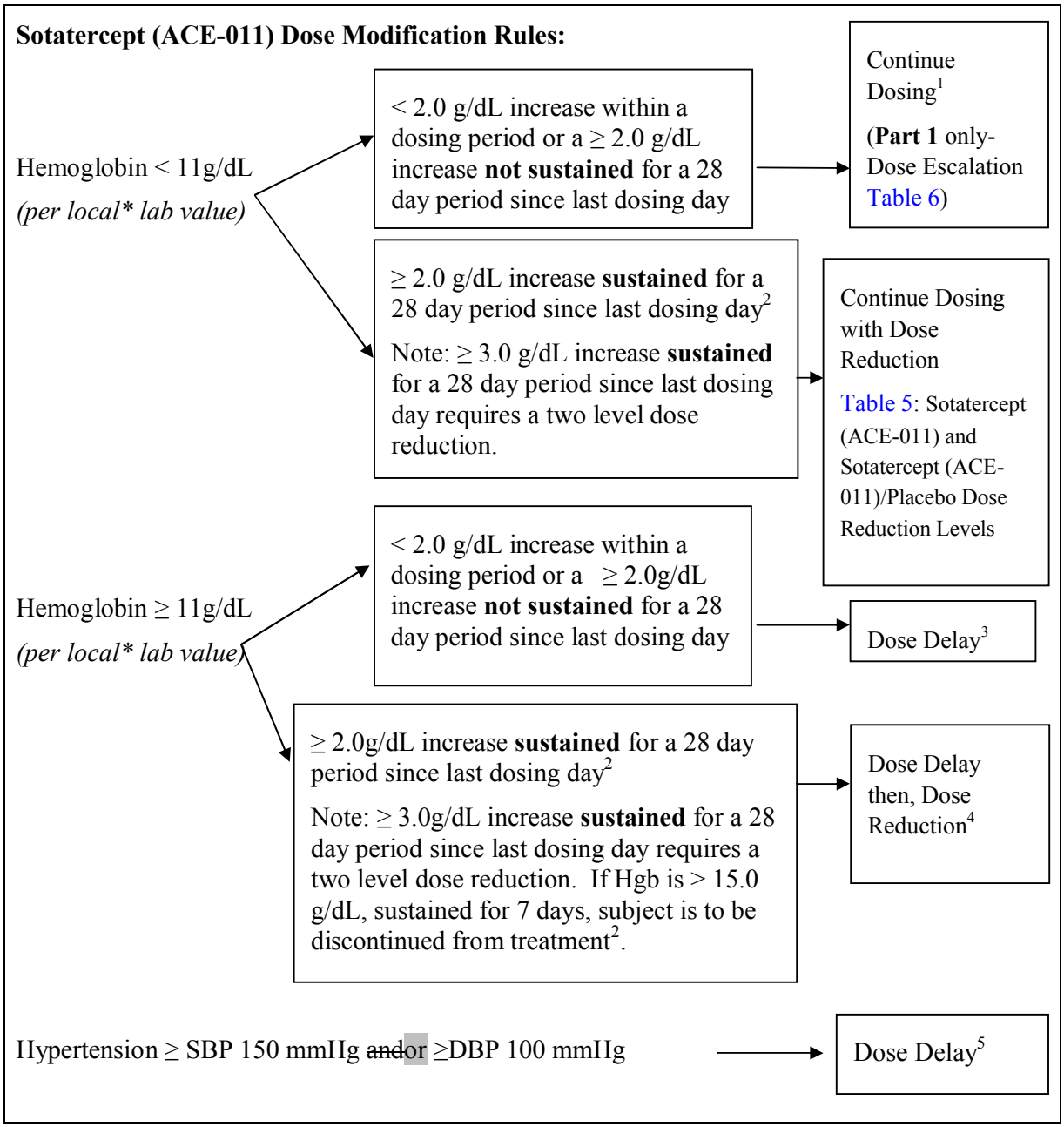
- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Clarify that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals.
- Allow subjects to be randomized while receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Confirm that only subjects with metastatic NSCLC are eligible for **Part 2** of the study.

2.6. Section 4.1.1: Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules (pages 43-45)

Revised Text:

(Appears on following page.)

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained at least five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) or sotatercept (ACE-011)/placebo for the subject's **second** dose of study treatment and beyond.



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

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011) should not be administered ≤ 7 days post RBC transfusion.

For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** sotatercept (ACE-011)/placebo dose if the transfusion was given greater than 7 days from the previous dose of sotatercept (ACE-011)/placebo AND the Hgb level is < 11 g/dL AND hypertension is < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011)/placebo should not be administered ≤ 7 days post RBC transfusion.

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , ~~22~~21 (after first dose of study treatment) and 28 days after dosing, and reviewed in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels (Refer to sotatercept (ACE-011) and sotatercept (ACE-011)/Placebo Dose Reduction Levels (Table 5). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > SBP 150 mmHg ~~and~~or > DBP 100 mmHg and/or sotatercept (ACE-011) related toxicity).

[4]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be held until hypertension resolves to < SBP 150mmHg and < DBP 100 mmHg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

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Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

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Rationale:

Modified to:

- Clarify timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.

- Correct typographical error in hypertension criteria determining sotatercept (ACE-011) dose delay:
    - Hypertension ≥ SBP 150 mmHg **and** ≥DBP 100 mmHg → Dose Delay

    To be modified with:

    - Hypertension ≥ SBP 150 mmHg **or** ≥DBP 100 mmHg → Dose Delay
- Correct hemoglobin collection day 21 post first dose of sotatercept (ACE-011).

2.7. Section 4.2: Study Design Rationale (page 46)

Revised Text:

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a rapid, sustained and dose-dependent increases in hematopoietic parameters, (Hgb, HCT and RBC counts) which occurred earlier than would be expected from a stimulation of erythropoiesis by an ESA. This observation, coupled with nonclinical data demonstrating some level of erythrocyte stimulatory effect in the presence of anti-erthyropoietin (EPO) antibodies, suggests that the hematopoietic effect of sotatercept is different from that of ESAs. Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Guidelines, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

Rationale:

Modified to:

- Correct typographical error.

2.8. Section 4.3: Study Duration (page 49)

Revised Text:

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects with ~~selected~~advanced or metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2** will be randomized prior to receiving the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Clarify that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals.

2.9. Section 5: Table Of Events (pages 54-55)

Revised Text:

Table 7: Sotatercept (ACE-011) Schedule of Assessments

		Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
	Screening Period	Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	
Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X											
Targeted/Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[v]																		X

[a]Include cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and advanced or metastatic site involvement. Record prior ESA history, starting at ~~selected~~ solid tumor diagnosis. Record RBC transfusion history, starting from diagnosis of advanced or metastatic disease, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) or sotatercept (ACE-011)/ placebo dose, at Treatment Discontinuation, and at Study Discontinuation. Blood pressure should be confirmed by two measurements obtained at least five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

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Note: Footnotes [e], [f], [g]: Hematology, absolute reticulocyte count, serum chemistry and creatinine clearance are to be assessed ≤ 14 days prior to randomization.

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[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins ~~an every 3 week~~a platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo **may be given at any time following the first dose of ~~first-line~~ platinum-based chemotherapy. Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during a ~~the~~ chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

– – – – – – – – – – –

[s]~~Pemetrexed or erlotinib~~ [s] Targeted/maintenance therapy (e.g. pemetrexed, erlotinib, etc.) is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

– – – – – – – – – – –

[v]Survival data will be collected monthly, (can be via telephone contact~~.~~), following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

Rationale:

Modified to revise footnote text:

- Footnote 'a' - modified to expand eligible tumor types to include advanced solid tumors and clarify data collection of prior use of erythropoietic stimulating agents and red blood cell transfusion.
- Footnote 'b' – clarify timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.

- Footnote ‘e’, ‘f’, ‘g’ – added to clarify screening period for hematology, absolute reticulocyte, serum chemistry and creatinine clearance assessments.
- Footnote ‘q’ – clarify that subjects must have received at least one cycle of platinum based chemotherapy.
- Footnote ‘s’ – revise description of allowable concomitant and maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents).
- Footnote ‘v’ – clarify that monthly survival data can be collected via telephone contact.

2.10. Section 6: Procedures (pages 58-61)

Revised Text:

Screening Period (Day -28 to Day -1)

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The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – – –

- Cancer history, including date of original diagnosis, histopathology, clinical stage at screening, date of advanced or metastatic stage and site involvement
- Prior ESA treatment history starting from the initial solid tumor diagnosis ~~of one of the selected solid tumors~~
- RBC transfusion history starting from diagnosis of advanced or metastatic disease at a minimum of up two months prior to randomization
- Serum chemistry, hematology, absolute reticulocyte count to be assessed ~~within~~ ≤ 14 days prior to ~~of~~ randomization
- Creatinine clearance (per Cockroft-Gault formula) to be assessed ≤ ~~within~~ 14 days prior to ~~study treatment administration~~ randomization

– – – – – – – – – – –

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

– – – – – – – – – – –

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

– – – – – – – – – – –

- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and ~~43~~42 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and ~~43~~42 days after last dose of study treatment

– – – – – – – – – – –

- Documentation of concomitant platinum-based chemotherapy and/or targeted/maintenance therapy

Rationale:

Modified to:

- Expand reference to study population to include advanced disease.

- Clarify data collection of prior use of erythropoietic stimulating agents and red blood cell transfusion.
- Clarify screening period for hematology, absolute reticulocyte, serum chemistry and creatinine clearance assessments.
- Correct typographical error of ’43 days’ to ’42 days”.
- Add allowed targeted therapy.

2.11. Section 7: Study Population (page 67)

Revised Text:

~~Subjects must be receiving their first regimen of first-line platinum-containing chemotherapy, given, every three weeks, for the treatment of a selected metastatic solid tumor at~~ At the time of randomization~~: metastatic NSCLC, metastatic small cell lung cancer, metastatic bladder cancer, metastatic head~~ in **Part 1** and ~~neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy. Subjects may~~ **Part 2**, subjects must have already received:

- at least one cycle and up to 4 cycles (q3w schedule) of ~~this current~~ platinum-based ~~regimen~~chemotherapy and ~~must~~ be randomized prior to receiving Cycle 5~~.~~

OR

- at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.~~

~~Subjects~~In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for ~~the~~ first-line treatment ~~of metastatic solid tumors~~ prior to the regimen they are receiving at the time of randomization.

Rationale:

Modified to:

- Clarify that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals OR be receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Confirm only metastatic NSCLC subjects are eligible for **Part 2** of the study.

2.12. Section 7.1: Number of Subjects (page 67)

Revised Text:

This platinum-based CIA study will enroll approximately 840 subjects, approximately 90 subjects with ~~selected~~advanced or metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**.

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.

2.13. Section 7.2: Inclusion Criteria (page 68)

Revised Text:

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. **Part 1** – Histologically confirmed (cytology or biopsy) solid tumor malignancy, ~~including metastatic non-small cell lung cancer (NSCLC), metastatic small cell lung cancer, metastatic bladder cancer, metastatic head and neck cancer, and metastatic endometrial/cervical cancer, where the standard of care is first-line platinum-based chemotherapy~~excluding those solid tumors treated with curative intent.

   Part 2 - Histologically confirmed (cytology or biopsy) non-small cell lung cancer.
3. Documented advanced or metastatic disease.
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L~~)~~), due to chemotherapy-induced anemia
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function ~~(creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin concomitantly administered)~~:
     - creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin is concomitantly administered

       and
     - urine protein / creatinine ratio ≤ 1.0; or ≤ 2.0 if bevacizumab (Avastin®) is concomitantly administered
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤ 5.0 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL~~), previous~~) or ≤ Grade 1. Previous hypercalcemia treatment is allowed

6. Subjects ~~may~~must have received:
    - at least one cycle and up to 4 cycles (q3w schedule) of ~~their first regimen of first line~~ platinum-based chemotherapy ~~treatment.~~and be randomized prior to receiving Cycle 5

      OR
    - at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

      OR
    - currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

Rationale:

Modified to:

- Expand study population in **Part 1** of the study to include advanced or metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Clarify that hemoglobin levels ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L) must be attributed to chemotherapy-induced anemia.
- Consolidate definition of adequate renal function in Inclusion Criteria.
- Expand allowable corrected calcium levels.
- Clarify that subjects must have received at least one cycle of platinum-based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals.

2.14. Section 7.3: Exclusion Criteria (pages 70-71)

Revised Text:

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

– – – – – – – – – – –

3. ~~History~~Part 2 only, history of prior regimen(s) of platinum-based chemotherapy for metastatic ~~disease~~NSCLC and/or history of adjuvant platinum-based chemotherapy with last dose received less than six months prior to the start of current first-line platinum-based chemotherapy for metastatic ~~disease~~NSCLC.

– – – – – – – – – – –

9. ~~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).~~

– – – – – – – – – – –

~~11~~10. Uncontrolled hypertension. ~~If~~Controlled hypertension is considered clinically stable~~,~~ and systolic blood pressure (SBP) must be < 150 mmHg ~~or~~and diastolic blood pressure (DBP) must be < 100 mmHg.

– – – – – – – – – – –

~~17. Urine protein / creatinine ratio > 1.0.~~

~~18~~16. 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.

~~19~~17. Any prior use of sotatercept (ACE-011).

~~20~~18. Pregnant or lactating females or females planning to become pregnant.

~~21~~19. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).

~~22~~20. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

Rationale:

Modified to:

- Clarify allowed prior type and setting of platinum-based chemotherapy in **Part 2** only.
- Delete exclusion of subjects with second malignancy within the prior 3 years.
- Correct typographical error in blood pressure measurement exclusion.
- Delete of urine protein / creatinine ratio exclusion criterion and move to define adequate renal function in Inclusion Criteria.
- Renumbering of remaining Exclusion Criteria.

2.15. Section 8.1: Description of Investigational Product(s) (pages 72)

Revised Text:

Sotatercept (ACE-011) clinical drug product will be provided as a ~~frozen liquid formulation, Process IIa, or as a~~ lyophilized powder, Process III.

~~**Note:** Subjects receiving Process IIa clinical drug product will begin to receive Process III clinical drug product as soon as it becomes available at the study site.~~

~~**Process IIa Clinical Drug Product – Frozen Liquid Formulation:**~~

~~The clinical drug product consists of sotatercept (ACE-011) in phosphate buffered saline (PBS), pH 7.5. It is supplied as a 1 mL solution of 50 mg/mL sotatercept (ACE-011) in labeled, rubber stoppered, 2 mL vials providing 50 mg per vial. The recommended storage temperature for sotatercept (ACE-011) Process IIa frozen liquid drug product is ≤ -65˚C (colder than -65˚C) until thawed for administration. Vials of sotatercept (ACE-011) frozen liquid must be completely thawed (approximately 30 minutes at room temperature) prior to preparation for dosing and must be used within six (6) hours of being thawed.~~

2.16. Section 8.2: Treatment Administration and Schedule (pages 72-73)

Revised Text:

Sotatercept (ACE-011) or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization ~~all~~in **Part 1** and **Part 2**, subjects must ~~be receiving their first-line regimen~~have already received:

- at least one cycle and up to 4 cycles (q3w schedule) of platinum-~~containing chemotherapy, given every three weeks, for the treatment of a metastatic solid tumor. Subjects will~~based chemotherapy and be randomized prior to ~~this study during the time period in which they are~~ receiving Cycle ~~1 through Cycle 4 of this regimen. Subjects must not have received any prior regimens of first line~~ 5

OR

- at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy ~~for a~~

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~It is expected that subjects be eligible to continue to receive ≥ 2 additional platinum-based chemotherapy cycles while on study treatment.~~

In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic ~~solid tumor~~NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.

– – – – – – – – – – –

~~Subjects may receive 4-6 cycles of the~~Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents) which are approved for a given tumor type, are allowed ~~platinum-based regimen selected by the Investigator. Up~~in addition to ~~2 additional cycles (8 total cycles) of~~ platinum-based chemotherapy ~~may be given as determined by cancer response.~~ .

Platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

~~While on study treatment subjects will be allowed to receive maintenance therapy with a pemetrexed or erlotinib-containing regimen when indicated.~~

Rationale:

Modified to:

- Clarify that subjects must have received at least one cycle of platinum-based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals OR be randomized while receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Expand study population in **Part 1** of the study to include advanced and metastatic solid tumor types treated with ≥ first-line platinum-based chemotherapy, excluding those solid tumors treated with curative intent.
- Clarify allowed prior type and setting of platinum-based chemotherapy in **Part 2** only.
- Remove reference to ACE-011 Process IIa Clinical Drug Product - Frozen Liquid Formulation. In **Part 1** of the study, subjects will receive only ACE-011 Process III Clinical Drug Product – Lyophilized Powder Formulation. In **Part 2** of the study, subjects will receive ACE-011 Process III Clinical Drug Product – Lyophilized Powder Formulation or placebo.
- Expand allowable concomitant and maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents) which are approved for a given tumor type, in addition to platinum-based chemotherapy.

2.17. Section 8.2.2: Selection and Timing of Dosing for Each Subject (pages 74-75)

Revised Text:

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The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered **at any time after the first cycle and prior to the fifth cycle (q3w regimen) or prior to starting the fourth month (depending upon regimen) of ~~first-line~~ platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy. Subsequent doses** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during the chemotherapy cycle.

– – – – – – – – – – –

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their advanced or metastatic disease, whichever occurs first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of advanced or metastatic disease that requires the initiation of another treatment.

Rationale:

Modified to:

- Clarify that subjects must have received at least one cycle of platinum-based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals
- Allow subjects to be randomized while receiving maintenance therapy following treatment with platinum-based chemotherapy.
- Expand reference to study population to include advanced disease.

2.18. Section 8.2.3: Discontinuation (pages 75-76)

Revised Text:

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100mmHg) confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.

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  - Urine protein / creatinine ratio > 1.0; or > 2.0 (if bevacizumab [(Avastin®)] is concomitantly administered)

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- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months fromafter first dose of study treatment.

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- Protocol violation – as determined by the Sponsor

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Study Discontinuation:

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months fromafter first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse events(s)
- Disease progression
- Protocol violation

Rationale:

Modified to:

- Clarify that subjects must have received at least one cycle of platinum based chemotherapy and up to 4 cycles of a regimen administered every 3 weeks OR up to 3 months of a regimen administered at other intervals OR while receiving maintenance therapy following treatment with platinum-based chemotherapy.
- .Expand reference to study population to include advanced disease.
- Clarify timing interval between two blood pressure measurements required to assess sotatercept (ACE-011) dosing.
- Clarify that subject discontinuation from treatment and study due to protocol violation will be determined by the Sponsor.
- Correct grammatical and editorial errors.

2.19. Section 9: Concomitant Medications and Procedures (page 78)

Revised Text:

9.1. Permitted Concomitant Medications and Procedures

General concomitant medication usage

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Concomitant therapies considered as supportive care are acceptable while participating in this study, including growth colony stimulating factors (G-CSF), anti-emetics to limit chemotherapy-related nausea and vomiting ~~and~~, palliative radiation, and bisphosphonates and denosumab ~~(Refer to Inclusion Criterion, Section 7.2)~~therapy for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

Rationale:

Modified to:

- Delete reference to Section 7.2, not applicable following Amendment 2.

2.20. Section 9.2: Prohibited Concomitant Medications and Procedures (page 79)

Revised Text:

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate ~~therapy (see Section 7.2),,~~ other than for the treatment of hypercalcemia, ~~must~~and denosumab therapy for bone metastases can be started prior to randomization but should not be started on study.

Rationale:

Modified to:

- Delete reference to Section 7.2, not applicable following Amendment 2.
- Further clarify when bisphosphonate and denosumab therapy for metastatic bone disease is allowed to begin.

2.21. Section 10: Statistical Analyses (page 80)

Revised Text:

10.1. Overview

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with ~~selected~~advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. In **Part 1**, subjects will be randomized to one of three doses of sotatercept (ACE-011) plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected sotatercept (ACE-011) dose determined from **Part 1** plus platinum-based chemotherapy. Data from **Part 1** will not be combined with data from **Part 2** in all safety and efficacy analyses.

A DMC will be used to monitor the study conduct.

Rationale:

Modified to:

- Expand reference to study population to include advanced disease.

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY (PART 1) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
AMENDMENT 1.0 FINAL:	22 MARCH 2011
AMENDMENT 2.0 FINAL:	27 JUNE 2011
AMENDMENT 3.0 FINAL:	01 NOVEMBER 2011
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

MEDICAL MONITOR / **EMERGENCY CONTACT INFORMATION**

Contact Information:	
PPD	

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:	PPD

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:_____** By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

An open-label randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in Subjects with Advanced or Metastatic Solid Tumors

Part 1 – Advanced or metastatic solid tumors treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

Part 2 - Metastatic NSCLC

Objectives

The primary objectives are:

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

The secondary objectives are:

Part 1 and Part 2:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS).
- To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

The exploratory objectives are:

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only).
- To assess renal function biomarkers

Study Design

This is an open-label, randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy for CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.

The study will consist of two parts:

Part 1 is a dose-finding segment in which up to approximately 90 subjects will be randomized to one of three sotatercept (ACE-011) dose treatment arms. The primary objective is to determine a dose of sotatercept (ACE-011) that results in a hematopoietic response in the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapy, excluding those solid tumors treated with curative intent. The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.

Part 2 is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During **Part 2** (first and second stage) overall survival will be assessed. The total sample size of 750 subjects will allow observation of at least 536 deaths and thus, at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept

[ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Study Population

At the time of randomization in **Part 1** and **Part 2**, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening, Treatment Period, Post Treatment Follow-Up Period, and Survival Follow-Up Period. Study treatment is defined as sotatercept (ACE-011) in **Part 1** and sotatercept (ACE-011)/placebo in **Part 2**.

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks or as per standard care at the study site prior to randomization. **Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected and used for assessment of tumor response.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from the initial solid tumor diagnosis and red blood cell (RBC) transfusion history starting from diagnosis of advanced or metastatic disease, at a minimum of up to two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the Screening Period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Treatment Period (up to 6-9 months):

The Treatment Period is approximately six months (four doses of study treatment given on Day 1, every 42 days), two additional sotatercept (ACE-011)/placebo doses may be given only in **Part 2**, at the discretion of the Investigator.

In **Part 1** (the dose-ranging portion of the study), subjects with advanced or metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The effective dose of sotatercept (ACE-011) is defined as follows:

> An increase in hemoglobin (Hgb) of $\geq$ 1.0 g/dL above the study baseline value for 4 consecutive weeks during the first two doses of sotatercept (ACE-011) (Dose 1/Day 1 through and including Dose 2/Day 43 [prior to Dose 3]), in approximately 70% of subjects, in at least one or more treatment arms (in the absence of RBC transfusions and/or ESAs).

Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the sotatercept (ACE-011) dose for **Part 2**.

In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in **Part 2**.

In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in **Part 1**)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses. Up to two additional doses (in **Part 2** only) may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011) (at the dose determined from **Part 1**) or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered > 7 days from the date of the RBC transfusion.

In **Part 1**, blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers, in approximately 10 subjects for each sotatercept (ACE-011) dose group investigated. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment. In **Part 2**, blood samples will be collected for the sparse PK assessment that will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either **Part 1** full or sparse PK assessments or Part 2 sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension $\geq$ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] $\geq$ 160 mmHg or diastolic blood pressure [DBP] $\geq$ 100mmHg), confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.

  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months of sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0; or > 2.0 if bevacizumab (Avastin®) is concomitantly administered
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.

- In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months after first dose of study treatment.
- Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥ 3.0 g/dL following a two-level dose reduction due to a Hgb increase ≥ 3.0 g/dL
  - In **Part 2**: > 3 dose reductions and/or delays
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation - as determined by the Sponsor

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

Post Treatment Follow-Up Period (monthly visits for up to 6 months)

Subjects who enter the Post Treatment Follow-Up Period will be followed monthly for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to one year from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first.

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

- Completed study, per protocol (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months after first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse event(s)
- Disease progression
- Protocol violation

Survival Follow-up Period (monthly for up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo)

In both **Part 1** and **Part 2**, survival data will be collected monthly (can be via telephone contact) for up to 24 months following the subject's first dose of sotatercept (ACE-011) (**Part 1**) or sotatercept (ACE-011)/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit. Data to be collected will include:

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy, if any

Overview of Efficacy Assessments

- Serum hematology, absolute reticulocyte counts
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Tumor assessments
- Documentation of concomitant RBC transfusions

Overview of Safety Assessments

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac and thromboembolic events
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature.

- AE(s)
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy testing
- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone).
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- Lung Cancer Symptom Scale (LCSS) questionnaire – subjects with NSCLC
- Documentation of concomitant medications / procedures.

Overview of Exploratory Assessments

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- DXA scan
- Renal function biomarkers

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 19
2. STUDY OBJECTIVES 36
2.1. Primary Objective 36
2.2. Secondary Objectives 36
2.3. Exploratory Objectives 36
3. STUDY ENDPOINTS 37
3.1. Primary Endpoint(s) 37
3.2. Secondary Endpoint(s) 37
3.3. Exploratory Endpoint(s) 38
4. OVERALL STUDY DESIGN 39
4.1. Study Design 39
4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules 43
4.2. Study Design Rationale 46
4.2.1. Fixed Dose 46
4.2.2. Dosing Schedule 47
4.2.3. Starting Dose Levels in Part 1 47
4.2.4. Evaluation of Dosing Schema via Modeling/Simulation 48
4.3. Study Duration 49
5. TABLE OF EVENTS 50
6. PROCEDURES 58
7. STUDY POPULATION 67
7.1. Number of Subjects 67
7.2. Inclusion Criteria 68
7.3. Exclusion Criteria 70
8. DESCRIPTION OF STUDY TREATMENTS 72
8.1. Description of Investigational Product(s) 72
8.2. Treatment Administration and Schedule 72
8.2.1. Selection of Dose for the Study 73
8.2.2. Selection and Timing of Dosing for Each Subject 74

8.2.3. Discontinuation 75
8.3. Method of Treatment Assignment 76
8.4. Packaging and Labeling 76
8.5. Investigational Product Accountability And Disposal 77
8.6. Investigational Product Compliance 77
9. CONCOMITANT MEDICATIONS AND PROCEDURES 78
9.1. Permitted Concomitant Medications and Procedures 78
9.2. Prohibited Concomitant Medications and Procedures 79
9.3. Required Concomitant Medications and Procedures 79
10. STATISTICAL ANALYSES 80
10.1. Overview 80
10.2. Study Population Definitions 80
10.3. Sample Size and Power Considerations 80
10.4. Background and Demographic Characteristics 81
10.5. Subject Disposition 81
10.6. Efficacy Analysis 81
10.7. Safety Analysis 82
10.8. Interim Analysis 83
10.9. Other Topics 83
10.10. Data Monitoring Committee (DMC) 84
11. ADVERSE EVENTS 85
11.1. Monitoring, Recording and Reporting of Adverse Events 85
11.2. Evaluation of Adverse Events 85
11.2.1. Seriousness 85
11.2.2. Severity / Intensity 86
11.2.3. Causality 87
11.2.4. Duration 87
11.2.5. Action Taken 88
11.2.6. Outcome 88
11.3. Abnormal Laboratory Values 88
11.4. Pregnancy 88
11.4.1. Females of Childbearing Potential 88
11.4.2. Male Subjects 89

11.5. Immediate Reporting of Serious Adverse Events 89
11.6. Safety Queries 89
11.7. Expedited Reporting of Adverse Events 89
12. DISCONTINUATIONS 91
13. EMERGENCY PROCEDURES 92
13.1. Emergency Contact 92
13.2. Emergency Identification of Investigational Products 92
14. REGULATORY CONSIDERATIONS 93
14.1. Good Clinical Practice 93
14.2. Investigator Responsibilities 93
14.3. Subject Information and Informed Consent 93
14.4. Confidentiality 94
14.5. Protocol Amendments 94
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 94
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 95
14.8. Closure of the Study 95
15. DATA HANDLING AND RECORDKEEPING 96
15.1. Data/Documents 96
15.2. Data Management 96
15.3. Record Retention 96
16. QUALITY CONTROL AND QUALITY ASSURANCE 98
16.1. Study Monitoring and Source Data Verification 98
16.2. Audits and Inspections 98
17. PUBLICATIONS 99
18. REFERENCES 100
19. APPENDICES 103
Appendix A: Response Evaluation Criteria in Solid Tumors 103
Appendix B: ECOG Performance Status Scale 105
Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 106
Appendix D: New York Heart Association - Classification of Heart Failure 107

LIST OF TABLES

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation 28
Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall 31
Table 3: Summary of SAEs Reported 32
Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days 32
Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels 45
Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only) 46
Table 7: Sotatercept (ACE-011) Schedule of Assessments 50
Table 8: Schedule of Pharmacokinetic Assessments (Part 1) 56
Table 9: Schedule of Pharmacokinetic Assessments (Part 2) 57
Table 10: ECOG Performance Status Scale 105
Table 11: Classification of Heart Failure 107

LIST OF FIGURES

Figure 1: Study Design 42
Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population 48

1. INTRODUCTION

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapy will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study.

Part 2 will include only subjects with metastatic NSCLC and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

In the first stage of **Part 2** approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period. Based on the results of the futility analysis and upon recommendation to continue the study, up to an additional 570 subjects will be randomized in the second stage of **Part 2**, to achieve full study accrual.

A Data Monitoring Committee (DMC) will monitor the conduct of the study.

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The chemical structure of sotatercept (ACE-011) is composed of a disulfide-linked, glycosylated, dimeric protein. Sotatercept (ACE-011) competes with the activin receptor IIA and binds a number of TGF-β superfamily ligands including activin, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

In both a single and a multiple dose phase 1 study of sotatercept (ACE-011) in healthy volunteer, postmenopausal women, a dose and time dependent increase in hemoglobin (Hgb) and hematocrit (HCT), and red blood cell (RBC) levels were observed following sotatercept (ACE-011) treatment and remained elevated over the course of study.

Although the mechanism(s) underlying the stimulation effect of sotatercept (ACE-011) on erythropoiesis are not yet fully understood, the result of clinical experience showed a rapid and sustainable increase in mature erythrocytes released into circulation. The sotatercept (ACE-011) proposed mechanism of action may be different than that of known erythropoiesis-stimulating agents (ESAs) and may provide a different clinical profile in the treatment of CIA.

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

Chemotherapy-Induced Anemia

Chemotherapy-induced anemia (CIA) is an area of unmet medical need. It is a significant problem for patients with cancer, causing fatigue and reducing quality of life (QoL).

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002). The incidence and severity of chemotherapy-induced anemia (CIA) is further dependent on a variety of factors, such as the type, schedule, and intensity of chemotherapy administered, and whether the patient has received prior myelosuppressive chemotherapy and/or radiation therapy (Groopman, 1999). Platinum-based treatments (eg, cisplatin and carboplatin), commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity. Antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan) are also considered particularly myelosuppressive (Groopman, 1999). Dose intensity, the increasingly widespread practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression

The association between uncorrected anemia before or during chemotherapy and poorer patients' outcomes has been reported in several studies (Grogan, 1999; Laurie, 2006; MacRae, 2002; Obermair, 2003). Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and may also have an adverse impact on co-morbid conditions, such as cardiac and pulmonary disease. The most common patient complaints are dyspnea on exertion and chronic fatigue, which may interfere with a patient's ability to perform normal daily activities (Groopman, 1999). A key differentiating characteristic of cancer-related fatigue versus fatigue in healthy individuals is its likelihood of persistence at rest (National Comprehensive Cancer Network, 2008) In various published surveys, fatigue has been represented as a symptom that has affected patients' everyday life the most and has been linked to changes in employment status among patients and even caregivers (Schwartz, 2007). The association between Hgb levels and fatigue is well documented, with one analysis of 5 randomized trials linking an increase in Hgb concentrations of at least 2 g/dL with an improvement in fatigue, and consequently, in energy, ability to perform usual activities, and overall health (Cella, 2004).

In looking at the impact of CIA on survival, a meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer and anemia compared with patients without anemia (Carlos, 2001). The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that also is supported by other retrospective studies. Tumor hypoxia, resulting from the reduced oxygen-carrying capacity of blood in patients with anemia, has been hypothesized to be a major contributor to reduced survival. Several studies have shown that tumor hypoxia also reduces the effectiveness of radiotherapy and chemotherapy, and is associated with tumor progression (Aapro, 2006).

Treatment of Chemotherapy-Induced Anemia

The current treatment options for CIA include blood transfusion and erythropoiesis-stimulating agents (ESAs). However, blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients receiving chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. However, the past five years has seen a major change in the use of ESAs for cancer related and chemotherapy induced anemia. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. Retrospective statistical analysis in one study in head and neck cancer patients, and two studies with adjuvant breast cancer revealed substantial safety concerns of increased thromboembolic events, and decreased PFS and overall survival.

Sotatercept (ACE-011) Treatment of Chemotherapy-Induced Anemia

Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and HCT levels were observed in two phase 1 studies in healthy volunteers, as well as in a phase 2a study in multiple myeloma (MM) subjects. The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

In a phase 1 single-dose and multiple-dose studies of sotatercept in postmenopausal women (Studies A011-01 and A011-02, respectively), and in a phase 2 study in subjects with osteolytic lesions associated with MM that examined concurrent administration of sotatercept with melphalan, prednisolone, and thalidomide (MPT) anti-myeloma therapy, increases in Hgb, RBC count and HCT were observed following sotatercept treatment, and these increases remained detectable throughout the course of study. The observed Hgb, RBC count, and HCT effects of sotatercept were dose-dependent and time-dependent. These phase 1 and phase 2 clinical data are consistent with the increased hematologic parameters observed in nonclinical studies, The results from the three completed clinical studies A011-01, A011-02, and A011-04 are summarized in Summary of Clinical Experience

The mechanism of action of sotatercept with regards to increased RBC counts is not known; however, the mechanism of action for the hematopoietic effect of sotatercept may be different than that of ESAs, as some level of erythrocyte stimulatory effect was observed in the presence of anti-EPO antibodies in one nonclinical study. As such, sotatercept may provide a unique clinical profile with a favorable benefit-risk profile in the chemotherapy-induced anemia patient population, thereby addressing some of the unmet medical needs in chemotherapy-induced anemia treatment.

Non-Small Cell Lung Cancer Current Therapy Status

Lung cancer is the leading cause of cancer death in the world, accounting for 32% of cancer deaths in males and 25% in females, affecting approximately 171,000 people annually in the US (Parker, 1997; Sandler, 2006) and more than 200,000 people in Europe (Rossi, 2006). Of these patients, approximately 85% have NSCLC, including squamous carcinoma, adenocarcinoma and large cell carcinoma (Rossi, 2006; Sandler, 2006). These histologies are typically classified together because the approaches to diagnosis, staging and prognosis, and treatment are similar.

Patients are often diagnosed with an advanced stage of disease. Studies of advanced NSCLC patients treated with platinum-based chemotherapy report a one year survival rate that ranges from 30% to 43% and a median survival that ranges from seven to ten months (Dang, 2008). The 5-year survival rate of patients with NSCLC varies by stage, from 60% to 70% for patients with stage I disease to < 1% for patients with stage IV disease (Hong, 2008). Patients having stage IIIb/IV NSCLC are not considered to be candidates for curative resection surgery or radiation, and radiation therapy is primarily used as palliative treatment in advanced stages of NSCLC.

The role of chemotherapy is now well established as the recommended treatment of advanced NSCLC (Non-small Cell Lung Cancer Collaborative Group, 1995). The current globally accepted standard of treatment for NSCLC is platinum-based combination therapy. In advanced-stage (stage IIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine (Gemzar®), vinorelbine, taxanes (paclitaxel or docetaxel) or pemetrexed are reference regimens. When compared head-to-head in phase 3 studies, these doublets have shown comparable efficacy, in regards to overall survival (Schiller, 2002) with differences in toxicity profiles (Schiller, 2002). When administered in a 3-week schedule, cisplatin plus gemcitabine, or cisplatin plus pemetrexed are effective and are widely used regimens for first-line treatment of NSCLC. A recent phase 3 study in NSCLC compared cisplatin plus gemcitabine with cisplatin plus pemetrexed (Scagliotti, 2008). Both had similar efficacy, with cisplatin plus pemetrexed having better tolerability and more convenient administration than cisplatin/gemcitabine. This study was also the first prospective phase 3 study in NSCLC to show a survival difference based on histologic type (non-squamous benefited from pemetrexed plus cisplatin). Drug-related grade (G) 3 or 4 anemia was at the rate of 6% for cisplatin/pemetrexed versus 10% for cisplatin/gemcitabine. The incidence of RBC transfusion was 16.1% versus 27.3% and administration of erythropoietic agents 10.4% versus 18.1% respectively. There was no significant difference between treatment arms in the incidence of or reason for deaths (7%).

In the pivotal Aranesp (darbepoetin alfa) study for CIA in NSCLC, 27 % of patients were transfused with packed red blood cells (PRBC's) at 4 months versus 52% in the placebo arm.

Activin Biology

The activins (A-E) are a group of proteins that form dimers and heterodimers. All are part of the TGF-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 A was also 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).

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

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

In a retrospective study (Seder, 2009) activin immunoreactivity was found in 78% of lung adenocarcinomas surveyed (n=164). Expression ranged from moderate in the majority of individuals to high in approximately 19.7% of samples evaluated. Gene expression analysis was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples. An average of three-fold more activin transcript was detected in diseased tissue relative to normal samples and particularly high levels of overexpression were associated with worse overall survival in stage I patients with NSCLC.

Additionally, in the NIH “directors challenge” study for NSCLC adenocarcinoma (Shedden, 2008), 3 of the 12 molecular subgroups, including the subgroup with the worst survival prognosis, demonstrated overexpression of Activin A. Thus, overexpression of activin may play a role in NSCLC tumor progression.

Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below. Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

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 (IP) twice per week for 3 months resulted in a 16-26% increase in RBC counts compared to control animals. Rats treated with sotatercept (ACE-011) at 0.3, 3 and 30 mg/kg once per week for 3 months showed RBC count increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of sotatercept (ACE-011) twice per month for 3 months, there was a 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 sotatercept (ACE-011).

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

RAP-011 has also been shown to significantly increase bone mineral density (BMD) and strength in normal animals and in a variety of animal models of bone loss (Chantry, 2010; Lotinun, 2008; Pearsall, 2008). In a murine ovariectomy (OVX)-induced model of osteopenia, RAP-011 (10 mg/kg intravenous [IV], twice per week x 12 weeks) increased trabecular BMD > 25% in 6-12 weeks compared to the phosphate buffered saline (PBS)-treated controls ($p<0.002$). RAP-011 treatment was able to reverse the accelerated bone loss associated with ovariectomy. As expected, sham-operated (SHAM) mice (i.e., intact ovaries) started the study with a greater trabecular BMD than OVX mice. PBS-treated SHAM mice showed a 10% decrease in trabecular BMD after 12 weeks of treatment compared to baseline, while SHAM-RAP-011 mice had a 32% increase in trabecular BMD over the same period. These data demonstrate that RAP-011 is able to increase trabecular BMD in both the normal state and in a model of established bone loss. The femurs of both the RAP-011 treated OVX and SHAM mice showed statistically significant increases in all measured parameters of bone strength (i.e., maximum load, stiffness, energy, ultimate strength, and elastic modulus). In summary, treatment with RAP-011 produced bone of superior quality consistent with an anabolic agent.

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

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

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model demonstrated that RAP-011 could prevent the development of osteolytic bone disease in a preventative setting.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

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

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

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

Toxicology

Sotatercept (ACE-011) has been evaluated for toxicological effects in two species, Sprague-Dawley rats and cynomolgus monkeys. The dose levels ranged from 0.3 to 30 mg/kg in rats and

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

Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-sotatercept (ACE-011) antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats as well as demonstration, by immunohistochemistry, of immunoglobulin and complement at the site of injury in monkeys, consistent with immune complex deposition. However, high plasma concentrations of sotatercept (ACE-011) in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (NOAELs) in rats and monkeys were 3 (3-month study) and 1 mg/kg (9-month study), respectively.

Summary of Clinical Experience

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

Sotatercept (ACE-011) was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal females (Ruckle, 2009). Sotatercept (ACE-011) was diluted in normal saline administered as an IV infusion (over approximately 1 hour) or as a SC injection on Day 1. Dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg IV and 0.03 and 0.1 mg/kg SC. A total of 48 subjects were enrolled; 5 active and 1 placebo at each of the IV and SC dose levels. All subjects were followed for 4 months following a single dose administration.

The pharmacokinetics (PK) of sotatercept (ACE-011) was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (CL) ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half life in serum ($t_{1/2,}$ z) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, sotatercept (ACE-011) was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs was mild in severity and were judged to be unrelated to sotatercept (ACE-011). No deaths, serious AEs (SAEs), or AEs leading to discontinuation were

reported. Changes in RBCs, Hgb, reticulocytes, liver function tests, glucose, uric acid, amylase and lipase occurred in some subjects. Mild, transient elevations in pancreas enzymes, liver enzymes, or glucose were reported as AEs in five subjects.

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

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

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

Sotatercept (ACE-011) was studied in a phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalating study to evaluate the safety, tolerability and pharmacodynamics of sotatercept (ACE-011) in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following dose levels: 0.1, 0.3, 1.0, and 2.0 mg/kg administered SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of sotatercept (ACE-011) or placebo every 28 days for a total of 4 doses. All subjects were to be followed for 12 weeks after the last dose.

The treatment phase of the study was terminated early after a dose-limiting pharmacodynamic effect was observed. While on study, one subject in the 1.0 mg/kg cohort experienced an SAE of progressive and persistent hypertension that was attributed to a rapid and significant rise in Hgb levels, up to 20 g/dL and HCT levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting pharmacodynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and treated. Dose levels of sotatercept (ACE-011) administered included 0.1, 0.3, and 1.0 mg/kg (Cohorts 1, 2, and 3 respectively). All subjects randomized to active treatment in Cohort 1 received all 4 planned doses of sotatercept (ACE-011). Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of sotatercept (ACE-011), and subjects randomized to active treatment in Cohort 3 received 2 doses of sotatercept (ACE-011). Subjects randomized to placebo treatment received between 1 and 4 doses of study treatment.

In the analysis of the data, after the administration of the first dose, a dose and time dependent increase in Hgb, 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]	**Sotatercept (ACE-011) 0.1 mg/kg N=8**	**Sotatercept (ACE-011) 0.3 mg/kg N=8**	**Sotatercept (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

Other than the serious case of Hgb increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the

subjects in the 1.0 mg/kg group with elevated Hgb levels underwent phlebotomies and all Hgb elevations were resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups.

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

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

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

The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ((apparent) volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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

Study A011-04 is a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety, tolerability and efficacy of sotatercept (ACE-011) in subjects with osteolytic lesions of multiple myeloma (MM).

In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of sotatercept (ACE-011) (0.1, 0.3 and 0.5 mg/kg) or placebo, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept (ACE-011) was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg sotatercept (ACE-011), 8 subjects received 0.3 mg/kg sotatercept (ACE-011), and 8 subjects received 0.5 mg/kg sotatercept (ACE-011). Twenty six (86.7%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

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

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

Fourteen out of 24 subjects (58%) who received study treatment (sotatercept [ACE-011]) did receive 3 doses or more (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level).

Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (i.e., those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept (ACE-011) or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg sotatercept (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to sotatercept (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups and Table 3 is a summary of SAEs reported.

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

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

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

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug (sotatercept (ACE-011) or placebo).

Table 3: Summary of SAEs Reported

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

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

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

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hgb values were observed within 28 days after administration of the first dose of sotatercept (ACE-011)/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	0.1 mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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

Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies

were as a result of the expected biologic activity of sotatercept 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 erythropoiesis.

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 sotatercept (ACE-011) treatment and is being targeted as a therapeutic intervention for conditions associated with anemia.
- In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~1.4-fold greater than the projected serum exposure in humans at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject. Because sotatercept is a fully human molecule, immunogenicity and, by extension, kidney injury is not expected in humans. In the single- and multiple-dose studies in healthy postmenopausal women, there have been no changes in serum chemistry or urinalysis profiles suggestive of kidney injury. Subjects administered sotatercept (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. These changes were also considered related to the formation of anti-drug antibodies. Findings at 1 mg/kg were limited to mononuclear cell infiltrates and were not considered 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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, liver enzymes will continue to be monitored in this study.

- Pregnancy and Lactation
  - 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 in rats at doses ≥ 15 mg/kg (2.8-fold greater exposure than the projected exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject). In addition, at 50 mg/kg (4.7-fold the exposure at the maximum proposed human dose), there was an increase in late fetal death coupled with an overall increase in post implantation loss and a reduction in live litter size, as well as an increase in the incidence of developmental variations of supernumerary ribs with corresponding increases and decreases in thoracic and lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg (1.5-fold greater exposure than the exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject) based on reduced fetal weights and associated delays in ossification.
  - In an embryo-fetal development study in rabbits, post implantation loss was increased and average litter size and live fetuses were reduced at 15 and 50 mg/kg. In addition, fetal body weights were reduced in all sotatercept dosage groups. Abortions occurred in one rabbit in the 5 mg/kg dosage group and two rabbits in the 50 mg/kg dosage group. Based on these findings, an NOAEL was not identified in this study and was therefore less than 5 mg/kg (<1.2-fold greater exposure than the exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject)
  - Precautions should be taken to protect females of childbearing potential. Nonclinical studies on breast milk have not been done.
  - If sotatercept (ACE-011) is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all sotatercept (ACE-011) protocols describe pregnancy prevention requiring females of child-bearing potential to use highly effective methods of birth control. In addition, since it is unknown if sotatercept (ACE-011) is found in breast milk, breast feeding is prohibited in all protocols.
- Fertility
  - In male rats, sperm granulomas and testicular degeneration were observed histologically. In addition, sperm analysis revealed a reduction in sperm counts and motility as well as sperm fragmentation in isolated animals (2/10 males) at doses of 30 mg/kg IV. Sperm fragmentation was also noted in 2/5 males administered 10 mg/kg IV at the end of the recovery period. Overall, there was some evidence of recovery (motility similar to controls) at the end of the 4-week recovery period. There was no evidence of a treatment-related impact on reproductive organs (testes, ovary, uterus) of monkeys in the toxicity studies; however, the monkeys on these studies, were too immature to fully assess the potential impact on reproductive organs. The NOAEL for reproductive effects

(testicular or ovarian) was 1 mg/kg IV. Serum exposure (AUC_{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 61 mg every 6 weeks (estimated AUC_{28d} ~ 4248 µg·hr/mL in a 50 kg subject).

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

Because of the potential risks sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) was first studied in healthy postmenopausal in two completed phase 1 clinical trials. In addition, due to the potential for effects on hormones in the pituitary, levels of growth hormone, ACTH, and thyroid stimulating hormone (TSH) were monitored closely in the phase 1 studies.

Completed studies in humans carried out in postmenopausal females showed a dose-dependent decrease in circulating levels of FSH, with mean levels in the multi-dose study in the two higher dose groups remaining below baseline at study end. FSH will continue to be evaluated in ongoing studies. No abnormal effects of sotatercept (ACE-011) on growth hormone, ACTH, and TSH and kidney toxicities were observed.

Based on the safety data from the two completed phase 1 studies, single doses of sotatercept (ACE-011) up to 3.0 mg/kg IV and multiple doses of sotatercept (ACE-011) up to 0.3 mg/kg 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 sotatercept (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 sotatercept (ACE-011).

2. STUDY OBJECTIVES

2.1. Primary Objective

- **Part 1**: To determine a dose of sotatercept (ACE-011) that results in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent,.
- **Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.

2.2. Secondary Objectives

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS). To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the PK of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

2.3. Exploratory Objectives

Part 1 and **Part 2**:

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism.
- To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only).
- To assess renal function biomarkers.

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Part 1: Dose Finding

The following are decision rules for dose determination in **Part 1** in order to move forward to **Part 2**:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In order to determine the dose of sotatercept (ACE-011) to be used in **Part 2**, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).
- In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in **Part 2**.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

Part 2: Phase 2b/3 Double-Blind

- Rate of RBC transfusion within four months following the date of randomization to sotatercept (ACE-011)/placebo treatment

3.2. Secondary Endpoint(s)

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- TTP
- PFS (including at 6 and 12 months)
- OS (at 12 months and up to 24 months)
- ORR
- Duration of hematopoietic response
- Sotatercept (ACE-011) concentration in serum
- Non-compartmental PK parameters for sotatercept (ACE-011) (**Part 1** only)
- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1993; Hollen, 1994a; Hollen, 1994b; Hollen, 1995, Hollen, 1999)

3.3. Exploratory Endpoint(s)

- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or sotatercept (ACE-011) mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- A population PK model for sotatercept (ACE-011)
- A population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics
- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue (**Part 2** only).
- Change in renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an open-label randomized, phase 2a, dose-ranging study (**Part 1**) of sotatercept (ACE-011) therapy in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic regimens followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.

The study will consist of two parts. **Part 1** is a dose finding segment in which subjects with advanced or metastatic solid tumor types will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study in subjects with metastatic NSCLC.

A DMC will monitor the conduct of the study.

Part 1 is planned to be conducted at selected sites and will be extended to additional global sites for the conduct of **Part 2.**

Study treatment is defined as sotatercept (ACE-011) in **Part 1** and sotatercept (ACE-011)/placebo in **Part 2**.

Three starting sotatercept (ACE-011) dose levels, 15, 30, and 45 mg, were selected for **Part 1** of the study. Up to approximately 90 subjects with advanced or metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for a total of four doses.

In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) (at the dose determined in **Part 1**) or placebo, at a ratio of 1:1:

- 375 subjects will receive sotatercept (ACE-011) (at the dose determined in **Part 1**)
- 375 subjects will receive placebo

Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses; two additional doses may be given at the discretion of the Investigator.

Part 2 will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.

The Treatment Period for **Part 1** is approximately six months, which includes up to 4 doses of sotatercept (ACE-011) and for **Part 2** approximately nine months, which includes up to 6 doses of sotatercept (ACE-011/placebo). Subjects who enter the Post Treatment Follow-Up Period will be followed for up to 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first.

Survival data will be collected monthly for up to 24 months following the subject's first dose of sotatercept (ACE-011) in **Part 1** or sotatercept (ACE-011)/placebo in **Part 2**.

At the time of randomization in **Part 1** and **Part 2**, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.

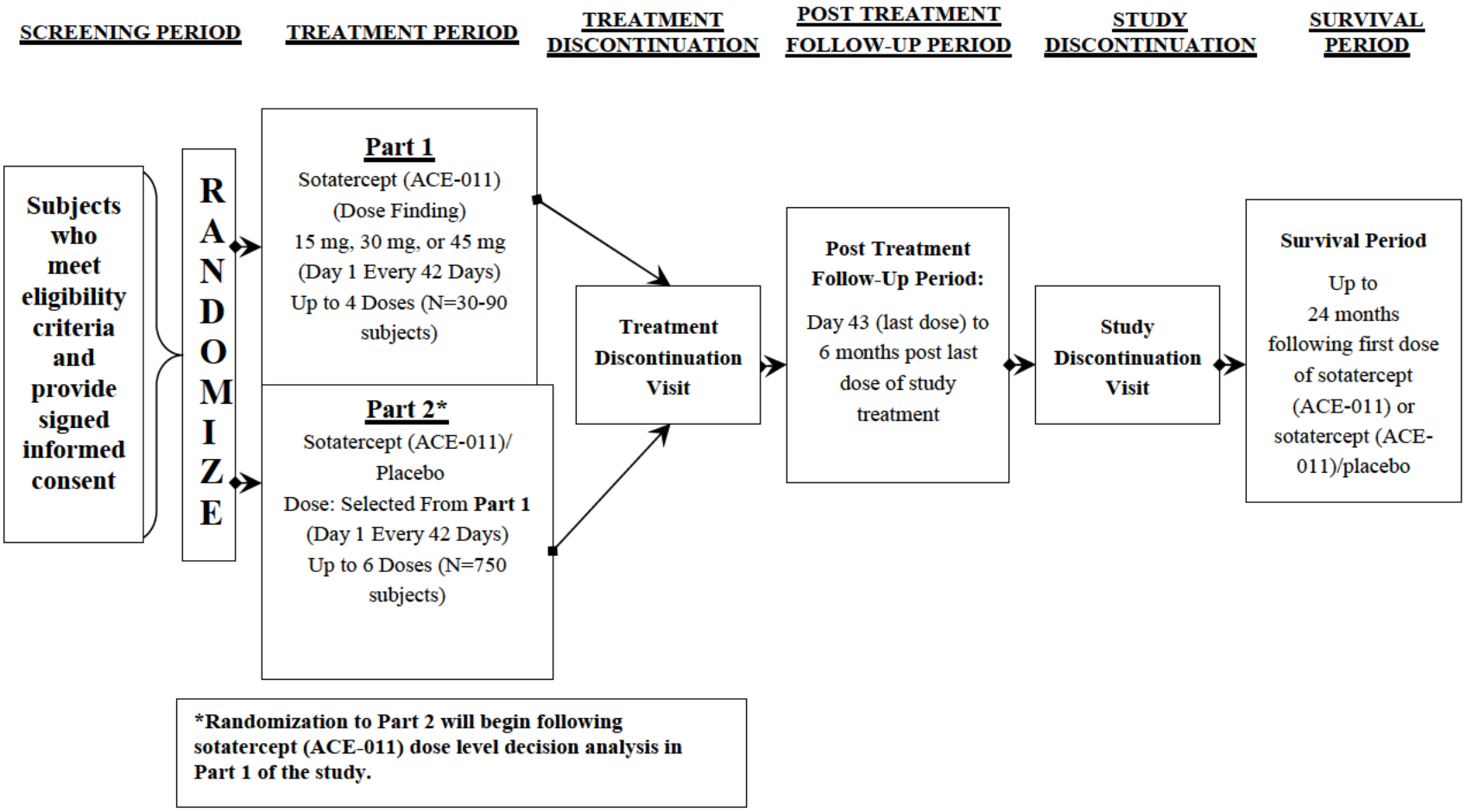
Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

- In **Part 1**, subjects will be randomized to one of three sotatercept (ACE-011) dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL

2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)

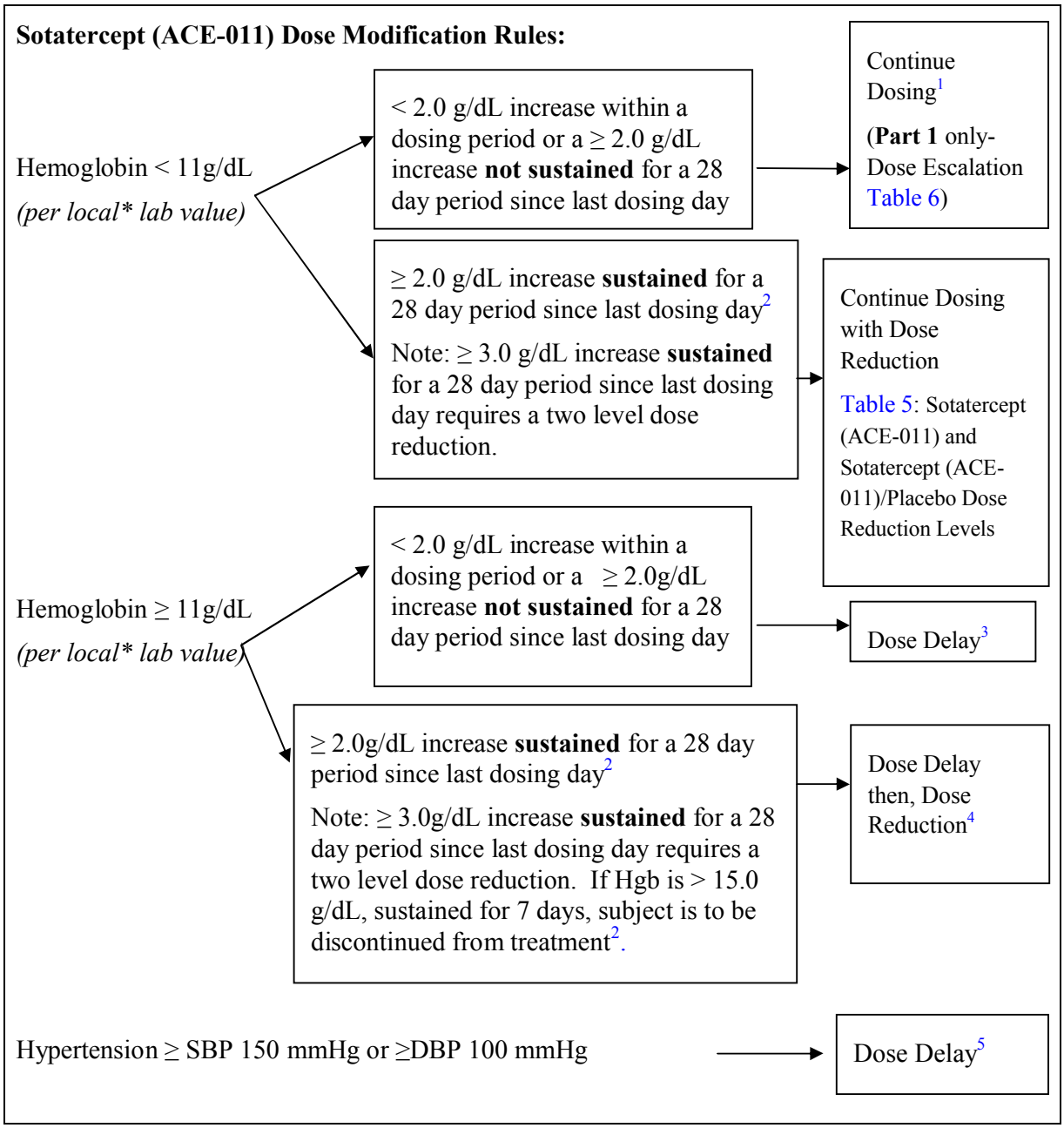
- In **Part 2** subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
  3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
  4. ECOG Performance Status 0-1 vs. 2

Figure 1: Study Design



4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained at least five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) or sotatercept (ACE-011)/placebo for the subject's **second** dose of study treatment and beyond.



*Note: Local laboratory assessments are allowed in cases when timely results are needed (e.g., randomization, study treatment and chemotherapy dosing decisions, hematology assessments between clinic visits). Whenever

possible a "split" sample should also be forwarded to the central laboratory for analysis. Local laboratory data should be collected in the eCRF.

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

For **Part 1** only: if the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011) should not be administered ≤ 7 days post RBC transfusion.

For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** sotatercept (ACE-011)/placebo dose if the transfusion was given greater than 7 days from the previous dose of sotatercept (ACE-011)/placebo AND the Hgb level is < 11 g/dL AND hypertension is < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011)/placebo should not be administered ≤ 7 days post RBC transfusion.

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , 21 (after first dose of study treatment) and 28 days after dosing, and reviewed in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels (Refer to sotatercept (ACE-011) and sotatercept (ACE-011)/Placebo Dose Reduction Levels (Table 5). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose that was **delayed**. Subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose is defined as a dose administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > SBP 150 mmHg or > DBP 100 mmHg and/or sotatercept (ACE-011) related toxicity).

[4]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011)or sotatercept (ACE-011)/placebo should be held until hypertension resolves to < SBP 150mmHg and < DBP 100 mmHg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: Sotatercept (ACE-011) and Sotatercept (ACE-011)/Placebo Dose Reduction Levels

When required, per dose modification rules above, sotatercept (ACE-011) dose(s) in **Part 1** and sotatercept (ACE-011)/placebo dose(s) in **Part 2** should be reduced as follows:

Dose Schedule Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days- 45 mg	38 mg	33 mg	28 mg
Every 42 days- 30 mg	26 mg	22 mg	18 mg
Every 42 days- 15 mg	13 mg	11 mg	9 mg

*Note: Any Hgb increase of ≥3.0 g/dL sustained for a 28 day period since last doing day will require a subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for four doses. An additional two doses (total of 6 doses) may be given only during **Part 2** at the discretion of the Investigator.

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

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. A dose level may not be increased following a dose reduction.

In **Part 2**, dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. Subjects in the placebo group who are designated to undergo dose reduction will continue to receive placebo.

Placebo will be administered at the same volume as the corresponding sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction.

Sotatercept (ACE-011) Dose Escalation Levels:

The following dose escalation rules apply for sotatercept (ACE-011) dose(s) in **Part 1** only. Dose escalations are not allowed in **Part 2**:

- Less than 1.0 g/dL increase in Hgb in response to prior sotatercept (ACE-011) dose
- Hgb level must be < 11.0 g/dL and hypertension < SBP 150mmHg and < DBP 100 mmHg
- Dose escalation to begin at next treatment visit

- Sotatercept (ACE-011) should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of Sotatercept (ACE-011) at the subsequent visit per the escalation table below.

Table 6: Sotatercept (ACE-011) Dose Escalation Levels (Part 1 Only)

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days-45 mg	50 mg	55 mg	61 mg
Every 42 days-30 mg	33 mg	36 mg	40 mg
Every 42 days-15 mg	17 mg	20 mg	23 mg

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011) and sotatercept (ACE-011)/placebo.

4.2. Study Design Rationale

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a rapid, sustained and dose-dependent increases in hematopoietic parameters, (Hgb, HCT and RBC counts) which occurred earlier than would be expected from a stimulation of erythropoiesis by an ESA. This observation, coupled with nonclinical data demonstrating some level of erythrocyte stimulatory effect in the presence of anti-erthyropoietin (EPO) antibodies, suggests that the hematopoietic effect of sotatercept is different from that of ESAs. Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Guidelines, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

4.2.1. Fixed Dose

Sotatercept (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 sotatercept (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 sotatercept (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 sotatercept (ACE-011) exposure. Because the Hgb response is dependent on sotatercept (ACE-011) exposure and because body weight is not a major source for the intersubject variability of sotatercept (ACE-011) exposure, a fixed dosing approach is considered to be appropriate for the current study.

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 by taking into consideration the rapid and prolonged Hgb response to sotatercept (ACE-011) as well as the dosing schedule for the platinum-based chemotherapies. The Hgb-increasing effect of sotatercept (ACE-011) was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks. In addition, as platinum-based chemotherapy is often administered once every 3 weeks, a once every 6 weeks dosing schedule allows administration of sotatercept (ACE-011) at the same visit for the chemotherapy, which is convenient to both subjects and study sites.

4.2.3. Starting Dose Levels in Part 1

Three starting dose levels, 15, 30, and 45 mg, were chosen for **Part 1** of the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of sotatercept (ACE-011) at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, sotatercept (ACE-011) had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal sotatercept (ACE-011) concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The three starting dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg, 31.5 mg, and 52.5 mg, respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three sotatercept (ACE-011) doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to sotatercept (ACE-011). In this study, the starting dose level of 45 mg (during the dose finding **Part 1**) will be implemented only after at least 10 subjects at each lower dose level (10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level) have been evaluated as well as following DMC review of safety data and assessment of dose effects on Hgb levels.

In addition, in this study, during the first 6-week treatment period for a 70 kg subject receiving the starting dose at 45 mg, the sotatercept (ACE-011) exposure ($C_{max,\ day\ 1\text{-}43}$ and $AUC_{1\text{-}43}$) is projected to be approximately 10% lower than the exposure for the dose regimen of 0.5 mg/kg once every 4 weeks. Afterwards, safety measures (Hgb and blood pressure) will be used to guide the adjustment of the second dose and beyond. Thus, the use of the 45 mg starting dose in the current study is not anticipated to significantly compromise subject safety.

In this study, the 45 mg group will have the highest starting dose, and it may be titrated up to 61.0 mg for the last dose (Dose 4). Assuming a 70 kg subject who receives the maximal amount of dose during the entire study (i.e., starting at 45 mg followed by dose escalation every 6 weeks to 50.0, 55.0, and 61.0 mg for Doses 2, 3, and 4, respectively), the projected cumulative AUC during the treatment period (168 days) would be approximately 60% of the steady state AUC cumulated during the same period at the NOAEL level of 1 mg/kg (given every 4 weeks for a

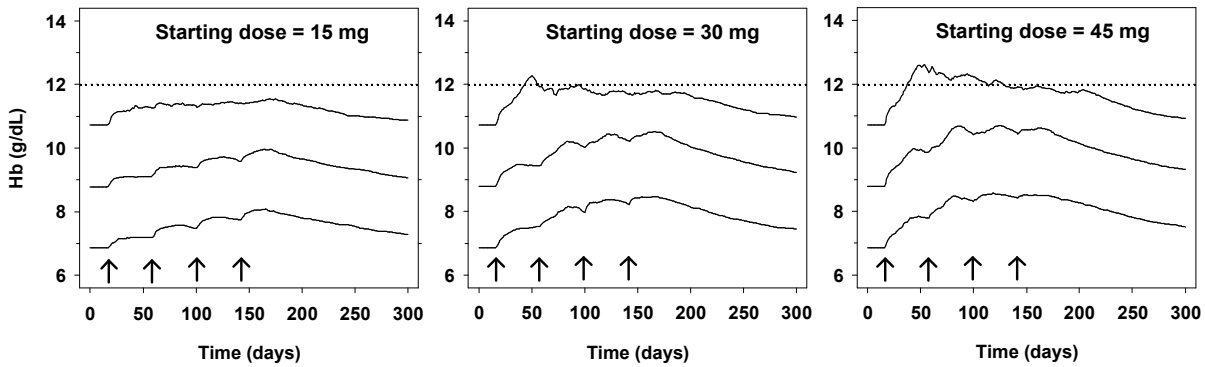
total of 6 doses) as reported in the 9-month, repeat-dose toxicity study in monkeys. The projected highest C_{max} for the current study would be less than 50% of the steady state C_{max} in the monkey study.

4.2.4. Evaluation of Dosing Schema via Modeling/Simulation

The performance of the proposed dosing schema (three fixed starting dose levels, 6-week dosing interval, and dose adjustment rules [see Section 4.1.1 for details]) for this study was evaluated via PK/pharmacodynamic modeling/simulation. A tentative mechanistic PK/pharmacodynamic model for Hgb was developed using PK and Hgb data from healthy postmenopausal women and the model was extended to include MM subjects as a sub-population. The model was required to appropriately reproduce the observed PK and Hgb profiles in MM subjects. Monte Carlo simulations of the Hgb response to sotatercept (ACE-011) in a hypothetical anemic population (6.5 ≤ baseline Hgb < 11 g/dL; body weight 47 – 108 kg) were performed using the model parameterized with preliminary PK and pharmacodynamic parameters from MM subjects. In this simulation analysis, efficacy refers to an Hgb increase > 1 g/dL from the baseline for 28 consecutive days while safety refers to both the absolute Hgb levels and the rate of Hgb increase.

The simulation predicts that the desired efficacy would be achieved 6 weeks after the second dose in approximately 70% subjects of the 45 mg group and 6 weeks after the last dose in >70% subjects of the 30 mg group. Further, the simulation predicts the Hgb level would be maintained under 12 g/dL in 90% subjects and under 13 g/dL in 95% of subjects during the course of the study (Figure 2). No subjects are predicted to have a Hgb level above the upper limit of the normal range for Hgb (16 g/dL). Approximately 6% subjects are predicted to have an Hgb rise > 2 g/dL within 28 days of the first dose, mostly from the 45 mg group (4%); however, the fraction of subjects with an Hgb rise > 3 g/dL per 28 days is predicted to be similar between the three dose groups (approximately 2.5% for each group).

Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population



The middle solid lines represent the median Hgb level. The top and bottom solid lines represent the Hgb level at 5% and 95% percentile, respectively. The area between 5% and 95% percentiles represents 90% prediction interval. The straight dot lines represent the Hgb level of 12 g/dL. The arrows indicate the dosing time of sotatercept (ACE-011). The two level dose reductions upon ≥ 3 g/dL increase sustained for 28 days of a dose (Table 5) was not included in the simulation.

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 60-90 subjects with advanced or metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2** will be randomized prior to receiving the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy. Each subject will be on the study for approximately 12 – 15 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up Period). The Treatment Period is approximately 6 to 9 months (four to six doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up Period of six months from the subjects' last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Subjects who discontinue treatment early will still continue to the Post Treatment Follow-Up Period for six months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

5. TABLE OF EVENTS

Table 7: Sotatercept (ACE-011) Schedule of Assessments

	Screening Period	Treatment Period									Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)										
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Complete Medical History	X																	
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X			X		X		X	X	X	X	X	X	X	
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X		X	X	X	X	X	
12-Lead Electrocardiogram (ECG) – **Part 1**[c]	X	X	X				X				X							
12-Lead Electrocardiogram (ECG) – **Part 2**[c]	X	X									X							
Pregnancy Testing[d]	X	X					X				X	X	X	X			X[d]	

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[f]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X		X	X	X	X	X	
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X							
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X		X					
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X	X	X	X	X	X	X	
FSH and LH – Males and Females	X	X	X				X		X		X			X			X	
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X			X			X	
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X			X			X	
TSH[k]	X	X					X[k]						X					

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose/End of Study Tx[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Sotatercept (ACE-011) drug antibody test (pre-dose)		X		X			X				X			X		X		
Bone Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[l] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X			X				
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X													X				
Activin A and other proteins/biomarkers in blood (serum) (pre-dose study treatment in a subset of subjects)		X	X				X					X						
Activin and other proteins/biomarkers in archival tumor tissue (**Part 2** only - optional)	X																	
Pharmacokinetics– (**Part 1** and **Part 2**)[n]		Refer to Table 8 and Table 9 – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X[o]	≤ Every 9 weeks or as per standard of care at study site																
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose only AEs assessed as related to study treatment are to be reported																
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X		X			X	X	

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 6 Schedule (± 3 days)											
Assessments	**Day -28 to Day -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D43/ D1**	**D8**	**D15**	**D29**	**D43 Post Last Dose/End of Study Tx[t]**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**5 Month**	**6 Month/ Study DC[u]**	**Survival**
Concomitant Procedures	X	X		X			X		X		X		X			X	X	
Hospitalizations (Record)	X	X		X			X		X		X		X			X	X	
Randomization		X																
Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X											
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice																
Targeted/Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[v]																		X
Post Treatment Anti-Neoplastic Therapy											X	X	X	X	X	X	X	X

[a]Include cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and advanced or metastatic site involvement. Record prior ESA history, starting at solid tumor diagnosis. Record RBC transfusion history, starting from diagnosis of advanced or metastatic disease, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) or sotatercept (ACE-011)/ placebo dose, at Treatment Discontinuation, and at Study Discontinuation. Blood pressure should be confirmed by two measurements obtained at least five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: For **Part 1**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011) dose, Day 8 post dose 1, every sotatercept (ACE-011) dosing Visit (post-dose) and at end of study treatment (day 43 post last dose).

For **Part 2**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011)/placebo dose and at end of study treatment (day 43 post last dose).

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days **prior** to the start of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo during the Treatment Period. Subjects must agree to use highly effective birth control measures (e.g., oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo to ensure levels are within normal limits and that sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment (**Part 1**).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the Treatment Period, every month (except month 1) during the Post Treatment Follow-Up Period and at study discontinuation .

Note: Footnotes [e], [f], [g]: Hematology, absolute reticulocyte count, serum chemistry and creatinine clearance are to be assessed ≤ 14 days prior to randomization.

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and end of study treatment (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. For full PK assessment, weekly after first dose of sotatercept (ACE-011).

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at 2 month post-treatment follow-up visit.

[l]Bone Biomarkers- Collected for **full** PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. For all other subjects collected prior to dose 1, prior to dose 2 , post last dose day 43 and month 3 post treatment follow-up visit. Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan of lumbar spine and hip to evaluate overall health on approximately 200 subjects at selected US site(s). Performed at Screening, and Month 3 during the Post Treatment Follow-Up Period.

[n]Pharmacokinetics (**Part 1**): Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15, 30 and 45 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.

Pharmacokinetics (**Part 2**): Sparse PK blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011) in approximately 300 (40%) of 750 subjects. Sotatercept (ACE-011) doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).

REFER TO Table 8 and Table 9, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening Period tumor assessments may be performed within six weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected. Following randomization, tumor assessments will be performed ≤ every 9 weeks or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments, FACIT Fatigue Scale (Version 4) – all subjects and LCSS questionnaire – only subjects with NSCLC, to be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the schedule, and at Study Discontinuation/One-Year Follow-Up Visit.

[q]Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing repeats every 42 days and will start after the subject begins a platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo **may be given at any time following the first dose of platinum-based chemotherapy. Subsequent doses** of Sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

[r]Platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded.

[s] Targeted/maintenance therapy (e.g. pemetrexed, erlotinib, etc.) is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose corresponds to the end of Treatment Period. Subjects who discontinue the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo Treatment Period early will continue to the Post Treatment Follow-Up Period and be followed for up to 6 months after their last dose of sotatercept (ACE-011)/placebo.

[u]Study Discontinuation visit should occur 12 months after starting treatment with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

[v]Survival data will be collected monthly, (can be via telephone contact), following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

Table 8: Schedule of Pharmacokinetic Assessments (Part 1)

Scheduled Time	Time relative to Sotatercept (ACE-011)	Part 1[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days
PT[f] Follow up, 1 month	72 days after final dose	X	-	± 1 week
PT Follow up, 2 month	102 days after final dose	X	-	± 1 week
PT Follow up, 3 month	132 days after final dose	X	X	± 1 week
PT Follow up, 4 month	162 days after final dose	X	-	± 1 week
PT Follow up, 5 month	192 days after final dose	X	X	± 1 week

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first sotatercept (ACE-011) dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first sotatercept (ACE-011) dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 30 subjects (approximately 10 subjects in each dose group).

[d] To be collected in subjects participating in sparse PK sampling and not participating in full PK sampling.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

[f] PT = Post Treatment

Table 9: Schedule of Pharmacokinetic Assessments (Part 2)

Scheduled Time	Time relative to Sotatercept (ACE-011)/placebo dose	Sparse PK[a,b,c]	Collection Window[d]
Dose 1, D1	pre-Dose 1	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	±1 hour
Dose 1, D8	7 days after Dose 1	X	± 3 day
Dose 1, D15	14 days after Dose 1	X	± 3 day
Dose 1, D29	28 days after Dose 1	X	± 3 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	± 3 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	± 3 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	± 3 days
Dose 4, D43 (Dose 5, D1)	pre-Dose 5	X	± 3 days
Dose 5, D43 (Dose 6, D1)	pre-Dose 6	X	± 3 days
PT[e] Follow up, 3 month	132 days after final dose	X	± 1 week
PT Follow up, 5 month	192 days after final dose	X	± 1 week

[a] For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

[d] Except for Day 1 (Dose 1, D1), the collection window will be the same as the visit window defined in Table 7.

[e] PT = Post Treatment

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed ≤ 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization or as per study site standard of care. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed ≤ 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac, renal and thromboembolic events
- Cancer history, including date of original diagnosis, histopathology, clinical stage at screening, date of advanced or metastatic stage and site involvement
- Prior ESA treatment history starting from the initial solid tumor diagnosis
- RBC transfusion history starting from diagnosis of advanced or metastatic disease at a minimum of up two months prior to randomization
- 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, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration
- Serum chemistry, hematology, absolute reticulocyte count to be assessed ≤ 14 days prior to randomization
- Creatinine clearance (per Cockroft-Gault formula) to be assessed ≤ 14 days prior to randomization
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and RBC folate levels
- Serum erythropoietin

- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Estrogen and estradiol – females only
- TSH
- Bone imaging – DXA scan (optional at selected sites)
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

In **Part 1** (the dose-ranging portion of the study), subjects who meet all eligibility criteria will be randomized utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

- In **Part 2**, subjects meeting all inclusion and exclusion criteria will enter into the Treatment Period and be randomized by a double-blind procedure utilizing IVRS to receive sotatercept (ACE-011) or placebo (1:1 ratio).

- A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days during the Treatment Period, as specified in the Table of Events (see Section 5).

In **Part 1**, the Treatment Period will last approximately 6 months, where subjects randomized to sotatercept (ACE-011) will receive treatment on Day 1 every 42 days for a planned 4 doses.

In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional 2 doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration.
- Serum chemistry, hematology, absolute reticulocyte count**.**
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and at subsequent sotatercept (ACE-011) or sotatercept (ACE-011)/placebo doses collected at 7, 14 days and 28 days post-dose.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 42 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and 42 days after last dose of study treatment
- Serum erythropoietin

- Urinalysis
- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (**pre-dose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre- dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo
    - pre-dose on Day 1 subsequent dosing visits
  - in archival tumor tissue (**Part 2** only)
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or per standard of care at the study site, starting from the previous [screening] tumor assessment) and following the chemotherapy schedule
- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and all AE/SAE reporting (regardless of causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or targeted/maintenance therapy
- Administration of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo at: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will enter the Post Treatment Follow-Up Period and be followed for 6 months after their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Upon completion of the Post Treatment Follow-Up Period, subjects will have a discontinuation visit and be followed for survival for up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

Post Treatment Follow-Up Period (Day 43 post last dose of study treatment to six months post last dose of study treatment)

Following completion or early discontinuation from the Treatment Period, subjects will enter the Post Treatment Follow-Up Period and continue to be followed for 6 months after their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every month. The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)
- Vitamin B12 and RBC folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH (at 2 month end of treatment follow-up visit)
- Serum for sotatercept (ACE-011) drug antibody test (pre-sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Bone imaging – DXA scan (optional at selected sites-performed at 3 month end of treatment follow-up visit)
- Activin A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood at 1 month end of treatment follow-up visit)
- Pharmacokinetics
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or as per standard of care at the study site, and following the chemotherapy schedule

- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Study Discontinuation

Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects.

Subjects who discontinue from treatment early will enter the Post Treatment Follow-Up Period and be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Follow-up for twelve months for TTP and PFS will be performed from the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/Placebo. Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) – if Study Discontinuation date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Estrogen and estradiol – females only
- Dihyroepiandosterone and testosterone (free and total) – males only

- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1) (PFS at 12 months)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

Survival Follow-Up Period:

Monthly collection of survival data will begin following the Study Discontinuation Visit and continue for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

- Overall survival
- Post-Treatment Anti-Neoplastic Therapy

Additional Procedure Descriptions:

Central ECG

Part 1 – ECGs will be performed and read per Central ECG vendor.

Part 2 – ECGs will be performed locally and read per Central ECG vendor.

Please refer to vendor manual for procedures.

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone) will be performed by a central laboratory.

Please refer to vendor manual for procedures.

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

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin) and in archival tumor tissue in a subset of subjects (**Part 2** only).

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin will be evaluated in all subjects.

Pharmacokinetics

- **Part 1** -Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 30 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group). For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.
- **Part 2**- Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).

For subjects who do not participate in either **Part 1** full or sparse PK assessments or in **Part 2** sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Detailed PK sampling schedule is presented in Table 8 and Table 9: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

Bone Biomarkers

Bone biomarkers will be evaluated in all subjects. The serum and urine bone biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

Bone Imaging - optional

DXA scan to evaluate overall bone health will be performed on approximately 200 subjects at select site(s).

Quality of Life Assessments

QoL Assessment (FACIT Fatigue Scale [Version 4]) will be completed by all subjects and LCSS questionnaire will be completed for subjects with NSCLC. Each assessment will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).

Independent External Radiology Review (Part 2 Only)

At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).

Independent Review Committee (IRC) (Part 2 Only)

The IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression for each subject. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS for the Clinical Study Report.

7. STUDY POPULATION

At the time of randomization in **Part 1** and **Part 2**, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.

7.1. Number of Subjects

This platinum-based CIA study will enroll approximately 840 subjects, approximately 90 subjects with advanced or metastatic solid tumor types in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**.

In **Part 1**, up to 90 subjects will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC
- Sotatercept (ACE-011) 45 mg SC

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)

In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in **Part 1**, or placebo at a ratio of 1:1. Subjects will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL

2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)
3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)
4. ECOG Performance Status 0-1 vs. 2

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. **Part 1** – Histologically confirmed (cytology or biopsy) solid tumor malignancy, excluding those solid tumors treated with curative intent.

   Part 2 - Histologically confirmed (cytology or biopsy) non-small cell lung cancer.
3. Documented advanced or metastatic disease.
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L), due to chemotherapy-induced anemia
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function:
     - creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin is concomitantly administered

       and
     - urine protein / creatinine ratio ≤ 1.0; or ≤ 2.0 if bevacizumab (Avastin®) is concomitantly administered
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤ 5.0 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL) or ≤ Grade 1. Previous hypercalcemia treatment is allowed
6. Subjects must:
   - have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

     OR
   - have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

     OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy
- For **Part 1**- any platinum-based regimen approved for the specific indication
- For **Part 2** -allowed regimens for the treatment of metastatic NSCLC are:
  - gemcitabine plus cisplatin or carboplatin ± bevacizumab
  - pemetrexed plus cisplatin or carboplatin ± bevacizumab
  - taxanes plus cisplatin or carboplatin ± bevacizumab

7. ≥ 28 days must have elapsed since previous treatment with ESA
8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 30 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)
10. 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 at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days **prior** to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).
11. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, even if he has undergone a successful vasectomy.
12. Life expectancy of ≥ 3 months.
13. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.

14. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C]) at the time of screening, including Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g., asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non-hematological events (e.g., nausea, vomiting, fatigue, or muscle or bone/joint pain), occurring during the chemotherapy period and resolving.
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 subject participation in the study, at the discretion of the Investigator.
3. Part 2 only, history of prior regimen(s) of platinum-based chemotherapy for metastatic NSCLC and/or history of adjuvant platinum-based chemotherapy with last dose received less than six months prior to the start of current first-line platinum-based chemotherapy for metastatic NSCLC.
4. CNS metastases **(exception: subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks prior to randomization)**.
5. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying malignancy.
6. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).
7. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.
8. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
9. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
10. Uncontrolled hypertension. Controlled hypertension is considered clinically stable and systolic blood pressure (SBP) must be < 150 mmHg and diastolic blood pressure (DBP) must be < 100 mmHg.
11. Known infection with human immunodeficiency virus (HIV).

12. Known active hepatitis B or C antibody defined by positive serology.
13. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.
14. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
15. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.
16. 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.
17. Any prior use of sotatercept (ACE-011).
18. Pregnant or lactating females or females planning to become pregnant.
19. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).
20. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

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 sotatercept (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 sotatercept (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 sotatercept (ACE-011). The reconstituted sotatercept (ACE-011), in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.

Placebo (Part 2 Only):

In **Part 2**, the sotatercept (ACE-011) placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Sterile, normal saline will be supplied by the investigational site's pharmacy. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.

8.2. Treatment Administration and Schedule

Sotatercept (ACE-011) or placebo will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization in **Part 1** and **Part 2**, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.

Allowed concomitant platinum-based chemotherapy regimens are:

- For **Part 1**- any platinum-based regimen approved for the specific indication
- For **Part 2** -allowed regimens for the treatment of metastatic NSCLC are:
  - gemcitabine plus cisplatin or carboplatin ± bevacizumab
  - pemetrexed plus cisplatin or carboplatin ± bevacizumab
  - taxanes plus cisplatin or carboplatin ± bevacizumab

Investigative sites will utilize commercial supply of these medications.

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

In **Part 1** and **Part 2**, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb. Dose delays of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

In **Part 1**, subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-30 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.

Following this analysis, the addition of a third dose level:

- Sotatercept (ACE-011) 45 mg SC

to the randomization schema will be determined.

Each dose level will be administered every 42 days for up to four doses.

The following are decision rules for dose determination in **Part 1** in order to move forward to **Part 2**:

- After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.
- Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions and/or ESAs. In order to determine the dose of sotatercept (ACE-011) to be used in

Part 2, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) dose 1/day 1 through and including dose 2/day 43 (prior to dose 3).

- In addition to the hematopoietic response, safety profile, dose modifications and extent of exposure will be taken into account for dose level selection for **Part 2**.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

In **Part 2**, subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in **Part 1**) or placebo.

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo starting on Day 1 (one SC dose every 42 days) and continuing during the six-month (**Part 1**) or nine-month (**Part 2**) Treatment Period, as outlined in the Table of Events (see Section 5).

In **Part 1**, subjects will be randomized to receive one of three dose levels of sotatercept (ACE-011), with 10-30 subjects per arm. In **Part 2**, 750 subjects will be randomized to receive sotatercept (ACE-011) or placebo at a ratio of 1:1.

Each subject will return to the site on each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) or sotatercept (ACE-011)/placebo every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated weekly after the first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.

The **first dose** of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered **at any time after the first cycle and prior to the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy.**

Subsequent doses of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) or sotatercept (ACE-011)/placebo administration does not need to be delayed until start of next chemotherapy cycle.

Following completion of the Treatment Period, subjects who enter the Post Treatment Follow-Up Period will be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their advanced or metastatic disease, whichever occurs first.

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of advanced or metastatic disease that requires the initiation of another treatment.

Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).

8.2.3. Discontinuation

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100mmHg) confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy.
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0; or > 2.0 if bevacizumab (Avastin®) is concomitantly administered
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week
- In **Part 1**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).
- Concomitant use of ESAs – In **Part 1** if administered at any time and in **Part 2** if administered < 4 months after first dose of study treatment.
- Sotatercept (ACE-011) or Sotatercept (ACE-011)/placebo Dose Modifications
  - In **Part 1** and **Part 2**: A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL
  - In **Part 2:** > 3 dose reductions and/or delays
- Disease Progression
- Withdrawal of consent

- Death
- Lost to follow-up
- Protocol violation – as determined by the Sponsor

The reason for treatment discontinuation should be recorded in the eCRF 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 (subject has completed six- to nine- month Treatment Period plus up to six-month Post Treatment Follow-Up Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months after first dose of study treatment.
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse events(s)
- Disease progression
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF 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.

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to 4 doses of sotatercept (ACE-011) in **Part 1**. In **Part 2**, subjects will be randomized at a ratio of 1:1 and receive up to 4 doses of study treatment and may receive 2 additional doses of sotatercept (ACE-011)/placebo, if clinically indicated, at the discretion of the Investigator. A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

8.4. Packaging and Labeling

The label(s) for investigational product (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 sotatercept (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 secured location. The investigational site must maintain accurate records demonstrating dates and amounts of sotatercept (ACE-011) received, to whom it was administered (subject-by-subject accounting), and accounts of any sotatercept (ACE-011) accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of sotatercept (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 sotatercept (ACE-011) to the Sponsor at the end of the study, or the sotatercept (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 investigational medicinal product.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF 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

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 and 7.3 Inclusion Criteria and 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 eCRF throughout the course of the study.

Concomitant therapies considered as supportive care are acceptable while participating in this study, including growth colony stimulating factors (G-CSF); anti-emetics to limit chemotherapy-related nausea and vomiting; palliative radiation; bisphosphonates and denosumab therapy for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

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.

Iron supplementation

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

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment. The use of ESAs will need to result in immediate notification to the study Sponsor and Medical Monitor, as well as to the clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

In **Part 1**, all subjects who receive an ESA will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up Period. In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up Period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the Treatment Period as follows: **The unblinded pharmacist will ensure that subjects randomized to receive treatment with**

sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo. The investigator, site personnel and subject will remain blinded.

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered >7 days from the date of the RBC transfusion.

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate , other than for the treatment of hypercalcemia, and denosumab therapy for bone metastases can be started prior to randomization but should not be started on study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. In **Part 1**, subjects will be randomized to one of three doses of sotatercept (ACE-011) plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected sotatercept (ACE-011) dose determined from **Part 1** plus platinum-based chemotherapy. Data from **Part 1** will not be combined with data from **Part 2** in all safety and efficacy analyses.

A DMC will be used to monitor the study conduct.

10.2. Study Population Definitions

- Three study populations will be used for analyses.
- The Intent-to-Treat (ITT) Population – All randomized subjects.
- Safety Population – All subjects who take at least one dose of study medication.
- Efficacy Evaluable (EE) Population – All ITT subjects who take at least one dose of study medication and have baseline and at least one post-baseline efficacy assessment without major protocol deviation.

10.3. Sample Size and Power Considerations

In **Part 1**, up to 90 subjects will be randomized among three dosing groups. This sample size is for the purpose of hypothesis generation. However, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a two-sided significance level (alpha) of 0.05.

In **Part 2**, subjects will be enrolled in two stages. In the first stage, approximately 180 subjects will be randomized in a 1:1 ratio to the selected sotatercept (ACE-011) dose group or placebo group. An interim analysis of transfusion rate will be performed after these 180 subjects have received at least two doses of sotatercept (ACE-011)/placebo, and have been followed for at least 4 months from randomization. A Data Monitoring Committee will review the results and provide recommendations on continuing or stopping the study. Based on the results of the futility analysis, further enrollment in the second stage of **Part 2** of the study could be continued.

Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in **Part 2** (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to

exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics by treatment arm, 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 by treatment arm. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

In **Part 1**, the primary endpoint will be the hematopoietic response defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.

In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the date of randomization. It will be estimated based on Kaplan-Meier method for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects who have documented RBC transfusion(s) from randomization until the last dose of concomitant platinum-based chemotherapy plus 30 days or from the initiation date of non-platinum-based chemotherapy, whichever is earlier, will be considered as having the event on the date of first RBC transfusion. Subjects who are discontinued from study treatment due to reasons other than disease progression or death will be considered as having the event on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Subjects who discontinue from study treatment due to disease progression or death will be censored on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Otherwise subjects will be censored on the date of last contact, or on the date of last dose of concomitant platinum-based chemotherapy plus 30 days or on the initiation date of non-platinum-based chemotherapy, whichever is earliest. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test, and the associated hazard ratio and 95% confidence interval will be provided using Cox proportional hazard model. The proportion of subjects receiving a transfusion based on Kaplan-Meier estimates at specific time points will also be provided by treatment arms.

As secondary endpoints for **Part 2** of the study, time to progression, progression free survival and overall survival will be analyzed based on the ITT population.

Time to progression (TTP) is defined as the time between the randomization date and date of disease progression. **Disease progression is based on the IRC reviewed progression date.** If a subject dies due to reasons other than disease progression, the subject will be censored at the death date. If a subject does not have disease progression, then the subject will be censored at the last tumor assessment (prior to or on the first day of the first subsequent antitumor therapy).

Progression free survival (PFS) is defined as the time between the randomization and disease progression or death. **Disease progression is based on the IRC reviewed progression date.** Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the subject is censored at the time of last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. The date of progression is taken as the earliest date of: Date of PD as evaluation of response, date of new lesion on tumor measurements page, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who did not progress nor died (lost to follow-up or still being treated without documented disease progression or started subsequent antitumor therapy) will be censored at the date of the last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. PFS based on investigators' assessment will also be analyzed.

Overall survival (OS) is defined as the time between the randomization and death. A subject who dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.

For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the distribution function, six-month and one-year survival rates, as well as the medians and 95% confidence intervals will be provided. The stratified log rank test will be used to compare the distributions of TTP, PFS and OS respectively. The stratification factors are described in Section 4.1 . The associated hazard ratios and confidence intervals will be provided using stratified Cox proportional hazard model respectively for each endpoint.

Sensitivity analyses will be performed on TTP, PFS, and efficacy analyses will also be performed using EE population. Data listings will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.

10.7. Safety Analysis

All safety subjects will be used for safety analyses. Sotatercept (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 study part and treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized.

Safety information obtained during the Post Treatment Follow-Up Period during each segment will be incorporated into these analyses.

10.8. Interim Analysis

There are two interim analyses planned for this study. At the first interim analysis, the transfusion rate result will be used for go/no go decision, and overall survival will also be analyzed. At the second interim analysis, only the overall survival will be analyzed.

The first interim analysis on transfusion rate will be conducted after the first 180 eligible subjects randomized in **Part 2** of the study (stage 1) who have received at least two doses of sotatercept (ACE-011)/placebo, have been followed for at least 4 months from randomization. This sample size would allow at least 90% power to detect a 15% difference between two arms (sotatercept [ACE-011] arm 15% vs. placebo 30%) in 4 month transfusion rates at two-sided 5% significance level based on the stratified log rank test and the assumption of exponential distribution for time to RBC transfusion. If the p-value at the interim analysis does exceed significance level of 0.05, the result will be considered as lack of efficacy. If the p-value is less than or equal to 0.05, additional subjects will be enrolled and the study will move on to the **Part 2**; however, the futility analysis result based on RBC transfusion rate may be up to DMC evaluation. For superiority, Type I error 0.0001 will be spent at this interim for transfusion rate, and the remaining 0.0499 will be spent at the final analysis after 750 subjects being enrolled.

Overall survival will also be analyzed at this interim, Type I error spending will be based on O'Brien and Fleming Boundary.

The second interim analysis will be performed when approximately 265 deaths are observed in **Part 2**. Type I error spending will be based on O'Brien and Fleming boundary.

The final analysis will be performed when approximately 536 deaths are observed in **Part 2**.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 10 subjects will be enrolled for full PK sampling in each treatment cohort of **Part 1**. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC_{42}, and $t_{1/2}$,z, will be estimated for subjects providing full PK samples. Dose proportionality will be assessed by regression analysis using the exposure data after the first dose. Descriptive statistics will be provided for plasma concentrations and PK parameters.

In exploratory population PK analysis, covariates to be tested may include type of chemotherapy, the presence of anti-sotatercept (ACE-011) antibodies, demographics (age, race, gender, and body weight), markers for hepatic and renal function, and other factors as deemed appropriate. Both full and sparse PK data will be included for population PK analyses.

The relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) will be explored.

10.10. Data Monitoring Committee (DMC)

A DMC will review safety and efficacy data to ensure the protection of study subjects. The DMC will receive periodic updates of all serious treatment-related toxicities and SAEs leading to deaths from all causes. The first planned review by the DMC will be conducted following the randomization and treatment of twenty subjects. The DMC will continue to monitor safety on an ongoing basis including recommendation of sotatercept (ACE-011) dose selection for **Part 2**. The first interim analysis will be conducted after the first 180 eligible subjects in **Part 2** of the study (stage 1) have been followed for at least 4 months for RBC transfusion rate. The second interim analysis will be performed when approximately 265 deaths are observed in **Part 2**. The final analysis will be performed when approximately 536 deaths are observed in **Part 2**.

Ad hoc meetings will be scheduled as needed.

The DMC will have a consultative role with respect to the Sponsor. The Sponsor will make the final decision regarding the recommendation proposed by the committee. A separate DMC charter will detail the activities of this committee.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. Seriousness

An 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of 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 (delay) 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 an SAE.

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

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

The female subject should be referred to an 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 investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Immediate 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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (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.

11.6. 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.

11.7. Expedited Reporting of Adverse Events

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

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics

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

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (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

Please refer to Section 8.2.3.

Stopping Rules

In addition to Celgene routine pharmacovigilance surveillance, a DMC will review unblinded data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

In both **Part 1** and **Part 2** the blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.

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 eCRFs 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via an electronic data capture (EDC) system rather than paper. Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. The Clinical team and investigational site personnel will be alerted of discrepant data by the functionality of the system. 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMEA, 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

Aapro M, Vaupel P. Erythropoietin: effects on life expectancy in patients with cancer-related anemia. *Curr Med Res Opin.* 2006; 22(suppl 4):5-13.

Carlos JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer.* 2001; 91:2214-2221.

Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue, and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol.* 2004; 15:979-986.

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. J Bone Miner Res 2010; 25 (12), 2633-46, Erroatum in J Bone Miner Res 2011; 26 (2), 439

Chen Y-G, Lui HM, Lin S-L, Lee JM, and Ying S-Y. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. *Exp Biol Med* 2002; 227: 75-87.

Dang TP, Carbone DP: Cancer of the Lung, in DeVita, VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 8th edition, Philadelphia, PA. Lippincott Williams & Wilkens, 2008, 887-971.

Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F Version 4. *http://www.facit.org/qview/qlist.aspx*, last accessed 21Jul2010.

Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer.* 1999; 86:1528-1536.

Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *Journal of the National Cancer Institute* 1999, 91, 1616-1634.

Hollen, PJ, Gralla, RJ, Kris, MG, and Potanovich, LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). European Journal of Cancer, 1993; 29A, S51-S58.

Hollen, PJ, Gralla, RJ, Kris, MG, & Cox, C. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1994a; 2, 213-222.

Hollen, PJ, Gralla, RJ, Kris, MG, Cox, C, Belani, CP, Grunberg, SM, Crawford, J, and Neidhart, JA. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer, 1994b; 73, 2087-98.

Hollen PJ, Gralla RJ, Kris MG 'Lung Cancer Symptom Scale (LCSS)', *Administration, Scoring and Procedures Manual*, (1995) Ver.1.1.

Hollen, PJ, Gralla, RJ, Kris, MG, Eberly, SW, and Cox, C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1999; 7, 140-148.

Hong WK, Tsao AS, in Lung Carcinoma: Tumors of the Lungs: Merck Manuals Online Medical Library for Healthcare Professionals, 2008.
http://www.merck.com/mmpe/print/sec05/ch062/ch062b.html

Laurie SA, Jeyabalan N, Nicholas G, Dahrouge S. Association between anemia arising during therapy and outcomes of chemoradiation for limited small-cell lung cancer. *J Thorac Oncol.* 2006;146-151.

Lotinun S, Fajardo RJ, Pearsall RS, Bouxsein ML, and Baron R. A soluble activin receptor type IIA fusion protein, ACE-011, increases bone mass by stimulating bone formation and inhibiting bone resorption in cynomolgus monkeys. ASBMR 30th annual meeting, 2008.

MacRae R, Shyr Y, Jonson D, Choy H. Declining hemoglobin Turing chemoradiotherapy for locally advanced non-small cell lung cancer is significant. *Radiother Oncol.* 2002;64:37-40.

Mathews LS. Activin receptors and cellular signaling by the receptor serine kinase family. *Endocr Rev* 1994; 15: 310-25.

Murata M, Onomichi K, Eto Y, Shibai H, and Muramatsu M. Expression of erythroid differentiation factor (EDF) in Chinese hamster ovary cells. *Biochem Biophys Res Commun* 1988; 151: 230-5.

Nakao K, Kosaka M and Saito S. Effects of erythroid differentiation factor (EDF) on proliferation and differentiation of human hematopoietic progenitors. *Exp Hematol* 1991; 19: 1090-5.

National Heart, Lung, and Blood Institute, National Institutes of Health. New York Heart Association Classification. 2008.

NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, V.2. 2010 http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf; 2009.

Non-small Cell Lung cancer Collaborative Group 'Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials', *British Medical Journal* 1995 vol. 311, no.7010, 899-909.

Obermair A, Cheuk R, Horwood K, et al. Anemia before and during concurrent chemoradiotherapy in patients with cervical carcinoma: effect on progression-free survival. *Int J Gynecol Cancer.* 2003; 13:633-639.

Oken, MM., Creech, R.H., Tormey, D.C., et. al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982; 5:649-655.

Parker SL, Tong T, Bolden S, et. al. Cancer statistics, 1997. *CA Cancer J Clin*, 1997, 47, no. 1, 5-27.

Pearsall RS, Canalis E, Cornwall-Brady M, Underwood KW, Haigis B, Ucran J, Kumar R, Pobre E, Grinberg A, Werner ED, Glatt V, Stadmeyer L, Smith D, Seehra J, and Bouxsein ML. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. Proc Natl Acad Sci USA 2008, 105: 7082-7.

Perrien DS, Akel NS, Edwards PK, et. al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology* 2007; 148: 1654-65.

Rivier J, Spiess J, McClintock R, Vaughan J and Vale W. Purification and partial characterization of inhibin from porcine follicular fluid. *Biochem Biophys Res Commun* 1985; 133: 120-7.

Rossi A, Maione P, Gridelli C Cetuximab in advanced non-small cell lung cancer. *Critical Reviews in Oncology/Hematology*, 2006 59, 139-149.

Ruckle J, Jacobs M, Kramer W, et. al. A single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res* 2009; 24 (4): 744-52.

Sandler A, Gray R, Perry M, et al Paclitaxel-Carboplatin alone or with Bevacizumab for Non Small Cell Lung Cancer, *NEJM*, 2006 vol.355, no.24, 2542-50.

Scagliotti G, Parikh P, von Pawel J, et al Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve patients With Advanced-Stage Non-Small-Cell Lung Cancer, JCO, 2008, 26 (21): 3543-51.

Schiller J, Harrington D, Belani C, et al Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. *Am J Health Syst Pharm.* 2007; 64 (suppl 2):S5-S13.

Seder C, Hartojo W, Lin L, et al Upregulated INHBA Expression May Promote Cell Proliferation and Is Associated with Poor Survival in Lung Adenocarcinoma, Neoplasia, 2009, 11: 388-396.

Shedden K, Taylor J, Enkemann S, et al Gene Expression-Based Survival prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validation Study: Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Nat Med, 2008, 14 (8): 822-827.

Shiozaki M, Sakai R, Tabuchi M, et. al. Evidence for the participation of endogenous activin A/erythroid differentiation factor in the regulation of erythropoiesis. *Proc Natl Acad Sci USA* 1992; 89: 1553-6.

Shiozaki M, Sakai R, Tabuchi M, et. al. In vivo treatment with erythroid differentiation factor (EDF/activin A) increases erythroid precursors (CFU-E and BFU-E) in mice. *Biochem Biophys Res Commun* 1989; 165: 1155-61.

Vansteenkiste J, Pirker R, Massuti B, et. al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute, 2002, 94: 16: 1211-1220.

Woodruff TK. Regulation of cellular and system function by activin. *Biochem Pharmacol* 1998; 55: 953-63.

Ying S-Y. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine Rev* 1988; 9: 267-93.

19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Terms	**Definition**
Measurable disease	The presence of at least one measurable lesion by CT or MRI. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions	Lesions that can be accurately measured in least one dimension by CT scan with longest diameter $\geq$ 10 mm (CT scan thickness no greater than 5 mm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Non-measurable lesion	All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

RECIST Criteria-Response Evaluation

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
***Partial Response (PR)*:**	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
***Stable Disease (SD)*:**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
***Progressive Disease (PD)*:**	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

RECIST Criteria-Response Evaluation (continued)

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of best overall response	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (2009). European Journal of Cancer 45, 228-247.

Appendix B: 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 10: 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 C: 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 D: New York Heart Association - Classification of Heart Failure

Table 11: 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

– SUMMARY OF CHANGES –

AMENDMENT NO. 4

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
ORIGINAL DATE:	17 SEPTEMBER 2010
AMENDMENT No. 4 DATE:	02 MAY 2012
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

Contact Information:	
PPD	

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

Area Head

02 May 2012

dd mmm yyyy

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

On February 15, 2012 a letter was sent to all ACE-011-NSCL-001 study sites notifying them that Celgene and Acceleron had decided to discontinue further enrollment of subjects into the study. This action was taken in response to slow enrollment into the study. Despite significant efforts made by study sites and sponsor support, recent substantial changes in the standard of care for cancer patients with anemia have resulted in challenges to timely accrual and completion of the study. The discontinuation of enrollment and thereby early termination of Study ACE-011-NSCL-001 is not related to subject safety. This protocol amendment is provided to include revisions to the current protocol based on this decision. Research and development of ACE-011 remains ongoing in several other indications.

Completion of study enrollment is targeted for the end of 1Q2012.

Significant changes included in this amendment are summarized below. These changes were based on feedback obtained from investigators/sites, key opinion leaders and internal discussions:

- Modified to remove all procedures, reviews and assessments specific to Phase 2B/3 (Part 2) of the study.
- Modified to remove all reference to the Phase 2B/3 (Part 2) of the study.
- Modified to remove reference to study treatment as "sotatercept (ACE-011)/placebo" due to removal of Phase 2B/3 portion of the study.
- Modified to remove the term "Part 1" of the study and all references to "Part 1".
- Modified to remove the sotatercept (ACE-011) 45 mg dose level.
- Modified to revise sample size from approximately 90 subjects to approximately 30 subjects in Part 1 of the study.
- Modified to revise the number of subjects planned for the remaining sotatercept (ACE-011) dose levels of 15 mg and 30 mg from approximately 30 to approximately 10-15.
- Modified to remove reference to safety data analysis of 15mg and 30mg sotatercept (ACE-011) dose levels prior to addition of the 45mg sotatercept (ACE-011) dose level.
- Modified to:
    a. Abbreviate Post-Treatment Follow-Up Period from six months to 42 days (six weeks).
    b. Revise term "**Post-Treatment Follow-Up Period**" to "**Post-Treatment Follow-Up Visit**".
    c. Clarify that the Post-Treatment Follow-Up Visit will also serve as the End of Treatment/End of Study Visit.

d. Add sotatercept (ACE-011) drug antibody repeat assessments following the Post Treatment Follow-Up / End of Treatment / End of Study Visit for subjects with a positive sotatercept (ACE-011) titer.

- Revision of Study Objectives:
  a. Modified to change all study objectives to exploratory.
  b. Modified to delete objective to estimate effect of sotatercept (ACE-011) on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) due to smaller sample size and abbreviated follow-up period.
  c. Modified to delete objective to explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) due to smaller sample size and abbreviated follow-up period.
  d. Modified to delete objective to evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only) due to removal of Phase 2B/3 portion of the study.
- Revision of Study Endpoints:
  a. Modified to change all study endpoints to exploratory.
  b. Modified to revise definition of hematopoietic response to remove criterion needed to move from **Part 1** to **Part 2** of the study and clarify that sotatercept (ACE-011) doses and hemoglobin levels will be reviewed.
  c. Modified to delete endpoints of effect of sotatercept (ACE-011) on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) due to smaller sample size and abbreviated follow-up period.
  d. Modified to delete population PK model for sotatercept (ACE-011) due to smaller sample size.
  e. Modified to delete population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics due to smaller sample size and abbreviated follow-up period.
  f. Modified to delete endpoint of the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only) due to removal of Phase 2B/3 portion of the study.
- Modified to remove references to the Data Monitoring Committee (DMC). An organization Data Monitoring Committee meeting was held to discuss the objectives of the committee and the charter but there were no additional meetings held and no study data was reviewed by the committee. Safety data will continue to be monitored by the sponsor.

- Modified to clarify that subjects will receive "**up to** four doses" of sotatercept (ACE-011) versus "four doses" as subjects may receive from one to four doses of sotatercept (ACE-011).
- Modified to remove Survival Follow-Up Period including collection of overall survival and post treatment anti-neoplastic therapy data past the 42 day (six week) Post-Treatment Follow-Up Visit.
- Modified to clarify that the study will only be conducted at sites in the United States.
- Modified to revise stratification to include other non-cisplatin platinum-based chemotherapy in addition to carboplatin due to addition of other allowed tumor types in Amendment 3.
- Modified to revise Pharmacokinetics Assessments to reflect decrease in sample size and abbreviated follow-up period.
- Modified to delete Section 4.2.4 : Evaluation of Dosing Schema via Modeling/Simulation as simulation performed does not seem to be supported by the observed clinical data in subjects with chemotherapy-induced anemia.
- Revision of Table 7: Sotatercept (ACE-011) Schedule of Assessments:
    a. Modified to delete Post-Treatment Follow-Up Period and Survival Follow-Up Period.
    b. Modified to replace "D43 Post Last Dose/End of Study Treatment" with "D43 Post Treatment Follow-Up/End of Treatment/ End of Study Visit".
    c. Addition of the following assessments to the "D43 Post Treatment Follow-Up/End of Treatment/ End of Study Visit":
        i. TSH
        ii. Bone Imaging (DXA)- optional
        iii. Activin A and other proteins/biomarkers in blood (serum)
    d. Addition of sotatercept (ACE-011) drug antibody repeat assessments following the Post Treatment Follow-Up / End of Treatment / End of Study Visit for subjects with a positive sotatercept (ACE-011) titer.
- Modified to better clarify that the LCSS questionnaire consists of two scales, a Patient Scale and an Observer Scale.
- Modified to provide additional instructions on the storage of reconstituted sotatercept (ACE-011) drug product.
- Modified to revise Statistical Section to reflect changes in analyses due to decrease in the sample size, abbreviated follow-up period, and removal of the Phase 2B/3 portion of the study.
- Modified to revise Section 13 Emergency Procedures from those applicable to a blinded study to procedures applicable to an open label study.

Other administrative changes (e.g., correction of typographical errors, editorial changes, etc.) 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: Title Page (Page 1)

Revised Text:

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY ~~(PART 1)~~ OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS ~~FOLLOWED BY A PHASE 2B/3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY (PART 2) OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH METASTATIC NON-SMALL CELL LUNG CANCER TREATED WITH FIRST-LINE PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS~~

Rationale:

Modified to:

- Remove the Phase 2B/3 portion and reference to Part 1 and Part 2 in the study title.

2.2. Section: Protocol Summary (Pages 6-10)

Revised Text:

Study Title

An open-label randomized, phase 2a, dose-ranging study ~~(**Part 1**)~~ of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens~~ followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.~~.

Indication

Chemotherapy Induced Anemia (CIA) in S~~s~~ubjects with ~~Advanced or Metastatic Solid Tumors~~

~~**Part 1** -~~ Advanced~~advanced~~ or metastatic solid tumors treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

~~**Part 2** - Metastatic NSCLC~~

Objectives

The ~~primary~~exploratory objectives are:

- ~~**Part 1**:~~ To explore ~~determine a~~ doses of sotatercept (ACE-011) that result~~s~~ in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent.
- ~~**Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.~~

~~The secondary objectives are:~~

~~**Part 1 and Part 2:**~~

- ~~To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS).~~
- To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

~~The exploratory objectives are:~~

~~**Part 1** and **Part 2**:~~

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism.
- ~~To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).~~
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- ~~To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only).~~
- To assess renal function biomarkers.

Study Design

This is an open-label, randomized, phase 2a, dose-ranging study ~~(**Part 1**)~~ of sotatercept (ACE-011) therapy for CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens~~ followed by a phase 2b/3, double-blind, randomized, placebo-controlled study (**Part 2**) of sotatercept (ACE-011) therapy for CIA in subjects with metastatic non-small cell lung cancer treated with first-line platinum-based chemotherapeutic regimens.~~ .

The study ~~will consist of two parts:~~

~~**Part 1** is a~~ dose-finding ~~segment~~ in which up to approximately ~~90~~30 subjects will be randomized to one of ~~three~~two sotatercept (ACE-011) dose treatment arms. The main exploratory ~~primary~~ objective is to determine a dose of sotatercept (ACE-011) that results in a hematopoietic response in the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapy, excluding those solid tumors treated with curative intent. ~~The sample size is for the purpose of hypothesis generation; however, it would allow approximately 80% power to detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a significance level (alpha) of 0.05.~~

~~**Part 2** is the phase 2b/3 double-blind, randomized, placebo-controlled segment of the study and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.~~

~~In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.~~

~~During **Part 2** (first and second stage) overall survival will be assessed. The total sample size of 750 subjects will allow observation of at least 536 deaths and thus, at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept~~

~~[ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11.~~

~~A Data Monitoring Committee (DMC) will monitor the conduct of the study.~~

Study Population

At the time of randomization ~~in **Part 1** and **Part 2**,~~ subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent. Subjects must also:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~In **Part 1,** subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.~~

~~In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum-containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.~~

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening~~,~~ and Treatment Period, including a Post Treatment Follow-Up ~~Period, and Survival Follow-Up Period.~~Visit. Study treatment is defined as sotatercept (ACE-011~~) in **Part 1** and sotatercept (ACE-011)/placebo in **Part 2**.~~).

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks or as per standard care at the study site prior to randomization. **Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected and used for assessment of tumor response.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from the initial solid tumor diagnosis and red blood cell (RBC) transfusion history starting from diagnosis of

advanced or metastatic disease, at a minimum of up to two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the Screening Period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Treatment Period (~~up to~~ and Post-Treatment Follow-Up / End of Treatment / End of Study Visit (approximately ~~6–9~~ months):

The Treatment Period is approximately six months (~~and~~ and includes up to four doses of ~~study treatment~~sotatercept (ACE-011) given on Day 1, every 42 days~~), two additional sotatercept (ACE-011)/placebo doses may be given only in **Part 2**, at~~, followed by a Post-Treatment Follow-Up / End of Treatment / End of Study Visit.

The Post-Treatment Follow-Up Visit will occur approximately 42 days (6 weeks) after the ~~discretion of the Investigator.~~ subjects' last dose of sotatercept (ACE-011). The Post-Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

~~In **Part 1** (the dose-ranging portion of the study), subjects~~Subjects with advanced or metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-~~30~~15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

~~Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.~~

~~Following this analysis, the addition of a third dose level:~~

- ~~Sotatercept (ACE-011) 45 mg SC~~

~~to the randomization schema will be determined.~~

Each dose level will be administered every 42 days for up to four doses.

The effective dose of sotatercept (ACE-011) is defined as follows:

An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks~~ during the first two doses of sotatercept (ACE-011) (Dose 1/Day 1 through and including Dose 2/Day 43 [prior to Dose 3]), in approximately 70% of subjects, in at least one or more treatment arms (in the absence of RBC transfusions and/or ESAs).~~

~~Evaluation of hemoglobin response decision status will be completed after dosing arms have separately enrolled up to 30 subjects, as needed, to determine the sotatercept (ACE-011) dose for **Part 2**.~~

~~In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in **Part 2**.~~

~~In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) or placebo, at a ratio of 1:1:~~

- ~~375 subjects will receive sotatercept (ACE-011) (at the dose determined in **Part 1**)~~
- ~~375 subjects will receive placebo~~

~~Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses. Up to two additional doses (in **Part 2** only) may be given at the discretion of the Investigator.~~

~~**Part 2** will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011) (at the dose determined from **Part 1**) or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.~~).

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered > 7 days from the date of the RBC transfusion.

~~In **Part 1**, blood~~Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from ~~approximately 30~~ subjects at select centers, in approximately 5 - 10 subjects for each sotatercept (ACE-011) dose group investigated. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment. ~~In **Part 2**, blood samples will be collected for the sparse PK assessment that will be performed in approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).~~

~~For subjects who do not participate in either **Part 1** full or sparse PK assessments or Part 2 sparse PK assessments, the~~ ACE-011 (sotatercept) concentration may be determined in ~~their~~ anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK~~.~~, in subjects who do not participate in the full or sparse PK assessments.

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100mmHg), confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy.
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months of sotatercept (ACE-011) therapy.
  - Any thromboembolic event > Grade 2.
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment).
  - Urine protein / creatinine ratio > 1.0; or > 2.0 if bevacizumab (Avastin®) is concomitantly administered.
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.
- ~~In **Part 1**, lack~~Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. ~~In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).~~
- Concomitant use of ESAs ~~– In **Part 1** if administered at any time and in **Part 2** if administered < 4 months after first dose of study treatment.~~ .
- Sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dose modifications
  - ~~– In **Part 1** and **Part 2**: –~~ A second Hgb increase of ≥ 3.0 g/dL following a two-level dose reduction due to a Hgb increase ≥ 3.0 g/dL
  - ~~– In **Part 2**: > 3 dose reductions and/or delays~~
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation - as determined by the Sponsor

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

Post Treatment Follow-Up ~~Period (monthly visits for up to 6 months)~~Visit

~~Subjects who enter the~~ The Post-Treatment Follow-Up ~~Period~~Visit will ~~be followed monthly for up to 6 months from their~~occur approximately 42 days (6 weeks) after the subjects' last dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo. All subjects~~). The Post-Treatment Follow-Up Visit will ~~continue to be followed for TTP and PFS up to one year from their first dose~~also serve as the End of ~~sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression~~Treatment / End of ~~their advanced or metastatic disease, whichever occurs first.~~ Study Visit.

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

- Completed study, per protocol (subject has completed approximately six~~ to nine~~ month Treatment Period including a 42 day [6 week]~~up to six month~~ Post Treatment Follow-Up/End of Treatment/End of Study Visit~~) Period including one year tumor assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months after first dose of study treatment~~.
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse event(s)
- Disease progression
- Protocol violation

~~**Survival Follow-up Period (monthly for up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo)**~~

~~In both **Part 1** and **Part 2**, survival data will be collected monthly (can be via telephone contact) for up to 24 months following the subject's first dose of sotatercept (ACE-011) (**Part 1**) or sotatercept (ACE-011)/placebo (Part 2). Collection of survival data will begin following Study Discontinuation Visit. Data to be collected will include:~~

- ~~Overall survival~~
- ~~Post-Treatment Anti-Neoplastic Therapy, if any~~

Rationale:

Modified to:

- Remove the Phase 2B/3 portion and reference to Part 1 and Part 2 in the study title and Protocol Summary.

- Revise primary, secondary and exploratory objectives to exploratory due to smaller sample size and abbreviated follow-up period.
- Delete all objectives related to the Phase 2B/3 portion of the study.
- Delete objectives due to smaller sample size and abbreviated follow-up period:
    e. To estimate effect of sotatercept (ACE-011) on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS)
    f. To explore the relationship between sotatercept (ACE-011) exposure on response
- Revise the design of Phase 2a portion of the study to :
    a. include approximately 30 versus 90 subjects
    b. delete the 45mg sotatercept (ACE-011) dose level
    c. delete the safety analysis to determine addition of the sotatercept (ACE-011) 45mg dose level following treatment of 10 subjects at 15mg and 10 subjects at 30mg
    d. change the number of subjects from approximately 30 to approximately 10-15 per dose level
- Delete description of statistical analysis of the Phase 2a portion of the study due to the smaller sample size.
- Delete reference to the Data Monitoring Committee (DMC).
- Revise Post-Treatment Follow-Up Period of six months to the Post-Treatment Follow-Up/End of Treatment/End of Study Visit occuring 42 days (6 weeks) following the last dose of sotatercept (ACE-011).
- Revise the defined effective dose of sotatercept (ACE-011) due to smaller sample size.
- Delete all references to the Phase 2B/3 study treatment of sotatercept (ACE-011) / placebo.
- Delete the Survival Follow-Up Period. Collection of Overall Survival and Post-Treatment Anti-Neoplastic Therapy will discontinue at the Post-Treatment Follow-Up/End of Treatment/End of Study Visit.

2.3. Section 1: Introduction (Pages 17-28)

Revised Text:

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic ~~agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens. The study will consist of two parts. **Part 1** is a dose finding segment in which up to 90 subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapy will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study~~regimens.

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The chemical structure of sotatercept (ACE-011) is composed of a disulfide-linked, glycosylated, homodimeric protein. Sotatercept (ACE-011) competes with the activin receptor IIA and binds a number of TGF-β superfamily ligands including activin, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

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~~**Part 2** will include only subjects with metastatic NSCLC and will be performed in two stages. Its primary objective is to determine the transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.~~

~~In the first stage of **Part 2** approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period. Based on the results of the futility analysis and upon recommendation to continue the study, up to an additional 570 subjects will be randomized in the second stage of **Part 2**, to achieve full study accrual.~~

~~A Data Monitoring Committee (DMC) will monitor the conduct of the study.~~Safety data will be continuously monitored by the sponsor.

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

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The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ((([apparent)]) volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (i.e., those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept ([ACE-011)] or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg sotatercept (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to sotatercept (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Rationale:

Modified to:

- Remove the Phase 2B/3 portion and reference to Part 1 and Part 2 in the study title.
- Delete reference to the Data Monitoring Committee (DMC).
- Clarify chemical structure of sotatercept (ACE-011).
- Correct typographical errors.

2.4. Section 2: Study Objectives (Page 34)

Revised Text:

2.1. ~~Primary Objective~~Exploratory Objectives

- **~~Part 1~~**: ~~To explore determine a~~ doses of sotatercept (ACE-011) that results~~s~~ in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent~~,~~.
- ~~**Part 2**: To assess transfusion rate following initiation of sotatercept (ACE-011) treatment versus placebo in subjects with CIA who have metastatic NSCLC treated with first-line platinum-based chemotherapeutic regimens.~~

~~**2.2. Secondary Objectives**~~

~~**Part 1** and **Part 2**:~~

- ~~To estimate the effect of sotatercept (ACE-011) treatment on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS).~~ • To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the PK of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).

~~**2.3. Exploratory Objectives**~~

~~**Part 1** and **Part 2**:~~

- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism.
- ~~To explore the relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate).~~
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- ~~To evaluate the expression of Activin A and other proteins/biomarkers in archival tumor tissue (**Part 2** only).~~
- To assess renal function biomarkers.

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

Rationale:

Modified to:

- Revise primary, secondary and exploratory objectives to exploratory due to smaller sample size and abbreviated follow-up period.
- Delete all objectives related to the Phase 2B/3 portion of the study.
- Delete objectives due to smaller sample size and abbreviated follow-up period:
    a. To estimate effect of sotatercept (ACE-011) on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS)
    b. To explore the relationship between sotatercept (ACE-011) exposure on response

2.5. Section 3: Study Endpoints (Page 35)

Revised Text:

3.1. ~~Primary~~Exploratory Endpoint(s)

~~**Part 1**: Dose Finding~~

~~The following are decision rules for dose determination in **Part 1** in order to move forward to **Part 2**:~~

- ~~After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.~~

~~•~~ Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In ~~order~~addition to ~~determine~~ the ~~dose of sotatercept (ACE-011) to be used in **Part 2**, evaluation of~~ hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be ~~determined from sotatercept (ACE-011) Dose 1/ Day 1 through and including Dose 2/Day 43 (prior to Dose 3).~~reviewed.

- ~~In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be taken into account to determine the study dose to be used in **Part 2**.~~

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

~~**Part 2**: Phase 2b/3 Double-Blind~~

- ~~Rate of RBC transfusion within four months following the date of randomization to sotatercept (ACE-011)/placebo treatment~~

~~**3.2. Secondary Endpoint(s)**~~

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- ~~TTP~~
- ~~PFS (including at 6 and 12 months)~~
- ~~OS (at 12 months and up to 24 months)~~
- ~~ORR~~
- Duration of hematopoietic response
- Sotatercept (ACE-011) concentration in serum
- Non-compartmental PK parameters for sotatercept (ACE-011) ~~(**Part 1** only)~~
- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1993; Hollen, 1994a; Hollen, 1994b; Hollen, 1995, Hollen, 1999)

~~**3.3. Exploratory Endpoint(s)**~~

- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or sotatercept (ACE-011) mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- ~~A population PK model for sotatercept (ACE-011)~~
- ~~A population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics~~
- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin)~~ and in archival tumor tissue (**Part 2** only).~~
- Change in renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin

Rationale:

Modified to:

- Revise all study endpoints to exploratory.
- Revise definition of hematopoietic response to remove criterion needed to move from Part 1 to Part 2 of the study and clarify that sotatercept (ACE-011) doses and hemoglobin levels will be reviewed
- Delete endpoints of effect of sotatercept (ACE-011) on objective response rate (ORR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) due to smaller sample size and abbreviated follow-up period.
- Delete population PK model for sotatercept (ACE-011) due to smaller sample size.
- Delete population pharmacodynamic model describing Hgb response as a function of time, sotatercept (ACE-011) exposure, and subject characteristics due to smaller sample size and abbreviated follow-up period.
- Delete endpoint of the expression of Activin A and other proteins/biomarkers in archival tumor tissue (Part 2 only) due to removal of Phase 2B/3 portion of the study.

2.6. Section 4: Overall Study Design (Pages 36-43)

Revised Text:

4.1. Study Design

This is an open-label randomized, phase 2a, dose-ranging study ~~(**Part 1**)~~ of sotatercept (ACE-011) therapy in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic regimens ~~followed by a phase 2b/3, double-blind,~~. Subjects with advanced or metastatic solid tumor types will be randomized~~, placebo-controlled study~~ to one of two sotatercept (ACE-011) ~~therapy for CIA in subjects with metastatic NSCLC treated with platinum-based chemotherapeutic regimens.~~ dose treatment arms. Continuous monitoring of safety data will be conducted.

The study ~~will consist of two parts. **Part 1** is a dose finding segment in which subjects with advanced or metastatic solid tumor types will be randomized to one of three sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted, including the review of **Part 1** data to determine the sotatercept (ACE-011) dose to be used in **Part 2**, the phase 2b/3, double-blind, randomized placebo-controlled segment of the study in subjects with metastatic NSCLC.~~

~~A DMC will monitor the conduct of the study.~~

Part 1 is planned to be conducted ~~at selected sites and will be extended to additional global sites for the conduct of **Part 2.**~~ in the United States.

Study treatment is defined as sotatercept (ACE-011~~) in **Part 1** and sotatercept (ACE-011)/placebo in **Part 2**~~.).

~~Three~~Two ~~starting~~ sotatercept (ACE-011) dose levels, 15~~,~~ and 30~~, and 45~~ mg, were selected for **Part 1** ~~of~~ the study. Up to approximately ~~90~~30 subjects with advanced or metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-~~30~~15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

~~Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.~~

~~Following this analysis, the addition of a third dose level:~~

- ~~Sotatercept (ACE-011) 45 mg SC~~

~~to the randomization schema will be determined.~~

Each dose level will be administered every 42 days for a total of up to four doses.

~~In **Part 2**, a total of 750 subjects with metastatic NSCLC will be randomized to receive either sotatercept (ACE-011) (at the dose determined in **Part 1**) or placebo, at a ratio of 1:1:~~

- ~~375 subjects will receive sotatercept (ACE-011) (at the dose determined in **Part 1**)~~
- ~~375 subjects will receive placebo~~

~~Each dose of sotatercept (ACE-011) or placebo will be administered every 42 days for four doses; two additional doses may be given at the discretion of the Investigator.~~

~~**Part 2** will be performed in two stages. In the first stage, approximately 180 subjects will be randomized to receive sotatercept (ACE-011), at the dose determined from **Part 1**, or placebo at a ratio of 1:1. An interim futility assessment based on transfusion rate at 4 months will be performed as described in Section 10.8. It is expected that accrual will continue during the interim assessment period, with up to an additional 570 subjects randomized to achieve full study accrual.~~

The Treatment Period ~~for **Part 1**~~ is approximately six months, which includes up to 4four doses of sotatercept (ACE-011) and ~~for **Part 2** approximately nine months, which includes up to 6 doses of sotatercept (ACE-011/placebo). Subjects who enter the~~a Post Treatment Follow-Up ~~Period will be followed for up to 6 months from their~~ Visit. The Post Treatment Follow-Up Visit will occur approximately 42 days after the last dose of ~~sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first.~~

~~Survival data will be collected monthly for up to 24 months following the subject's first dose of sotatercept (ACE-011) in **Part 1** or sotatercept (ACE-011)/placebo in **Part 2**.~~ study treatment. The Post Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

At the time of randomization ~~in **Part 1** and **Part 2**,~~ subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~In **Part 1,** subjects~~Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

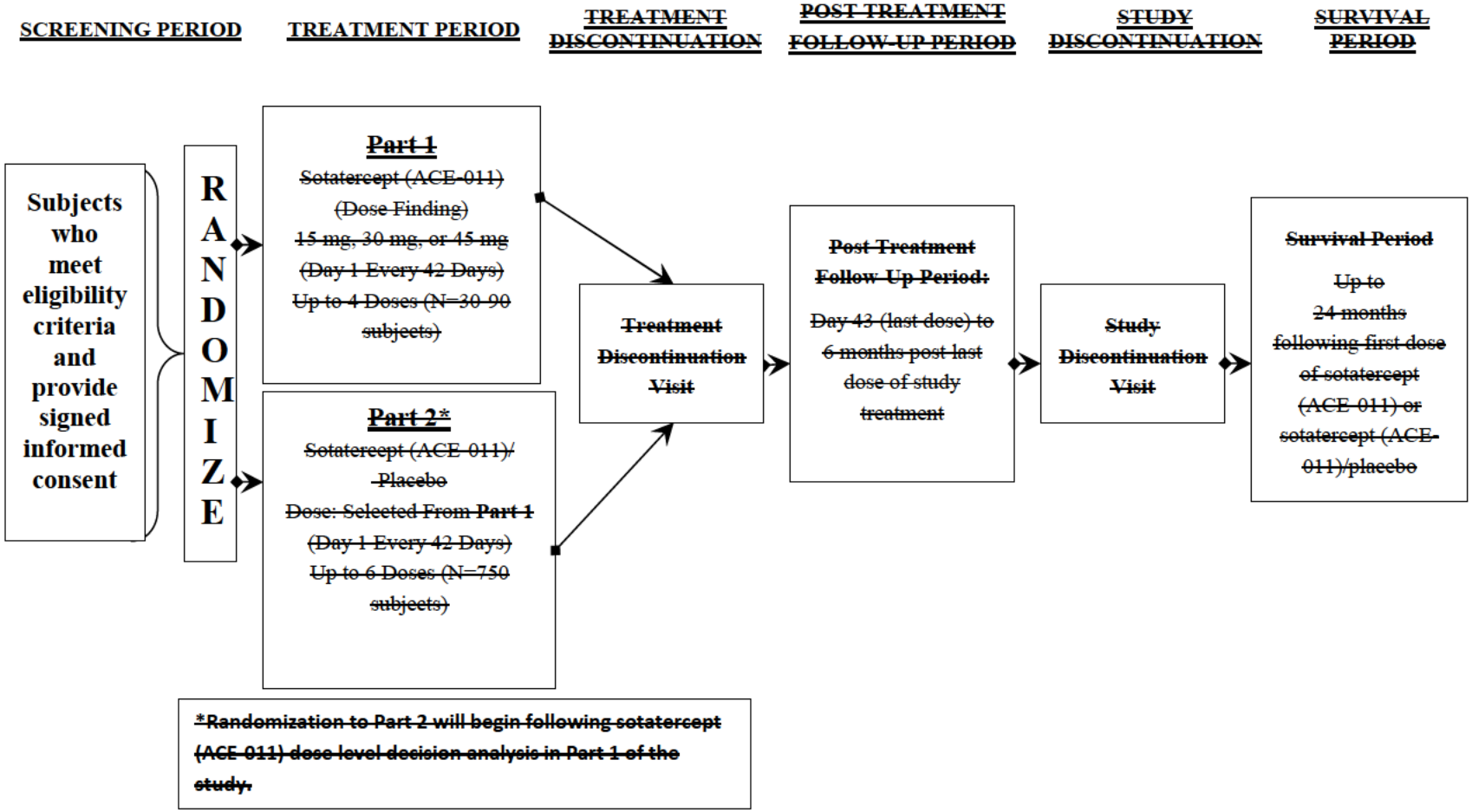
~~In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum-containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.~~

.Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

- ~~In **Part 1**, subjects~~Subjects will be randomized to one of ~~three~~two sotatercept (ACE-011) dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus ~~carboplatin~~other non-cisplatin chemotherapy)
- ~~In **Part 2** subjects will be randomized to receive either sotatercept (ACE-011) or placebo and will be stratified by:~~
  1. ~~Baseline Hgb level~~
     - ~~6.5 to < 9.0 g/dL~~
     - ~~9.0 to < 11.0 g/dL~~
  2. ~~Type of platinum-based chemotherapy (cisplatin versus carboplatin)~~
  3. ~~NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)~~
  4. ~~ECOG Performance Status 0-1 vs. 2~~

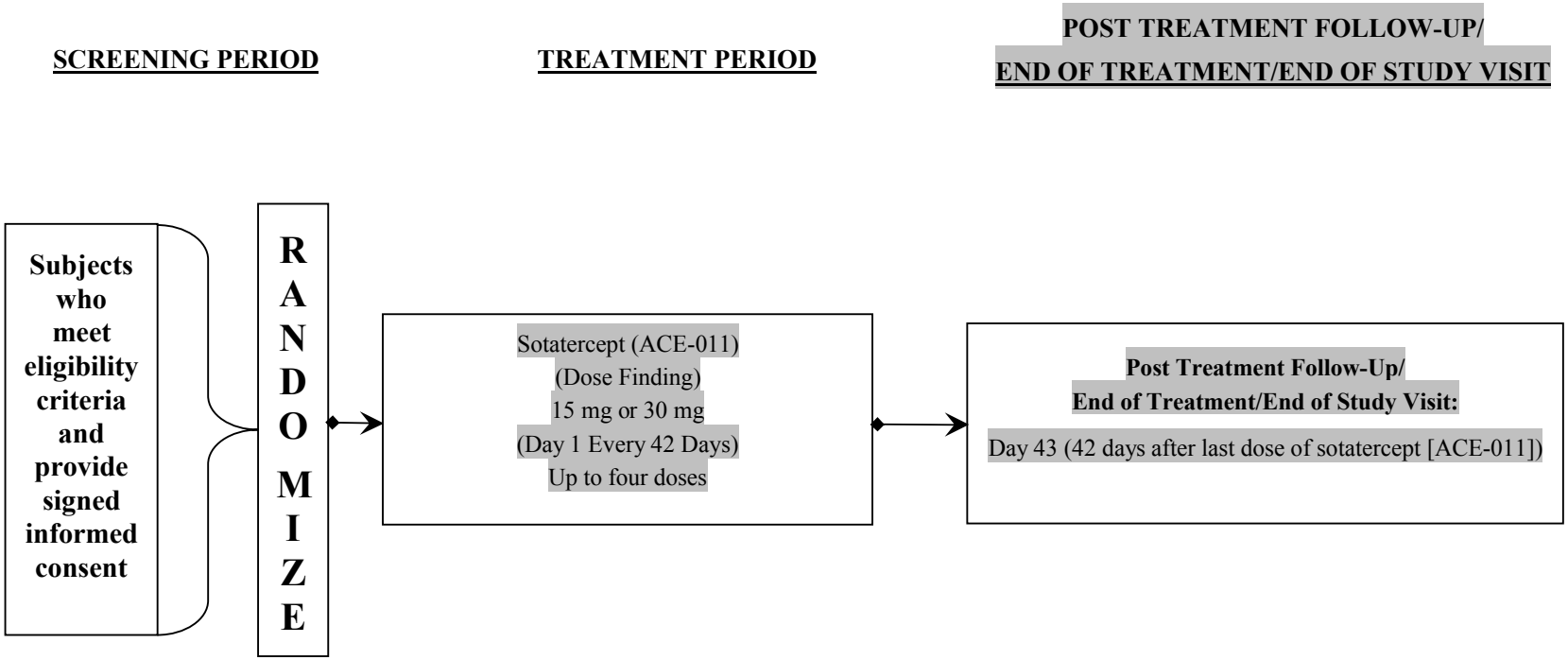
Note: The following strikethrough items were deleted; see following page for insertions.

Figure 1: Study Design



Note: The following insertions in Figure 1 are shaded:

Figure 1: Study Design



4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained at least five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ for the subject's **second** dose of study treatment and beyond.

Sotatercept (ACE-011) Dose Modification Rules:

Hemoglobin < 11g/dL *(per local* lab value)*

- < 2.0 g/dL increase within a dosing period or a ≥ 2.0 g/dL increase **not sustained** for a 28 day period since last dosing day → Continue Dosing[1] (~~**Part 1** only~~ Dose Escalation Table 6)
- ≥ 2.0 g/dL increase **sustained** for a 28 day period since last dosing day[2]
  Note: ≥ 3.0 g/dL increase **sustained** for a 28 day period since last dosing day requires a two level dose reduction.
  → Continue Dosing with Dose Reduction
  Table 5: Sotatercept (ACE-011) ~~and Sotatercept (ACE-011)/Placebo~~ Dose Reduction Levels

Hemoglobin ≥ 11g/dL *(per local* lab value)*

- < 2.0 g/dL increase within a dosing period or a ≥ 2.0g/dL increase **not sustained** for a 28 day period since last dosing day → Dose Delay[3]
- ≥ 2.0g/dL increase **sustained** for a 28 day period since last dosing day[2]
  Note: ≥ 3.0g/dL increase **sustained** for a 28 day period since last dosing day requires a two level dose reduction. If Hgb is > 15.0 g/dL, sustained for 7 days, subject is to be discontinued from treatment[2].
  → Dose Delay then, Dose Reduction[4]

Hypertension ≥ SBP 150 mmHg or ≥DBP 100 mmHg → Dose Delay[5]

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

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

~~For **Part 1** only: if~~If the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011) should not be administered ≤ 7 days post RBC transfusion.

~~For **Part 2**: Subjects who have received an RBC transfusion in the past 42 days should continue at the **same** sotatercept (ACE-011)/placebo dose if the transfusion was given greater than 7 days from the previous dose of sotatercept (ACE-011)/placebo AND the Hgb level is < 11 g/dL AND hypertension is < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011)/placebo should not be administered ≤ 7 days post RBC transfusion.~~

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , 21 (after first dose of study treatment) and 28 days after dosing, **and reviewed** in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dose reduction of two dose levels (Refer to sotatercept [ACE-011]~~ and sotatercept (ACE-011)/Placebo~~ Dose Reduction Levels [Table 5]). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011)~~ or sotatercept (ACE-011)/placebo~~ should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dose that was **delayed**. Subsequent sotatercept (ACE-011)~~ or sotatercept (ACE-011)/placebo~~ doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dose is defined as a dose administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > SBP 150 mmHg or > DBP 100 mmHg and/or sotatercept [ACE-011] related toxicity).

[4]Sotatercept (ACE-011)~~or sotatercept (ACE-011)/placebo~~ should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011)~~or sotatercept (ACE-011)/placebo~~ should be held until hypertension resolves to < SBP 150mmHg and < DBP 100 mmHg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: Sotatercept (ACE-011) ~~and Sotatercept (ACE-011)/Placebo~~ Dose Reduction Levels

When required, per dose modification rules above, sotatercept (ACE-011) dose(s) ~~in **Part 1** and sotatercept (ACE-011)/placebo dose(s) in **Part 2**~~ should be reduced as follows:

Dose Schedule Sotatercept (ACE-011) ~~or Sotatercept (ACE-011)/placebo~~	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
~~Every 42 days- 45 mg~~	~~38 mg~~	~~33 mg~~	~~28 mg~~
Every 42 days- 30 mg	26 mg	22 mg	18 mg
Every 42 days- 15 mg	13 mg	11 mg	9 mg

*Note: Any Hgb increase of ≥3.0 g/dL sustained for a 28 day period since last doing day will require a subsequent sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for ~~four doses. An additional two doses (total of 6 doses) may be given only during **Part 2** at the discretion of the Investigator.~~up to four doses.

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011~~) and sotatercept (ACE-011)/placebo.~~).

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. A dose level may not be increased following a dose reduction.

~~In **Part 2**, dose reduction steps and the subsequent administration of the reduced dose(s) of sotatercept (ACE-011)/placebo will be conducted in a manner that will preserve the blinded status of the original treatment group of each subject. Subjects in the placebo group who are designated to undergo dose reduction will continue to receive placebo.~~

~~Placebo will be administered at the same volume as the corresponding sotatercept (ACE-011) or sotatercept (ACE-011)/placebo dose reduction.~~

Sotatercept (ACE-011) Dose Escalation Levels:

The following dose escalation rules apply for sotatercept (ACE-011) dose(s~~) in **Part 1** only. Dose escalations are not allowed in **Part 2**~~:):

- Less than 1.0 g/dL increase in Hgb in response to prior sotatercept (ACE-011) dose
- Hgb level must be < 11.0 g/dL and hypertension < SBP 150mmHg and < DBP 100 mmHg
- Dose escalation to begin at next treatment visit

- Sotatercept (ACE-011) should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of Sotatercept (ACE-011) at the subsequent visit per the escalation table below.

Table 6: Sotatercept (ACE-011) Dose Escalation Levels ~~(Part 1 Only)~~

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
~~Every 42 days- 45 mg~~	~~50 mg~~	~~55 mg~~	~~61 mg~~
Every 42 days- 30 mg	33 mg	36 mg	40 mg
Every 42 days- 15 mg	17 mg	20 mg	23 mg

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011~~) and sotatercept (ACE-011)/placebo.~~).

_ _ _ _ _ _ _ _ _ _ _ _

4.2.3. ~~Starting~~ Dose Levels ~~in Part 1~~

~~Three~~Two ~~starting~~ dose levels, 15~~, 30,~~ and ~~45~~30 mg, were chosen for ~~**Part 1** of~~ the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of sotatercept (ACE-011) at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, sotatercept (ACE-011) had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal sotatercept (ACE-011) concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The ~~three~~two ~~starting~~ dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg~~,~~ and 31.5 mg~~, and 52.5 mg,~~ respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three sotatercept (ACE-011) doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to sotatercept (ACE-011). ~~In this study, the starting dose level of 45 mg (during the dose finding **Part 1**) will be implemented only after at least 10 subjects at each lower dose level (10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level) have been evaluated as well as following DMC review of safety data and assessment of dose effects on Hgb levels.~~

~~In addition, in this study, during the first 6-week treatment period for a 70 kg subject receiving the starting dose at 45 mg, the sotatercept (ACE-011) exposure ($C_{max, day\ 1-43}$ and AUC_{1-43}) is projected to be approximately 10% lower than the exposure for the dose regimen of 0.5 mg/kg once every 4 weeks. Afterwards, safety measures (Hgb and blood pressure) will be used to guide~~

the adjustment of the second dose and beyond. Thus, the use of the 45 mg starting dose in the current study is not anticipated to significantly compromise subject safety.

In this study, the 45 mg group will have the highest starting dose, and it may be titrated up to 61.0 mg for the last dose (Dose 4). Assuming a 70 kg subject who receives the maximal amount of dose during the entire study (i.e., starting at 45 mg followed by dose escalation every 6 weeks to 50.0, 55.0, and 61.0 mg for Doses 2, 3, and 4, respectively), the projected cumulative AUC during the treatment period (168 days) would be approximately 60% of the steady state AUC cumulated during the same period at the NOAEL level of 1 mg/kg (given every 4 weeks for a total of 6 doses) as reported in the 9-month, repeat-dose toxicity study in monkeys. The projected highest C_{max} for the current study would be less than 50% of the steady state C_{max} in the monkey study.

4.2.4. Evaluation of Dosing Schema via Modeling/Simulation

The performance of the proposed dosing schema (three fixed starting dose levels, 6-week dosing interval, and dose adjustment rules [see Section 4.1.1 for details]) for this study was evaluated via PK/pharmacodynamic modeling/simulation. A tentative mechanistic PK/pharmacodynamic model for Hgb was developed using PK and Hgb data from healthy postmenopausal women and the model was extended to include MM subjects as a sub-population. The model was required to appropriately reproduce the observed PK and Hgb profiles in MM subjects. Monte Carlo simulations of the Hgb response to sotatercept (ACE-011) in a hypothetical anemic population (6.5 ≤ baseline Hgb < 11 g/dL; body weight 47 – 108 kg) were performed using the model parameterized with preliminary PK and pharmacodynamic parameters from MM subjects. In this simulation analysis, efficacy refers to an Hgb increase > 1 g/dL from the baseline for 28 consecutive days while safety refers to both the absolute Hgb levels and the rate of Hgb increase.

The simulation predicts that the desired efficacy would be achieved 6 weeks after the second dose in approximately 70% subjects of the 45 mg group and 6 weeks after the last dose in >70% subjects of the 30 mg group. Further, the simulation predicts the Hgb level would be maintained under 12 g/dL in 90% subjects and under 13 g/dL in 95% of subjects during the course of the study (Figure 2). No subjects are predicted to have a Hgb level above the upper limit of the normal range for Hgb (16 g/dL). Approximately 6% subjects are predicted to have an Hgb rise > 2 g/dL within 28 days of the first dose, mostly from the 45 mg group (4%); however, the fraction of subjects with an Hgb rise > 3 g/dL per 28 days is predicted to be similar between the three dose groups (approximately 2.5% for each group).

~~**Figure 2: Simulated Hemoglobin Response in the Hypothetical Anemic Population**~~

~~The middle solid lines represent the median Hgb level. The top and bottom solid lines represent the Hgb level at 5% and 95% percentile, respectively. The area between 5% and 95% percentiles represents 90% prediction interval. The straight dot lines represent the Hgb level of 12 g/dL. The arrows indicate the dosing time of sotatercept (ACE-011). The two level dose reductions upon ≥ 3 g/dL increase sustained for 28 days of a dose (Table 5) was not included in the simulation.~~

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately ~~60-90~~30 subjects with advanced or metastatic solid tumor types ~~in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**~~ will be randomized prior to receiving the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy. Each subject will be on the study for approximately ~~12 – 15~~6 months (including the Screening Period, the Treatment Period, and the Post Treatment Follow-Up ~~Period~~Visit). The Treatment Period is approximately 6 ~~to 9~~ months (up to four ~~to six~~ doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up ~~Period of six months from~~Visit occurring at 42 days after the subjects' last dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo.~~). Subjects who discontinue treatment early will still continue to the Post Treatment Visit. The Post-Treatment Follow-Up ~~Period for six months from their last dose~~Visit will also serve as the End of Treatment / End of ~~sotatercept (ACE-011) or sotatercept (ACE-011)/placebo~~Study Visit.

~~All subjects will continue to be followed for TTP and PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or until progression of their advanced or metastatic disease, whichever occurs first. All subjects will continue to be followed for survival up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.~~

Rationale:

Modified to:

- Remove the Phase 2B/3 portion and reference to Part 1 and Part 2 in the study design.

- Delete reference to Data Monitoring Committee (DMC) and confirm that continuous monitoring of the safety data will be conducted by the sponsor.
- Confirm that the study will be conducted only in the United States.
- Delete all references to the Phase 2B/3 study treatment of sotatercept (ACE-011) / placebo.
- Revise the design of Phase 2a portion of the study to :
    a. Include approximately 30 versus 90 subjects
    b. Delete the 45mg sotatercept (ACE-011) dose level
    c. Delete the safety analysis to determine addition of the sotatercept (ACE-011) 45mg dose level following treatment of 10 subjects at 15mg and 10 subjects at 30mg
    d. Change the number of subjects from approximately 30 to approximately 10-15 per dose level
    e. Confirm that subjects will receive up to four doses of sotatercept (ACE-011)
- Revise Post-Treatment Follow-Up Period of six months to the Post-Treatment Follow-Up/End of Treatment/End of Study Visit occuring 42 days (6 weeks) following the last dose of sotatercept (ACE-011).
- Revise stratification to include other non-cisplatin platinum-based chemotherapy in addition to carboplatin versus cisplatin due to addition of other allowed tumor types in Amendment 3.
- Revise Figure 1: Study Design to incorporate study design changes
- Revise Sotatercept (ACE-011) Dose Modifications:
    a. Delete reference to sotatercept (ACE-011) / placebo
    b. Delete reference to 2B/3 portion and Part 1 and Part 2 in the study design.
    c. Delete the 45mg sotatercept (ACE-011) dose level.
    d. Confirm that subjects will receive up to four doses of sotatercept (ACE-011).

NOTE: Dose modification rules were not changed for the sotatercept (ACE-011) 15 mg and 30 mg dose levels.

- Delete section 4.2.4 : Evaluation of Dosing Schema via Modeling/Simulation as simulation performed dose not seem to be supported by the observed clinical data in subjects with chemotherapy-induced anemia.

2.7. Section 5: Table Of Events (Pages 44-50)

Revised Text:

Table 7: Sotatercept (ACE-011) Schedule of Assessments

Assessments	Screening Period	Treatment Period										~~Post Treatment Follow-Up Period (± 1 week)~~						~~Survival (±1wk)~~
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through ~~64~~ Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post ~~Last Dose~~ Treatment Follow-Up/ End of Treatment / End of Study ~~Tx~~ Visit[t]	~~1 Month~~	~~2 Month~~	~~3 Month~~	~~4 Month~~	~~5 Month~~	~~6 Month/ Study DC~~[u]	~~Survival~~
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Complete Medical History	X																	
Cancer History and Prior Therapies[a]	X																	
Prior ESA and RBC transfusion history[a]	X	X																
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
ECOG Performance Status	X	X		X			X		X		X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
12-Lead Electrocardiogram (ECG) ~~– Part 1~~[ec]	X	X	X				X				X							
~~12-Lead Electrocardiogram (ECG) – Part 2~~[e]	~~X~~	~~X~~									~~X~~							
Pregnancy Testing[d]	X	X					X				X	~~X~~	~~X~~	~~X~~			~~X~~[d]	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Serum Chemistry[f]	X	X		X		X	X		X	X	X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X							
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X		~~X~~					

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period										Post Treatment Follow-Up Period (± 1 week)						Survival (±1wk)
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 64 Schedule (± 3 days)											
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Last Dose Treatment Follow-Up/ End of Treatment / End of Study Tx Visit[t]	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month/ Study DC[u]	Survival
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X	X	X	X	X	X	X	
FSH and LH – Males and Females	X	X	X				X		X		X			X			X	
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X			X			X	
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X			X			X	
TSH[k]	X	X					X[k]				X		X					
Sotatercept (ACE-011) drug antibody test (pre-dose)[l]		X		X			X				X[l]			X		X		
Bone Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[l] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X			X				
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X										X			X				
Activin A and other proteins/biomarkers in blood (serum) (pre-dose study treatment in a subset of subjects)		X	X				X				X	X						
~~Activin and other proteins/biomarkers in archival tumor tissue (Part 2 only - optional)~~	~~X~~																	
Pharmacokinetics ~~(Part 1 and Part 2)~~[n]		Refer to Table 8 ~~and Table 9~~ – Schedule of Pharmacokinetic Assessments																
Tumor Assessments[o]	X[o]	≤ Every 9 weeks or as per standard of care at study site																
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X	X	X	X	X	X	X	
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose – Post Treatment Follow-Up /End of Treatment / End of Study Visit- only SAEs assessed as related to study treatment are to be reported																
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X		X			X	X	
Concomitant Procedures	X	X		X			X		X		X		X			X	X	
Hospitalizations (Record)	X	X		X			X		X		X		X			X	X	
Randomization		X																

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X											
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice																
Targeted/Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice																
Overall Survival[t,u]											X							~~X~~
Post Treatment Anti-Neoplastic Therapy[t]											X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~

[a]Include cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and advanced or metastatic site involvement. Record prior ESA history, starting at solid tumor diagnosis. Record RBC transfusion history, starting from diagnosis of advanced or metastatic disease, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011) ~~or sotatercept (ACE-011)/ placebo dose, at~~), and at the Post Treatment ~~Discontinuation, and at~~ Follow-Up / End of Treatment / End of Study ~~Discontinuation~~ Visit. Blood pressure should be confirmed by two measurements obtained at least five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: ~~For **Part 1**:~~ At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011) dose, Day 8 post dose 1, every sotatercept (ACE-011) dosing Visit (post-dose) and at ~~end~~Post Treatment Follow-Up / End of ~~study treatment~~Treatment / End of Study Visit (day 43 post last dose).

~~For **Part 2**: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011)/placebo dose and at end of study treatment (day 43 post last dose).~~

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days **prior** to the start of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ during the Treatment Period. Subjects must agree to use highly effective birth control measures (e.g., oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo. Pregnancy test will be performed at Study Discontinuation if date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.~~).

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ to ensure levels are within normal limits and that sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment ~~(**Part 1**)~~.

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 ~~([~~bicarbonate~~])~~, calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the Treatment Period~~, every month (except month 1) during~~ and at the Post Treatment Follow-Up ~~Period and at study discontinuation .~~/ End of Treatment / End of Study Visit (day 43 post last dose).

Note: Footnotes [e], [f], [g]: Hematology, absolute reticulocyte count, serum chemistry and creatinine clearance are to be assessed ≤ 14 days prior to randomization.

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ and ~~end~~at the Post Treatment Follow-Up / End of ~~study treatment~~Treatment / End of Study Visit (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo.~~). For full PK assessment, weekly after first dose of sotatercept (ACE-~~-~~011).

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo and at 2 month post-treatment follow-up visit.~~and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

[l]Bone Biomarkers- Collected for **full** PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 ~~, post last dose day 43~~ and ~~month 3 post treatment follow-up visit.~~at the Post Treatment Follow-Up / End of Treatment / End of Study Visit. For all other subjects collected prior to dose 1, prior to dose 2 , ~~post last dose day 43 and month 3 post treatment follow-up visit.~~and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose). Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan of lumbar spine and hip to evaluate overall health ~~on approximately 200 subjects~~ at selected US site(s). Performed at Screening, and ~~Month 3 during~~at the Post Treatment Follow-Up ~~Period.~~/ End of Treatment / End of Study Visit (day 43 post last dose).

[n]Pharmacokinetics~~**(Part 1)**~~: Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15~~, 30~~ and ~~45~~30 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.

~~Pharmacokinetics (**Part 2**): Sparse PK blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011) in approximately 300 (40%) of 750 subjects. Sotatercept (ACE-011) doses 5 and 6 will have **pre-dose** Day 1 PK (if applicable).~~

~~REFER TO Table 8 and Table 9~~REFER TO Table 8, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening Period tumor assessments may be performed within six weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected. Following randomization, tumor assessments will be performed ≤ every 9 weeks or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments~~,~~ FACIT Fatigue Scale (Version 4) – to be completed by all subjects and LCSS questionnaire – to completed by only subjects with NSCLC~~, to~~. NOTE: The LCSS consists of two scales: one scale for the subject (Patient Scale) and a counterpart scale for health professionals acting as observers (Observer Scale). All QoL assessments should be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the ~~schedule, and at Study Discontinuation/One-Year Follow-Up Visit.~~Schedule of Assessments.

[q]Sotatercept (ACE-011)~~ or sotatercept (ACE-011)/placebo~~ dosing repeats every 42 days and will start after the subject begins a platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ **may be given at any time following the first dose of platinum-based chemotherapy. Subsequent doses** of Sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration does not need to be delayed until start of next chemotherapy cycle.

[r]Platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded.

[s] Targeted/maintenance therapy (e.g. pemetrexed, erlotinib, etc.) is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose sotatercept (ACE-011) corresponds to the ~~end~~Post Treatment Follow-Up / End of Treatment ~~Period.~~/ End of Study Visit. Subjects who discontinue the sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ Treatment Period early will continue to the Post Treatment Follow-Up ~~Period and be followed for up to 6 months after their last dose of sotatercept (ACE-011)/placebo.~~/ End of Treatment / End of Study Visit. Survival Data and Post Treatment Anti-Neoplastic Therapy should be captured at this Visit. For subjects with a positive sotatercept (ACE-011) drug antibody assessment at the Post Treatment Follow-Up / End of Treatment / End of Study Visit, sotatercept (ACE-011) drug antibody assessments will be repeated every two months or as appropriate for up to one year or until the results are negative, whichever occurs first.

~~[u]Study Discontinuation visit should occur 12 months after starting treatment with sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.~~

~~[v]Survival data will be collected monthly, (can be via telephone contact), following the Study Discontinuation visit for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).~~

Table 8: Schedule of Pharmacokinetic Assessments ~~(Part 1)~~

Scheduled Time	Time relative to Sotatercept (ACE-011)	~~Part 1~~[a] PK Sampling[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days
~~PT[f] Follow up, 1 month~~	~~72 days after final dose~~	~~X~~	~~-~~	~~± 1 week~~
~~PT Follow up, 2 month~~	~~102 days after final dose~~	~~X~~	~~-~~	~~± 1 week~~
~~PT Follow up, 3 month~~	~~132 days after final dose~~	~~X~~	~~X~~	~~± 1 week~~
~~PT Follow up, 4 month~~	~~162 days after final dose~~	~~X~~	~~-~~	~~± 1 week~~
~~PT Follow up, 5 month~~	~~192 days after final dose~~	~~X~~	~~X~~	~~± 1 week~~

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first sotatercept (ACE-011) dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first sotatercept (ACE-011) dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin, and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately ~~30~~20 subjects (approximately 10 subjects in each dose group).

[d] To be collected in subjects participating in sparse PK sampling and not participating in full PK sampling.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

[f] ~~PT = Post Treatment~~

~~**Table 9: Schedule of Pharmacokinetic Assessments (Part 2)**~~

~~Scheduled Time~~	~~Time relative to Sotatercept (ACE-011)/placebo dose~~	~~Sparse PK[a,b,c]~~	~~Collection Window[d]~~
~~Dose 1, D1~~	~~pre-Dose 1~~	~~X~~	~~-2 to 0 hour~~
~~Dose 1, D1~~	~~4 hours after Dose 1~~	~~X~~	~~±1 hour~~
~~Dose 1, D8~~	~~7 days after Dose 1~~	~~X~~	~~± 3 day~~
~~Dose 1, D15~~	~~14 days after Dose 1~~	~~X~~	~~± 3 day~~
~~Dose 1, D29~~	~~28 days after Dose 1~~	~~X~~	~~± 3 day~~
~~Dose 1, D43 (Dose 2, D1)~~	~~pre-Dose 2~~	~~X~~	~~± 3 days~~
~~Dose 2, D43 (Dose 3, D1)~~	~~pre-Dose 3~~	~~X~~	~~± 3 days~~
~~Dose 3, D43 (Dose 4, D1)~~	~~pre-Dose 4~~	~~X~~	~~± 3 days~~
~~Dose 4, D43 (Dose 5, D1)~~	~~pre-Dose 5~~	~~X~~	~~± 3 days~~
~~Dose 5, D43 (Dose 6, D1)~~	~~pre-Dose 6~~	~~X~~	~~± 3 days~~
~~PT[e] Follow up, 3 month~~	~~132 days after final dose~~	~~X~~	~~± 1 week~~
~~PT Follow up, 5 month~~	~~192 days after final dose~~	~~X~~	~~± 1 week~~

~~[a] For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.~~

~~[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.~~

~~[e] To be collected for approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).~~

~~[d] Except for Day 1 (Dose 1, D1), the collection window will be the same as the visit window defined in Table 7.~~

~~[e] PT = Post Treatment~~

Rationale:

- Table 7: Sotatercept (ACE-011) Schedule of Assessments was modified to:
  a. Delete all Assessments referenced in the Phase 2B/3 portion of the study.
  b. Delete all references to Part 1 and/or Part 2 of the study.
  c. Delete the Post-Treatment Follow-Up Period and Survival Follow-Up Period.
  d. Replace the "D43 Post Last Dose/End of Study Treatment Visit" with the "D43 Post Treatment Follow-Up/End of Treatment/ End of Study Visit".
  e. Add the following assessments to the "D43 Post Treatment Follow-Up/End of Treatment/ End of Study Visit":
     i. TSH
     ii. Bone Imaging (DXA)- optional
     iii. Activin A and other proteins/biomarkers in blood (serum)
  f. Add sotatercept (ACE-011) drug antibody repeat assessments following the Post Treatment Follow-Up / End of Treatment / End of Study Visit for subjects with a positive sotatercept (ACE-011) titer.
  g. Clarify that the LCSS questionnaire consists of two scales, a Patient Scale and an Observer Scale.

- Table 8: Schedule of Pharmacokinetic Assessments (Part 1) was modified to:
    a. Delete all references to Part 1 of the study
    b. Delete Post-Treatment Follow Up PK assessments.
    c. Revise the number of subjects anticipated to participate in the Full PK assessment
- Table 9: Schedule of Pharmacokinetic Assessments (Part 2) was deleted.

2.8. Section 6: Procedures (Pages 51-56)

Revised Text:

Screening Period (Day -28 to Day -1)

– – – – – – – – – – –

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

– – – – – – – – – – –

- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration

– – – – – – – – – – –

- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

~~In **Part 1** (the dose-ranging portion of the study), subjects~~Subjects who meet all eligibility criteria will be randomized utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with approximately 10-~~30~~15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

~~Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.~~

~~Following this analysis, the addition of a third dose level:~~

- ~~Sotatercept (ACE-011) 45 mg SC~~

~~to the randomization schema will be determined.~~

Each dose level will be administered every 42 days for up to four doses.

- ~~In **Part 2**, subjects meeting all inclusion and exclusion criteria will enter into the Treatment Period and be randomized by a double-blind procedure utilizing IVRS to receive sotatercept (ACE-011) or placebo (1:1 ratio).~~

- A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~on Day 1 and every 42 days for up to four doses during the Treatment Period, as specified in the Table of Events (see Section 5).

~~In **Part 1**, the Treatment Period will last approximately 6 months, where subjects randomized to sotatercept (ACE-011) will receive treatment on Day 1 every 42 days for a planned 4 doses.~~

~~In **Part 2**, the Treatment Period will last approximately 6 to 9 months, where subjects randomized to sotatercept (ACE-011)/Placebo will receive treatment on Day 1 every 42 days for a planned 4 doses with an additional 2 doses of sotatercept (ACE-011)/placebo allowable, at the discretion of the Investigator, for a total of up to 6 doses.~~

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration.
- Serum chemistry, hematology, absolute reticulocyte count.
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ and at subsequent sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ doses collected at 7, 14 days and 28 days post-dose.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 42 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and 42 days after last dose of study treatment
- Serum erythropoietin

- Urinalysis
- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (**pre-dose** on the day of sotatercept ~~(~~[ACE-011]~~)~~ ~~or sotatercept (ACE-011)/placebo~~ administration)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre-dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~
    - pre-dose on Day 1 subsequent dosing visits

  ~~– in archival tumor tissue (**Part 2** only)~~
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks **or per standard of care at the study site,** starting from the previous [screening] tumor assessment) and following the chemotherapy schedule
- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Evaluation and all AE/SAE reporting (regardless of causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or targeted/maintenance therapy
- Administration of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo at~~on: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will ~~enter~~continue to the Post Treatment Follow-Up ~~Period and be followed for~~ / End of Treatment / End of Study Visit 42 days (6 ~~months~~weeks) after their last dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo. Upon completion of the Post Treatment Follow-Up Period, subjects will have a discontinuation visit and be followed for survival for up to 24 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.~~).

Post Treatment Follow-Up ~~Period~~/ End of Treatment / End of Study Visit (Day 43 post last dose of study treatment~~ to six months post last dose of study treatment~~)

Following completion or early discontinuation from the Treatment Period, subjects will ~~enter the~~have a Post Treatment Follow-Up ~~Period and continue to be followed for 6 months after their last dose~~/ **End of** ~~sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Visits will occur every month~~**Treatment / End of Study Visit.** The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)
- Vitamin B12 and RBC folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH ~~(at 2 month end of treatment follow-up visit)~~
- Serum for sotatercept (ACE-011) drug antibody test (pre-sotatercept ~~([~~[ACE-011]~~])~~ ~~or sotatercept (ACE-011)/placebo~~ dose). For subjects with a positive sotatercept (ACE-011) drug antibody assessment at the Post Treatment Follow-Up / End of Treatment / End of Study Visit, sotatercept (ACE-011) drug antibody assessments will be repeated every two months or as appropriate for up to one year or until the results are negative, whichever occurs first.
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Bone imaging – DXA scan (optional at selected sites~~ performed at 3 month end of treatment follow-up visit~~)
- Activin A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood~~ at 1 month end of treatment follow-up visit)~~

- Pharmacokinetics
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks **or as per standard of care at the study site,** and following the chemotherapy schedule)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks ~~after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.~~) after last dose of sotatercept (ACE-011).
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy

~~**Study Discontinuation**~~

~~Study Discontinuation is the final scheduled visit for this study and should be performed for all enrolled subjects.~~

~~Subjects who discontinue from treatment early will enter the Post Treatment Follow-Up Period and be followed for 6 months from their last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo. Follow-up for twelve months for TTP and PFS will be performed from the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/Placebo. Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).~~

~~The assessments and procedures that will be performed during the Study Discontinuation Visit are outlined in the Table of Events (see Section 5) and include:~~

- ~~ECOG performance status~~
- ~~Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature~~
- ~~Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) – if Study Discontinuation date is ≤ 112 days following the last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo.~~
- ~~Serum chemistry, hematology, absolute reticulocyte count~~
- ~~Creatinine clearance~~
- ~~Urinalysis~~

- ~~FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females~~
- ~~Estrogen and estradiol – females only~~
- ~~Dihyroepiandosterone and testosterone (free and total) – males only~~
- ~~Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1) (PFS at 12 months)~~
- ~~QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects~~
- ~~LCSS questionnaire – only subjects with NSCLC~~
- ~~Evaluation and reporting of all AEs regardless of causality (up to 6 weeks after last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo). After 6 weeks post last dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, only AEs assessed as related to sotatercept (ACE-011) or sotatercept (ACE-011)/placebo or study related procedures are to be reported.~~
- ~~Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations~~
- ~~Post-Treatment Anti-Neoplastic Therapy~~

~~**Survival Follow-Up Period:**~~

~~Monthly collection of survival data will begin following the Study Discontinuation Visit and continue for an additional 12 months (up to 24 months after first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).~~

- Overall survival
- ~~Post-Treatment Anti-Neoplastic Therapy~~

Additional Procedure Descriptions:

Central ECG

~~**Part 1** –~~ECGs will be performed and read per Central ECG vendor.

~~**Part 2** – ECGs will be performed locally and read per Central ECG vendor.~~

Please refer to vendor manual for procedures.

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Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin~~) and in archival tumor tissue in a subset of subjects (**Part 2** only).~~).

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Pharmacokinetics

- ~~**Part 1**~~ Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately ~~30~~20 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group). ~~For full PK sampling, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.~~
- ~~**Part 2** Sparse PK blood samples will be collected from approximately 300 (40%) of 750 subjects (approximately 150 subjects in each arm).~~

For subjects who do not participate in either ~~**Part 1**~~ full or ~~sparse PK assessments or in **Part 2**~~ sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Detailed PK sampling schedule is presented in Table 8 ~~and Table 9~~: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

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Quality of Life Assessments

The QoL Assessment (FACIT Fatigue Scale [Version 4]) will be completed by all subjects and LCSS questionnaire will be completed for subjects with NSCLC. Each assessment will be completed by the subject upon arrival at clinic and prior to any study procedures or testing. ~~The LCSS consists of two scales: one for the patient (Patient Scale) and a counterpart for health professionals acting as observers (Observer Scale).~~

~~**Independent External Radiology Review (Part 2 Only)**~~

~~At least 3 independent external radiologists (2 reviewers and 1 adjudicator) will perform a blinded, independent assessment of response, including the development of progressive disease (PD).~~

~~**Independent Review Committee (IRC) (Part 2 Only)**~~

NOTE: The ~~IRC will review the tumor response data (to include results from the central radiologist and relevant clinical laboratory and physical examination findings) and the dates of disease progression~~LCSS consists of two scales: one scale for ~~each subject. These data reviewed by the IRC will be used in the primary analyses ORR, TTP and PFS~~the patient (Patient Scale) and a counterpart scale for ~~the Clinical Study Report.~~ health professionals acting as observers (Observer Scale).

Rationale:

Modified to:

- Clarify that the LCSS questionnaire consists of two scales, a Patient Scale and an Observer Scale.
- Change the number of subjects from approximately 30 to approximately 10-15 per dose level
- Confirm that subjects will receive up to four doses of sotatercept (ACE-011)
- Remove the Phase 2B/3 portion of the study and all references to Part 1 and Part 2 in the study design.
- Delete all references to the Phase 2B/3 study treatment of sotatercept (ACE-011) / placebo.
- Revise Post-Treatment Follow-Up Period of six months to the Post-Treatment Follow-Up/End of Treatment/End of Study Visit occuring 42 days (6 weeks) following the last dose of sotatercept (ACE-011).
- Delete the Post-Treatment Follow-Up Period. assessments and procedures.
- Add sotatercept (ACE-011) drug antibody repeat assessments following the Post Treatment Follow-Up / End of Treatment / End of Study Visit for subjects with a positive sotatercept (ACE-011) titer.
- Delete the Study Discontinuation Visit assessments and procedures.
- Delete the Survival Follow-Up Period
- Include TSH, DXA scan, Activian A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin and Overall Survival Data Collection in the Post-Treatment Follow-Up/End of Treatment/End of Study Visit.
- Remove ECGs and archival tissue collection in Part 2 of the study.
- Revise the number of subjects anticipated to participate in the Full PK assessment
- Delete requirement to replace subjects in the Full PK assessment
- Remove the Independent External Radiology Review and the Independent Review Committee, required in Part 2 of the study.

2.9. Section 7: Study Population (Pages 57-61)

Revised Text:

At the time of randomization ~~in **Part 1** and **Part 2**~~, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~In **Part 1,** subjects~~Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

~~In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.~~

7.1. Number of Subjects

This platinum-based CIA study will enroll approximately ~~840 subjects, approximately 90~~30 subjects with advanced or metastatic solid tumor types ~~in **Part 1** and 750 subjects with metastatic NSCLC in **Part 2**~~.

~~In **Part 1**, up~~Up to ~~90~~approximately 30 subjects will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-~~30~~15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC
- ~~Sotatercept (ACE-011) 45 mg SC~~

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus ~~carboplatin~~other non-cisplatin chemotherapy)

~~In **Part 2**, an additional 750 subjects will be randomized to receive either sotatercept (ACE-011), at the dose determined in **Part 1**, or placebo at a ratio of 1:1. Subjects will be stratified by:~~

~~1. Baseline Hgb level~~

~~– 6.5 to < 9.0 g/dL~~

~~– 9.0 to < 11.0 g/dL~~

~~2. Type of platinum-based chemotherapy (cisplatin versus carboplatin)~~

~~3. NSCLC histology (Squamous NSCLC vs. Non-Squamous NSCLC)~~

~~4. ECOG Performance Status 0-1 vs. 2~~

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. ~~**Part 1** –~~Histologically confirmed (cytology or biopsy) solid tumor malignancy, excluding those solid tumors treated with curative intent.

   ~~**Part 2** - Histologically confirmed (cytology or biopsy) non-small cell lung cancer.~~
3. Documented advanced or metastatic disease.
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L), due to chemotherapy-induced anemia
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function:
     - creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin is concomitantly administered

       and
     - urine protein / creatinine ratio ≤ 1.0; or ≤ 2.0 if bevacizumab (Avastin®) is concomitantly administered
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤ 5.0 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL) or ≤ Grade 1. Previous hypercalcemia treatment is allowed

6. Subjects must:
   - have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

     OR

   - have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

     OR

   - currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

   - ~~For **Part 1** any~~Any platinum-based regimen approved for the specific indication

   - ~~For **Part 2** allowed regimens for the treatment of metastatic NSCLC are:~~
     - ~~gemcitabine plus cisplatin or carboplatin ± bevacizumab~~
     - ~~pemetrexed plus cisplatin or carboplatin ± bevacizumab~~
     - ~~taxanes plus cisplatin or carboplatin ± bevacizumab~~
7. ≥ 28 days must have elapsed since previous treatment with ESA
8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 30 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)
10. 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 at least 112 days following the last dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo.~~).

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days **prior** to sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).

11. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo,~~), even if he has undergone a successful vasectomy.
12. Life expectancy of ≥ 3 months.
13. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.
14. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C]) at the time of screening, including Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g., asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non-hematological events (e.g., nausea, vomiting, fatigue, or muscle or bone/joint pain), occurring during the chemotherapy period and resolving.
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 subject participation in the study, at the discretion of the Investigator.

~~3. Part 2 only, history of prior regimen(s) of platinum-based chemotherapy for metastatic NSCLC and/or history of adjuvant platinum-based chemotherapy with last dose received less than six months prior to the start of current first-line platinum-based chemotherapy for metastatic NSCLC.~~

~~4~~3. CNS metastases **(exception: subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks prior to randomization)**.

~~5~~4. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying malignancy.

~~6~~5. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).

~~7~~6. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.

~~8~~7. Diagnosis of a myeloid malignancy or known history of myelodysplasia.

~~9~~8. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).

~~10~~9. Uncontrolled hypertension. Controlled hypertension is considered clinically stable and systolic blood pressure (SBP) must be < 150 mmHg and diastolic blood pressure (DBP) must be < 100 mmHg.

~~11~~10. Known infection with human immunodeficiency virus (HIV).

~~12~~11. Known active hepatitis B or C antibody defined by positive serology.

~~13~~12. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.

~~14~~13. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.

~~15~~14. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.

~~16~~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.

~~17~~16. Any prior use of sotatercept (ACE-011).

~~18~~17. Pregnant or lactating females or females planning to become pregnant.

~~19~~18. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).

~~20~~19. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

Rationale:

Modified to:

- Remove the Phase 2B/3 portion of the study and all references to Part 1 and Part 2 in the study design.
- Change the number of subjects from approximately 30 to approximately 10-15 per dose level.
- Delete the 45mg sotatercept (ACE-011) dose level.
- Revise stratification to include other non-cisplatin platinum-based chemotherapy in addition to carboplatin due to addition of other allowed tumor types in Amendment 3
- Delete all references to the Phase 2B/3 study treatment of sotatercept (ACE-011) / placebo.

Section 8: Description Of Study Treatments (Pages 62-65)

Revised Text:

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 sotatercept (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 sotatercept (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 sotatercept (ACE-011). The reconstituted sotatercept (ACE-011), in its original container closure system, may be held for up to 6 hours at 2°C to 8°C.~~

~~**Placebo (Part 2 Only)**:~~

~~In **Part 2**, the sotatercept (ACE-011) placebo to be used in the study will be sterile normal saline (0.9% sodium chloride for injection) administered as a SC injection. Sterile, normal saline will be supplied by the investigational site's pharmacy. The manufacturer's directions for placebo storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the placebo.~~

Prior to administration, the lyophilized drug product is reconstituted with 1 mL sterile water for injection (WFI) in the closed product vial using sterile needles and syringes following institutional standards for reconstitution of sterile products. The reconstituted drug product consists of a 50 mg/mL solution of sotatercept (ACE-011). The solution must be refrigerated at 2°C to 8°C upon reconstitution.

The reconstituted sotatercept should be used immediately after reconstitution, and if not used immediately, the reconstituted sotatercept, in its original package, may be held for up to 6 hours at 2°C to 8°C.

8.2. Treatment Administration and Schedule

Sotatercept (ACE-011)~~ or placebo~~ will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization~~ in **Part 1** and **Part 2**~~, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

~~In **Part 1,** subjects~~Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

~~In **Part 2,** subjects must have metastatic NSCLC and must not have received any other regimens of platinum-containing chemotherapy for first-line treatment prior to the regimen they are receiving at the time of randomization.~~

Allowed concomitant platinum-based chemotherapy regimens are:

- ~~For **Part 1** any platinum-based regimen approved for the specific indication~~
- ~~For **Part 2** allowed regimens for the treatment of metastatic NSCLC are:~~
  - ~~gemcitabine plus cisplatin or carboplatin ± bevacizumab~~
  - ~~pemetrexed plus cisplatin or carboplatin ± bevacizumab~~
  - ~~taxanes plus cisplatin or carboplatin ± bevacizumab~~

Investigative sites will utilize commercial supply of these medications.

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

~~In **Part 1** and **Part 2**, sotatercept~~Sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb levels. Dose delays of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

~~In **Part 1**, subjects~~Subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-~~30~~15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

~~Analysis of safety data will be performed following the treatment of at least 10 subjects at the 15 mg dose level and 10 subjects at the 30 mg dose level, with each subject having received a minimum of one dose of sotatercept (ACE-011) and completed a 12-week follow-up period from the first dose.~~

~~Following this analysis, the addition of a third dose level:~~

- ~~Sotatercept (ACE-011) 45 mg SC~~

~~to the randomization schema will be determined.~~

Each dose level will be administered every 42 days for up to four doses.

~~The following are decision rules for dose determination in **Part 1** in order to move forward to **Part 2**:~~

- ~~After completion of two doses of sotatercept (ACE-011), a hematopoietic response in approximately 70% of subjects, in at least one or more treatment arms.~~

- ~~Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions and/or ESAs.~~ ~~In order to determine the dose of sotatercept (ACE-011) to be used in **Part 2**, evaluation of hematopoietic response will be determined from sotatercept (ACE-011) dose 1/day 1 through and including dose 2/day 43 (prior to dose 3).~~

- ~~In addition to the hematopoietic response, safety profile, dose modifications and extent of exposure will be taken into account for dose level selection for **Part 2**.~~

The effective dose of sotatercept (ACE-011) is defined as follows:

An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

~~In **Part 2**, subjects will be randomized to receive either sotatercept (ACE-011) (at the dose determined in **Part 1**) or placebo.~~

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ starting on Day 1 (one SC dose every 42 days) and continuing during the six-month ~~(**Part 1**) or nine-month (**Part 2**)~~ Treatment Period, as outlined in the Table of Events (see Section 5).

~~In **Part 1**, subjects~~Subjects will be randomized to receive one of ~~three~~two dose levels of sotatercept (ACE-011), with 10~~-30~~15 subjects per arm. ~~In **Part 2**, 750 subjects will be randomized to receive sotatercept (ACE-011) or placebo at a ratio of 1:1.~~

Each subject will return to the site on each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated weekly after the first dose of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~and then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011~~) or sotatercept (ACE-011)/placebo.~~).

The **first dose** of sotatercept (ACE-011)~~ or sotatercept (ACE-011)/placebo~~ can be administered **at any time after the first cycle and prior to the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy.**

Subsequent doses of sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose

delay, sotatercept (ACE-011) ~~or sotatercept (ACE-011)/placebo~~ administration does not need to be delayed until start of next chemotherapy cycle.

Following completion of the Treatment Period, subjects ~~who enter~~ will continue to the Post Treatment Follow-Up ~~Period will be followed for~~ / End of Treatment / End of Study Visit to occur 42 days (6 ~~months from their~~weeks) after the subjects' last dose of sotatercept (ACE-011~~)~~ ~~or sotatercept (ACE-011)/placebo. Visits will occur every **month.** All subjects will continue to be followed for PFS up to 12 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo, or until progression of their advanced or metastatic disease, whichever occurs first.~~).

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of advanced or metastatic disease that requires the initiation of another treatment.

~~Following the Study Discontinuation Visit, subjects will be contacted monthly and survival data collected for an additional 12 months (up to 24 months following the subject's first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo).~~

8.2.3. Discontinuation

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

– – – – – – – – – – –

- ~~In **Part 1**, lack~~Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations. ~~In **Part 2**, lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following two doses of sotatercept (ACE-011)/placebo (Dose 1/ Day 1 through and including Dose 2/Day 43, prior to Dose 3).~~
- Concomitant use of ESAs ~~In **Part 1** if administered at any time and in **Part 2** if administered < 4 months after first dose of study treatment~~.
- Sotatercept (ACE-011) ~~or Sotatercept (ACE-011)/placebo~~ Dose Modifications:

  ~~In **Part 1** and **Part 2**:~~ A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL

  ~~In **Part 2:** > 3 dose reductions and/or delays~~

– – – – – – – – – – –

Study Discontinuation:

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

- Completed study, per protocol (subject has completed approximately six ~~to nine~~ month Treatment Period including a 42 day [6 week]~~up to six month~~ Post Treatment Follow-Up/End of Treatment/End of Study Visit) ~~Period including one year tumor~~

~~assessment to determine TTP and PFS). Note: Survival data will continue to be collected for up to 24 months after first dose of study treatment~~.

– – – – – – – – – – –

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to ~~4 doses of sotatercept (ACE-011) in **Part 1**. In **Part 2**, subjects will be randomized at a ratio of 1:1 and receive up to 4 doses of study treatment and may receive 2 additional doses of sotatercept (ACE-011)/placebo, if clinically indicated, at the discretion of the Investigator.~~four doses of sotatercept (ACE-011). A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

– – – – – – – – – – –

Rationale:

Modified to:

- Clarify reconstitution instructions for the ACE-011 Process III lyophilized product reconstitution.
- Remove the Phase 2B/3 portion and all references to Part 1 and Part 2 of the study.
- Revise the defined effective dose of sotatercept (ACE-011) due to smaller sample size.
- Delete the 45mg sotatercept (ACE-011) dose level
- Delete all references to the Phase 2B/3 study treatment of sotatercept (ACE-011) / placebo.
- Revise Post-Treatment Follow-Up Period of six months to the Post-Treatment Follow-Up/End of Treatment/End of Study Visit occuring 42 days (6 weeks) following the last dose of sotatercept (ACE-011).
-

2.10. Section 9: Concomitant Medications And Procedures (Pages 67-68)

Revised Text:

9.1. Permitted Concomitant Medications and Procedures

– – – – – – – – – – –

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in ~~Part 1 of the study; however, ESAs are allowed in Part 2 only after a subject has received at least 4 months of study treatment.~~the study. The use of ESAs will need to result in immediate notification to the study Sponsor and Medical Monitor, as well as to the clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

~~In **Part 1**, all subjects~~Any subject who receive an ESA will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up ~~Period. In **Part 2**, subjects who receive an ESA at < 4 months from their first dose of sotatercept (ACE-011) or sotatercept (ACE-011)/placebo will be discontinued from the study Treatment Period and continue to the Post-Treatment Follow-Up Period. Subjects who receive an ESA at ≥ 4 months from their first dose of sotatercept (ACE-011)/placebo will continue in the Treatment Period as follows: **The unblinded pharmacist will ensure that subjects randomized to receive treatment with sotatercept (ACE-011) are changed over to receive treatment with placebo. Subjects randomized to treatment with placebo will continue to receive placebo. The investigator, site personnel and subject will remain blinded.**~~/ End of Treatment / End of Study Visit.

– – – – – – – – – – –

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate ~~,~~ therapy (other than for the treatment of hypercalcemia~~,~~), and denosumab therapy for bone metastases can be started prior to randomization but should not be started on study.

Rationale:

Modified to:

- Remove the Phase 2B/3 portion and all references to Part 1 and Part 2 of the study.
- Revise term “Post-Treatment Follow-Up Period” to “Post-Treatment Follow-Up Visit”.
- Correct typographical error.

2.11. Section 10: Statistical Analyses (Pages 69-70)

Revised Text:

10.1. Overview

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic ~~agents followed by a phase 2b/3, double-blind, randomized, placebo-controlled study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with platinum-based chemotherapeutic regimens.~~regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. ~~In **Part 1**, subjects~~Subjects will be randomized to one of ~~three~~two doses of sotatercept (ACE-011~~) plus platinum-based chemotherapy. In **Part 2**, subjects will be randomized to placebo or the selected sotatercept (ACE-011) dose determined from **Part 1** plus platinum-based chemotherapy. Data from **Part 1** will not be combined with data from **Part 2** in all safety and efficacy analyses.~~).

~~A DMC~~Analyses will be ~~used to monitor the study conduct.~~ exploratory.

– – – – – – – – – – –

10.3. Sample Size and Power Considerations

~~In **Part 1**, up~~Up to ~~90~~30 subjects will be randomized among ~~three~~two dosing groups. ~~This sample size is for the purpose of hypothesis generation. However, it would allow approximately 80% power~~Enrollment was limited and there were no power considerations due to ~~detect an effect size of 0.33 using a 2 degrees of freedom Chi-Square Test with a two-sided significance level (alpha) of 0.05.~~

~~In **Part 2**, subjects will be enrolled in two stages. In the first stage, approximately 180 subjects will be randomized in a 1:1 ratio to the selected sotatercept (ACE-011) dose group or placebo group. An interim analysis of transfusion rate will be performed after these 180 subjects have received at least two doses of sotatercept (ACE-011)/placebo, and have been followed for at least 4 months from randomization. A Data Monitoring Committee will review the results and provide recommendations on continuing or stopping the~~ study~~. Based on the results of the futility analysis, further enrollment in the second stage of **Part 2** of the study could be continued.~~

~~Upon recommendation to continue the study, an additional 570 subjects will be subsequently randomized in the second stage. The total sample size of 750 subjects in **Part 2** (first plus second stage) would allow observation of at least 536 deaths and thus at least 80% power to exclude more than 15% hazard increase in the sotatercept (ACE-011) arm compared with the placebo arm at one-sided significance level of 0.025, i.e., rejecting hazard ratio (Placebo:sotatercept [ACE-011]) of 0.87, assuming the sotatercept (ACE-011) arm actually reduces at least 10% hazard, i.e., true hazard ratio (Placebo:sotatercept [ACE-011]) of 1.11~~ closure.

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10.6. Efficacy Analysis

~~In **Part 1**, the~~The ~~primary endpoint will be the~~ hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. ~~The analysis will be based on the EE population. The proportion of subjects with hematopoietic response will be estimated and a Chi-square test will be performed to compare response rates across treatment groups.~~

~~In **Part 2**, the primary endpoint will be rate of RBC transfusion within 4 months following the date of randomization. It will be estimated based on Kaplan-Meier method for time to the first RBC transfusion. The analysis will be based on ITT population and will be conducted according to the approximate timeline as described in Section 10.8. Subjects who have documented RBC transfusion(s) from randomization until the last dose of concomitant platinum-based chemotherapy plus 30 days or from the initiation date of non-platinum-based chemotherapy, whichever is earlier, will be considered as having the event on the date of first RBC transfusion. Subjects who are discontinued from study treatment due to reasons other than disease progression or death will be considered as having the event on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Subjects who discontinue from study treatment due to disease progression or death will be censored on the date of study treatment discontinuation, or the last dose date of platinum-based chemotherapy plus 30 days or the initiation date of non-platinum-based chemotherapy, whichever is earliest. Otherwise subjects will be censored on the date of last contact, or on the date of last dose of concomitant platinum-based chemotherapy plus 30 days or on the initiation date of non-platinum-based chemotherapy, whichever is earliest. The comparison on the distribution difference between the treatment groups will be based on the stratified log-rank test, and the associated hazard ratio and 95% confidence interval will be provided using Cox proportional hazard model. The proportion of subjects receiving a transfusion based on Kaplan-Meier estimates at specific time points will also be provided by treatment arms.~~

~~As secondary endpoints for **Part 2** of the study, time to progression, progression free survival and overall survival will be analyzed based on the ITT population.~~

~~**Time to progression (TTP)** is defined as the time between the randomization date and date of disease progression. **Disease progression is based on the IRC reviewed progression date.** If a subject dies due to reasons other than disease progression, the subject will be censored at the death date. If a subject does not have disease progression, then the subject will be censored at the last tumor assessment (prior to or on the first day of the first subsequent antitumor therapy).~~

~~**Progression free survival (PFS)** is defined as the time between the randomization and disease progression or death. **Disease progression is based on the IRC reviewed progression date.** Subjects who progressed or died will be considered to have had an event, except if this event occurs after the start of subsequent antitumor therapy, in which case the subject is censored at the time of last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. The date of progression is taken as the earliest date of: Date of PD as evaluation of response, date of new lesion on tumor measurements page, death date, if death is caused by PD, treatment termination date if reason is PD, progression date as documented on treatment termination page, progression date as documented on the follow-up visit page. Subjects who did not progress nor died (lost to follow-up or still being treated without documented disease~~

~~progression or started subsequent antitumor therapy) will be censored at the date of the last tumor assessment prior to or on the first day of the first subsequent antitumor therapy. PFS based on investigators' assessment will also be analyzed.~~

~~**Overall survival (OS)** is defined as the time between the randomization and death. A subject who dies, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.~~

~~For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the distribution function, six-month and one-year survival rates, as well as the medians and 95% confidence intervals will be provided. The stratified log-rank test will be used to compare the distributions of TTP, PFS and OS respectively. The stratification factors are described in Section 4.1 . The associated hazard ratios and confidence intervals will be provided using stratified Cox proportional hazard model respectively for each endpoint.~~

~~Sensitivity analyses will be performed on TTP, PFS, and efficacy analyses will also be performed using EE population. Data listings will be provided for all relevant data collected during the studies. Further details will be included in the Statistical Analysis Plan.~~

10.7. Safety Analysis

All safety subjects will be used for safety analyses. Sotatercept (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 ~~study part and~~ treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized. Safety information obtained ~~during~~ through the Post Treatment Follow-Up / End of Treatment / End of Study Visit ~~Period during each segment~~ will be incorporated into these analyses.

10.8. Interim Analysis

~~There are two interim analyses planned for this study. At the first interim analysis, the transfusion rate result will be used for go/no go decision, and overall survival will also be analyzed. At the second interim analysis, only the overall survival will be analyzed.~~

~~The first interim analysis on transfusion rate will be conducted after the first 180 eligible subjects randomized in **Part 2** of the study (stage 1) who have received at least two doses of sotatercept (ACE-011)/placebo, have been followed for at least 4 months from randomization. This sample size would allow at least 90% power to detect a 15% difference between two arms (sotatercept [ACE-011] arm 15% vs. placebo 30%) in 4 month transfusion rates at two-sided 5% significance level based on the stratified log-rank test and the assumption of exponential distribution for time to RBC transfusion. If the p-value at the interim analysis does exceed significance level of 0.05, the result will be considered as lack of efficacy. If the p-value is less than or equal to 0.05, additional subjects will be enrolled and the study will move on to the **Part 2**; however, the futility analysis result based on RBC transfusion rate may be up to DMC evaluation. For superiority, Type I error 0.0001 will be spent at this interim for transfusion rate, and the remaining 0.0499 will be spent at the final analysis after 750 subjects being enrolled.~~

~~Overall survival will also be analyzed at this interim, Type I error spending will be based on O'Brien and Fleming Boundary.~~

~~The second interim analysis will be performed when approximately 265 deaths are observed in **Part 2**. Type I error spending will be based on O'Brien and Fleming boundary.~~

~~The final analysis will be performed when approximately 536 deaths are observed in **Part 2**.~~

There will be no interim analysis.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 5 - 10 subjects will be enrolled for full PK sampling in each treatment cohort~~ of **Part 1**. For this portion of the study, subjects who miss more than two PK sampling time points from Days 1 through 43 will be replaced~~.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, $AUC_{~~42~~}$, and $t_{1/2}$,z, may~~will~~ be estimated for subjects providing full PK samples. ~~Dose proportionality will be assessed by regression analysis using the exposure data after the first dose.~~ Descriptive statistics may~~will~~ be provided for plasma concentrations and PK parameters.

~~In exploratory population PK analysis, covariates to be tested may include type of chemotherapy, the presence of anti-sotatercept (ACE-011) antibodies, demographics (age, race, gender, and body weight), markers for hepatic and renal function, and other factors as deemed appropriate. Both full and sparse PK data will be included for population PK analyses.~~

The relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) ~~will~~may be explored~~.~~

~~**10.10. Data Monitoring Committee (DMC)**~~

- A DMC will review safety and efficacy data to ensure the protection of study subjects. The DMC will receive periodic updates of all serious treatment-related toxicities and SAEs leading to deaths from all causes. The first planned review by the DMC will be conducted following the randomization and treatment of twenty subjects. The DMC will continue to monitor safety on an ongoing basis including recommendation of sotatercept (ACE-011) dose selection for **Part 2**. The first interim analysis will be conducted after the first 180 eligible subjects in **Part 2** of the study (stage 1) have been followed for at least 4 months for RBC transfusion rate. The second interim analysis will be performed when approximately 265 deaths if data are observed in **Part 2**. The final analysis will be performed when approximately 536 deaths are observed in **Part 2**.

~~Ad hoc meetings will be scheduled as needed.~~

~~The DMC will have a consultative role with respect to the Sponsor. The Sponsor will make the final decision regarding the recommendation proposed by the committee. A separate DMC charter will detail the activities of this committee~~sufficient.

Rationale:

Modified to:

- Revise Statistical Section to reflect changes in analyses due to decrease in the sample size, abbreviated follow-up period, and removal of the Phase 2B/3 portion of the study. .
- Delete requirement to replace subjects in the Full PK assessment
- Delete population PK model for sotatercept (ACE-011) due to smaller sample size.
- Delete reference to the Data Monitoring Committee (DMC).

2.12. Section 12: Discontinuations (Page 77)

Revised Text:

Stopping Rules

~~In addition to~~ Celgene routine pharmacovigilance surveillance~~, a DMC~~ will review ~~unblinded~~ data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

Rationale:

Modified to:

- Delete reference to the Data Monitoring Committee (DMC).

2.13. Section 13: Emergency Procedures (Page 78)

Revised Text:

13.2. Emergency Identification of Investigational Products

~~In both **Part 1** and **Part 2** the blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.~~

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

Rationale:

Modified to:

- Delete Emergency Identification of IP for blinded study. This study is open – label.

AN OPEN-LABEL RANDOMIZED, PHASE 2A, DOSE-RANGING STUDY OF SOTATERCEPT (ACE-011) FOR CHEMOTHERAPY-INDUCED ANEMIA IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS TREATED WITH PLATINUM-BASED CHEMOTHERAPEUTIC REGIMENS

INVESTIGATIONAL PRODUCT (IP):	SOTATERCEPT (ACE-011)
PROTOCOL NUMBER:	ACE-011-NSCL-001
DATE FINAL:	17 SEPTEMBER 2010
AMENDMENT 1.0 FINAL:	22 MARCH 2011
AMENDMENT 2.0 FINAL:	27 JUNE 2011
AMENDMENT 3.0 FINAL:	01 NOVEMBER 2011
AMENDMENT 4.0 FINAL:	02 MAY 2012
EudraCT NUMBER:	2010-022561-10
IND NUMBER:	103362

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:	
PPD	

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: PPD

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

PPD

Head

PPD

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:_____** By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

An open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) for chemotherapy-induced anemia in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens.

Indication

Chemotherapy Induced Anemia (CIA) in subjects with advanced or metastatic solid tumors treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

Objectives

The exploratory objectives are:

- To explore doses of sotatercept (ACE-011) that result in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent.
- To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the pharmacokinetics (PK) of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).
- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism.
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To assess renal function biomarkers.

Study Design

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens.

The study is dose-finding in which up to approximately 30 subjects will be randomized to one of two sotatercept (ACE-011) dose treatment arms. The main exploratory objective is to determine a dose of sotatercept (ACE-011) that results in a hematopoietic response in the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapy, excluding those solid tumors treated with curative intent.

Study Population

At the time of randomization subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent. Subjects must also:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Length of Study and Study Treatments

This study will consist of the following consecutive periods: Screening and Treatment Period, including a Post Treatment Follow-Up Visit. Study treatment is defined as sotatercept (ACE-011).

Screening Period (28 days):

Potential study subjects will sign an informed consent form prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to randomization, as outlined in the Table of Events, Section 5. Note: Screening period tumor assessments should be performed within six weeks or as per standard care at the study site prior to randomization. **Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected and used for assessment of tumor response.**

Prior erythropoietic stimulating agent (ESA) treatment history starting from the initial solid tumor diagnosis and red blood cell (RBC) transfusion history starting from diagnosis of advanced or metastatic disease, at a minimum of up to two months prior to randomization will be collected.

All females of childbearing potential (FCBP) participating in the study are to use highly effective methods of birth control during the Screening Period, for at least 28 days before starting the study. Some highly effective methods of birth control include:

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

Treatment Period and Post-Treatment Follow-Up / End of Treatment / End of Study Visit (approximately 6 months):

The Treatment Period is approximately six months and includes up to four doses of sotatercept (ACE-011) given on Day 1, every 42 days, followed by a Post-Treatment Follow-Up / End of Treatment / End of Study Visit.

The Post-Treatment Follow-Up Visit will occur approximately 42 days (6 weeks) after the subjects' last dose of sotatercept (ACE-011). The Post-Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

Subjects with advanced or metastatic solid tumor types who meet all eligibility criteria will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Each dose level will be administered every 42 days for up to four doses.

The effective dose of sotatercept (ACE-011) is defined as follows:

An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks).

During the Treatment Period, subjects will be assessed for hematopoietic response, transfusion need, safety and tumor response. The severity of AEs will be graded according to the currently active minor version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered > 7 days from the date of the RBC transfusion.

Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from subjects at select centers, in approximately 5 - 10 subjects for each sotatercept (ACE-011) dose group investigated. In subjects participating in the full PK assessment, RBC, Hgb, and reticulocyte counts will be collected at each PK time point (excluding the 4-hour time point on

Day 1) from Day 1 to Day 43 after the first dose. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.

ACE-011 (sotatercept) concentration may be determined in anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK, in subjects who do not participate in the full or sparse PK assessments.

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (systolic blood pressure [SBP] ≥ 160 mmHg or diastolic blood pressure [DBP] ≥ 100mmHg), confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy.
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy.
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months of sotatercept (ACE-011) therapy.
  - Any thromboembolic event > Grade 2.
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment).
  - Urine protein / creatinine ratio > 1.0; or > 2.0 if bevacizumab (Avastin®) is concomitantly administered.
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week.
- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations.
- Concomitant use of ESAs if administered at any time.
- Sotatercept (ACE-011) dose modifications
  - A second Hgb increase of ≥ 3.0 g/dL following a two-level dose reduction due to a Hgb increase ≥ 3.0 g/dL
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation - as determined by the Sponsor

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

Post Treatment Follow-Up Visit

The Post-Treatment Follow-Up Visit will occur approximately 42 days after the subjects' last dose of sotatercept (ACE-011). The Post-Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

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

- Completed study, per protocol (subject has completed approximately six month Treatment Period including a 42 day [6 week] Post-Treatment Follow-Up/End of Treatment/End of Study Visit).
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse event(s)
- Disease progression
- Protocol violation

Overview of Efficacy Assessments

- Serum hematology, absolute reticulocyte counts
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Serum erythropoietin
- Tumor assessments
- Documentation of concomitant RBC transfusions

Overview of Safety Assessments

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac and thromboembolic events
- Vital signs including height, weight, heart rate, seated systolic and diastolic blood pressure, and temperature.
- AE(s)
- 12-lead electrocardiogram (ECG)
- Medically supervised pregnancy testing

- Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, Vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone).
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- Lung Cancer Symptom Scale (LCSS) questionnaire – subjects with NSCLC
- Documentation of concomitant medications / procedures.

Overview of Exploratory Assessments

- Bone or other potential mechanistic or disease-related proteins/biomarkers
- DXA scan
- Renal function biomarkers

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 17
2. STUDY OBJECTIVES 34
2.1. Exploratory Objectives 34
3. STUDY ENDPOINTS 35
3.1. Exploratory Endpoint(s) 35
4. OVERALL STUDY DESIGN 36
4.1. Study Design 36
4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules 39
4.2. Study Design Rationale 41
4.2.1. Fixed Dose 42
4.2.2. Dosing Schedule 42
4.2.3. Dose Levels 42
4.3. Study Duration 42
5. TABLE OF EVENTS 44
6. PROCEDURES 51
7. STUDY POPULATION 58
7.1. Number of Subjects 58
7.2. Inclusion Criteria 59
7.3. Exclusion Criteria 60
8. DESCRIPTION OF STUDY TREATMENTS 63
8.1. Description of Investigational Product(s) 63
8.2. Treatment Administration and Schedule 63
8.2.1. Selection of Dose for the Study 64
8.2.2. Selection and Timing of Dosing for Each Subject 64
8.2.3. Discontinuation 65
8.3. Method of Treatment Assignment 66
8.4. Packaging and Labeling 66
8.5. Investigational Product Accountability And Disposal 67
8.6. Investigational Product Compliance 67

9. CONCOMITANT MEDICATIONS AND PROCEDURES 68
9.1. Permitted Concomitant Medications and Procedures 68
9.2. Prohibited Concomitant Medications and Procedures 69
9.3. Required Concomitant Medications and Procedures 69
10. STATISTICAL ANALYSES 70
10.1. Overview 70
10.2. Study Population Definitions 70
10.3. Sample Size and Power Considerations 70
10.4. Background and Demographic Characteristics 70
10.5. Subject Disposition 70
10.6. Efficacy Analysis 70
10.7. Safety Analysis 71
10.8. Interim Analysis 71
10.9. Other Topics 71
11. ADVERSE EVENTS 72
11.1. Monitoring, Recording and Reporting of Adverse Events 72
11.2. Evaluation of Adverse Events 72
11.2.1. Seriousness 72
11.2.2. Severity / Intensity 73
11.2.3. Causality 74
11.2.4. Duration 74
11.2.5. Action Taken 75
11.2.6. Outcome 75
11.3. Abnormal Laboratory Values 75
11.4. Pregnancy 75
11.4.1. Females of Childbearing Potential 75
11.4.2. Male Subjects 76
11.5. Immediate Reporting of Serious Adverse Events 76
11.6. Safety Queries 76
11.7. Expedited Reporting of Adverse Events 76
12. DISCONTINUATIONS 78
13. EMERGENCY PROCEDURES 79
13.1. Emergency Contact 79

13.2. Emergency Identification of Investigational Products 79
14. REGULATORY CONSIDERATIONS 80
14.1. Good Clinical Practice 80
14.2. Investigator Responsibilities 80
14.3. Subject Information and Informed Consent 80
14.4. Confidentiality 81
14.5. Protocol Amendments 81
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 81
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 82
14.8. Closure of the Study 82
15. DATA HANDLING AND RECORDKEEPING 83
15.1. Data/Documents 83
15.2. Data Management 83
15.3. Record Retention 83
16. QUALITY CONTROL AND QUALITY ASSURANCE 85
16.1. Study Monitoring and Source Data Verification 85
16.2. Audits and Inspections 85
17. PUBLICATIONS 86
18. REFERENCES 87
19. APPENDICES 90
Appendix A: Response Evaluation Criteria in Solid Tumors 90
Appendix B: ECOG Performance Status Scale 92
Appendix C: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 93
Appendix D: New York Heart Association - Classification of Heart Failure 94

LIST OF TABLES

Table 1: A011-02: A Phase 1b Study in Healthy Postmenopausal Women, Hemoglobin Evaluation 26
Table 2: Summary of Adverse Events Reported in Greater Than or Equal To 5 Percent of Patients Overall 29
Table 3: Summary of SAEs Reported 30
Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days 30
Table 5: Sotatercept (ACE-011) Dose Reduction Levels 40
Table 6: Sotatercept (ACE-011) Dose Escalation Levels 41
Table 7: Sotatercept (ACE-011) Schedule of Assessments 44
Table 8: Schedule of Pharmacokinetic Assessments 50
Table 9: ECOG Performance Status Scale 92
Table 10: Classification of Heart Failure 94

LIST OF FIGURES

Figure 1: Study Design 38

1. INTRODUCTION

This is an open-label, randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens.

Safety data will be continuously monitored by the sponsor.

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3.

The chemical structure of sotatercept (ACE-011) is composed of a disulfide-linked, glycosylated, homodimeric protein. Sotatercept (ACE-011) competes with the activin receptor IIA and binds a number of TGF-β superfamily ligands including activin, GDF-11, BMP-10, GDF-3 and myostatin (growth differentiation factor [GDF]-8).

In both a single and a multiple dose phase 1 study of sotatercept (ACE-011) in healthy volunteer, postmenopausal women, a dose and time dependent increase in hemoglobin (Hgb) and hematocrit (HCT), and red blood cell (RBC) levels were observed following sotatercept (ACE-011) treatment and remained elevated over the course of study.

Although the mechanism(s) underlying the stimulation effect of sotatercept (ACE-011) on erythropoiesis are not yet fully understood, the result of clinical experience showed a rapid and sustainable increase in mature erythrocytes released into circulation. The sotatercept (ACE-011) proposed mechanism of action may be different than that of known erythropoiesis-stimulating agents (ESAs) and may provide a different clinical profile in the treatment of CIA.

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

Chemotherapy-Induced Anemia

Chemotherapy-induced anemia (CIA) is an area of unmet medical need. It is a significant problem for patients with cancer, causing fatigue and reducing quality of life (QoL).

Patients with cancer receiving multi-cycle chemotherapy are frequently anemic. The etiology of CIA is multifactorial, resulting from the myelosuppressive effects of chemotherapy and the decrease in the production of the bone-marrow-stimulating hormone erythropoietin due to repeated cycles of chemotherapy (Vansteenkiste, 2002). The incidence and severity of chemotherapy-induced anemia (CIA) is further dependent on a variety of factors, such as the type, schedule, and intensity of chemotherapy administered, and whether the patient has received prior myelosuppressive chemotherapy and/or radiation therapy (Groopman, 1999). Platinum-based treatments (eg, cisplatin and carboplatin), commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia due to combined bone marrow and kidney toxicity. Antimicrotubular agents (eg, taxanes and vinorelbine) and camptothecins (eg, irinotecan and topotecan) are also considered particularly myelosuppressive (Groopman, 1999). Dose intensity, the increasingly widespread practice of administering higher doses of chemotherapy over a shorter period of time, is also associated with an increased risk of myelosuppression.

The association between uncorrected anemia before or during chemotherapy and poorer patients' outcomes has been reported in several studies (Grogan, 1999; Laurie, 2006; MacRae, 2002; Obermair, 2003). Anemia can lead to a multitude of symptoms (eg, fatigue, tachycardia, cognitive impairment, shortness of breath, depression, and dizziness) and may also have an adverse impact on co-morbid conditions, such as cardiac and pulmonary disease. The most common patient complaints are dyspnea on exertion and chronic fatigue, which may interfere with a patient's ability to perform normal daily activities (Groopman, 1999). A key differentiating characteristic of cancer-related fatigue versus fatigue in healthy individuals is its likelihood of persistence at rest (National Comprehensive Cancer Network, 2008) In various published surveys, fatigue has been represented as a symptom that has affected patients' everyday life the most and has been linked to changes in employment status among patients and even caregivers (Schwartz, 2007). The association between Hgb levels and fatigue is well documented, with one analysis of 5 randomized trials linking an increase in Hgb concentrations of at least 2 g/dL with an improvement in fatigue, and consequently, in energy, ability to perform usual activities, and overall health (Cella, 2004).

In looking at the impact of CIA on survival, a meta-analysis of 60 clinical studies found a 65% increase in the risk of death and a shortened survival time among patients with cancer and anemia compared with patients without anemia (Carlos, 2001). The increased relative risk of death was particularly evident in patients with head and neck cancer (75%), a finding that also is supported by other retrospective studies. Tumor hypoxia, resulting from the reduced oxygen-carrying capacity of blood in patients with anemia, has been hypothesized to be a major contributor to reduced survival. Several studies have shown that tumor hypoxia also reduces the effectiveness of radiotherapy and chemotherapy, and is associated with tumor progression (Aapro, 2006).

Treatment of Chemotherapy-Induced Anemia

The current treatment options for CIA include blood transfusion and erythropoiesis-stimulating agents (ESAs). However, blood transfusion involves the risk of complications (such as potential transmission of infectious disease, alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression) for the patient, and donor blood is a limited resource. The practice of offering blood transfusions to cancer patients receiving chemotherapy has therefore been rather restricted, generally reserved for emergencies, and severely anemic patients with serious symptoms.

Erythropoiesis-stimulating agents have been approved for treating CIA. However, the past five years has seen a major change in the use of ESAs for cancer related and chemotherapy induced anemia. Clinical studies have demonstrated that ESAs can successfully mitigate transfusion need in a proportion of these patients; however, new concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations. Retrospective statistical analysis in one study in head and neck cancer patients, and two studies with adjuvant breast cancer revealed substantial safety concerns of increased thromboembolic events, and decreased PFS and overall survival.

Sotatercept (ACE-011) Treatment of Chemotherapy-Induced Anemia

Treatment with sotatercept (ACE-011) resulted in increased HCT, Hgb and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases in Hgb and

HCT levels were observed in two phase 1 studies in healthy volunteers, as well as in a phase 2a study in multiple myeloma (MM) subjects. The ability for sotatercept (ACE-011) to rapidly increase and sustain Hgb levels in anemic subjects supports the clinical development of ACE-011 for the treatment of CIA.

In a phase 1 single-dose and multiple-dose studies of sotatercept in postmenopausal women (Studies A011-01 and A011-02, respectively), and in a phase 2 study in subjects with osteolytic lesions associated with MM that examined concurrent administration of sotatercept with melphalan, prednisolone, and thalidomide (MPT) anti-myeloma therapy, increases in Hgb, RBC count and HCT were observed following sotatercept treatment, and these increases remained detectable throughout the course of study. The observed Hgb, RBC count, and HCT effects of sotatercept were dose-dependent and time-dependent. These phase 1 and phase 2 clinical data are consistent with the increased hematologic parameters observed in nonclinical studies, The results from the three completed clinical studies A011-01, A011-02, and A011-04 are summarized in Summary of Clinical Experience.

The mechanism of action of sotatercept with regards to increased RBC counts is not known; however, the mechanism of action for the hematopoietic effect of sotatercept may be different than that of ESAs, as some level of erythrocyte stimulatory effect was observed in the presence of anti-EPO antibodies in one nonclinical study. As such, sotatercept may provide a unique clinical profile with a favorable benefit-risk profile in the chemotherapy-induced anemia patient population, thereby addressing some of the unmet medical needs in chemotherapy-induced anemia treatment.

Non-Small Cell Lung Cancer Current Therapy Status

Lung cancer is the leading cause of cancer death in the world, accounting for 32% of cancer deaths in males and 25% in females, affecting approximately 171,000 people annually in the US (Parker, 1997; Sandler, 2006) and more than 200,000 people in Europe (Rossi, 2006). Of these patients, approximately 85% have NSCLC, including squamous carcinoma, adenocarcinoma and large cell carcinoma (Rossi, 2006; Sandler, 2006). These histologies are typically classified together because the approaches to diagnosis, staging and prognosis, and treatment are similar.

Patients are often diagnosed with an advanced stage of disease. Studies of advanced NSCLC patients treated with platinum-based chemotherapy report a one year survival rate that ranges from 30% to 43% and a median survival that ranges from seven to ten months (Dang, 2008). The 5-year survival rate of patients with NSCLC varies by stage, from 60% to 70% for patients with stage I disease to < 1% for patients with stage IV disease (Hong, 2008). Patients having stage IIIb/IV NSCLC are not considered to be candidates for curative resection surgery or radiation, and radiation therapy is primarily used as palliative treatment in advanced stages of NSCLC.

The role of chemotherapy is now well established as the recommended treatment of advanced NSCLC (Non-small Cell Lung Cancer Collaborative Group, 1995). The current globally accepted standard of treatment for NSCLC is platinum-based combination therapy. In advanced-stage (stage IIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine (Gemzar®), vinorelbine, taxanes (paclitaxel or docetaxel) or pemetrexed are reference regimens. When compared head-to-head in phase 3 studies, these doublets have shown comparable efficacy, in regards to overall survival (Schiller, 2002) with

differences in toxicity profiles (Schiller, 2002). When administered in a 3-week schedule, cisplatin plus gemcitabine, or cisplatin plus pemetrexed are effective and are widely used regimens for first-line treatment of NSCLC. A recent phase 3 study in NSCLC compared cisplatin plus gemcitabine with cisplatin plus pemetrexed (Scagliotti, 2008). Both had similar efficacy, with cisplatin plus pemetrexed having better tolerability and more convenient administration than cisplatin/gemcitabine. This study was also the first prospective phase 3 study in NSCLC to show a survival difference based on histologic type (non-squamous benefited from pemetrexed plus cisplatin). Drug-related grade (G) 3 or 4 anemia was at the rate of 6% for cisplatin/pemetrexed versus 10% for cisplatin/gemcitabine. The incidence of RBC transfusion was 16.1% versus 27.3% and administration of erythropoietic agents 10.4% versus 18.1% respectively. There was no significant difference between treatment arms in the incidence of or reason for deaths (7%).

In the pivotal Aranesp (darbepoetin alfa) study for CIA in NSCLC, 27 % of patients were transfused with packed red blood cells (PRBC's) at 4 months versus 52% in the placebo arm.

Activin Biology

The activins (A-E) are a group of proteins that form dimers and heterodimers. All are part of the TGF-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 A was also 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).

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

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

In a retrospective study (Seder, 2009) activin immunoreactivity was found in 78% of lung adenocarcinomas surveyed (n=164). Expression ranged from moderate in the majority of individuals to high in approximately 19.7% of samples evaluated. Gene expression analysis was also used to measure activin mRNA in 86 lung adenocarcinomas and 10 normal lung samples.

An average of three-fold more activin transcript was detected in diseased tissue relative to normal samples and particularly high levels of overexpression were associated with worse overall survival in stage I patients with NSCLC.

Additionally, in the NIH "directors challenge" study for NSCLC adenocarcinoma (Shedden, 2008), 3 of the 12 molecular subgroups, including the subgroup with the worst survival prognosis, demonstrated overexpression of Activin A. Thus, overexpression of activin may play a role in NSCLC tumor progression.

Sotatercept (ACE-011)

Sotatercept (ACE-011) (ActRIIA-IgG1Fc) is a recombinant human fusion protein consisting of the extracellular domain (ECD) of activin receptor IIA (ActRIIA) linked to the human IgG1 Fc domain, which includes the heavy chain hinge and constant domains, CH2 and CH3. The ECD sequence of ActRIIA is completely conserved among numerous species including mouse, rat, cynomolgus monkey and humans, thus mouse, rat and cynomolgus monkeys have been considered relevant species for nonclinical evaluation of sotatercept (ACE-011). However, in order to reduce the potential immunogenicity of the human molecule, sotatercept (ACE-011), and to maximize the opportunity to maintain exposures in chronic models, a murine surrogate molecule was constructed by exchanging the human immunoglobulin Fc sequence portion of sotatercept (ACE-011) with its murine IgG2a homolog. The resultant construct is referred to as RAP-011 (ActRIIA-mIgG2aFc), and is described in the pharmacology studies below. Both ACE-011 and RAP-011 bind with high affinity to activin A/B, GDF-11 and, with slightly lower affinity, to BMP-10.

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 (IP) twice per week for 3 months resulted in a 16-26% increase in RBC counts compared to control animals. Rats treated with sotatercept (ACE-011) at 0.3, 3 and 30 mg/kg once per week for 3 months showed RBC count increases of 6-15% over control animals. Finally, in cynomolgus monkeys treated with 10, 30 or 50 mg/kg of sotatercept (ACE-011) twice per month for 3 months, there was a 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 sotatercept (ACE-011).

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

RAP-011 has also been shown to significantly increase bone mineral density (BMD) and strength in normal animals and in a variety of animal models of bone loss (Chantry, 2010; Lotinun, 2008; Pearsall, 2008). In a murine ovariectomy (OVX)-induced model of osteopenia, RAP-011 (10 mg/kg intravenous [IV], twice per week x 12 weeks) increased trabecular BMD >

25% in 6-12 weeks compared to the phosphate buffered saline (PBS)-treated controls ($p<0.002$). RAP-011 treatment was able to reverse the accelerated bone loss associated with ovariectomy. As expected, sham-operated (SHAM) mice (i.e., intact ovaries) started the study with a greater trabecular BMD than OVX mice. PBS-treated SHAM mice showed a 10% decrease in trabecular BMD after 12 weeks of treatment compared to baseline, while SHAM-RAP-011 mice had a 32% increase in trabecular BMD over the same period. These data demonstrate that RAP-011 is able to increase trabecular BMD in both the normal state and in a model of established bone loss. The femurs of both the RAP-011 treated OVX and SHAM mice showed statistically significant increases in all measured parameters of bone strength (i.e., maximum load, stiffness, energy, ultimate strength, and elastic modulus). In summary, treatment with RAP-011 produced bone of superior quality consistent with an anabolic agent.

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

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

RAP-011 was also evaluated in osteolytic bone disease of multiple myeloma. Multiple myeloma is associated with the development of bone disease characterised by increased osteoclast activity and a suppression of osteoblastic bone formation.

Results obtained in the 5T2MM murine model demonstrated that RAP-011 could prevent the development of osteolytic bone disease in a preventative setting.

5T2MM cells promoted the development of osteolytic bone lesions ($p<0.001$), a reduction in trabecular volume ($p<0.001$) and cortical volume ($p<0.005$). RAP-011 completely prevented 5T2MM-induced decreases in trabecular volume and number in both tibia ($p<0.001$ and $p<0.01$), femur ($p<0.001$ and $p<0.001$) and vertebrae ($p<0.01$ and $p<0.01$) when compared to vehicle treated mice. Bone volume was 19% higher in the tibia, 35% higher in the femur and 12% higher in vertebrae of RAP-011 treated mice than naïve non-tumour bearing mice.

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

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

modestly decreased the tumor burden (in the case of mice bearing MCF-7 tumors) or delayed tumor growth by approximately 3 weeks (MDA-MB-231 model) as measured by bio-luminescence.

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

Toxicology

Sotatercept (ACE-011) has been evaluated for toxicological effects in two species, Sprague-Dawley rats and cynomolgus monkeys. The dose levels ranged from 0.3 to 30 mg/kg in rats and from 1 to 50 mg/kg in monkeys. These dose ranges were designed to support phase 1a single-dose levels of 0.01 to 3.0 mg/kg IV and phase 1b multiple doses of 0.1 to 2 mg/kg (monthly, SC). Weekly (rat and IV monkey studies) or every 2 week (SC monkey studies) dosing in animals was designed to provide continuous, but fluctuating serum concentrations of sotatercept (ACE-011), which would be mimicked by a one-month dosing interval in humans.

Test article related hematological (increase in RBC parameters) and reproductive (epididymal granulomas, testicular degeneration, decreased sperm counts and motility, and change in ovarian/uterine weights) findings were expected pharmacodynamic effects of ActRIIA signal inhibition, likely mediated via modulation of erythropoiesis and FSH secretion, respectively. Unique to rats were adrenocortical and pancreatic findings. Neither finding was associated with any clinical signs of adrenocortical (anorexia, weakness, gastrointestinal disturbances, serum electrolyte disturbances) or pancreatic (abnormal stool, weight loss) insufficiency. Kidney findings include membranoproliferative glomerulonephritis and/or tubulointerstitial nephritis in rats and monkeys. The glomerulonephritis was presumed to be due to anti-sotatercept (ACE-011) antibody deposition in the kidneys. This presumption is supported by a robust anti-drug antibody response observed in rats as well as demonstration, by immunohistochemistry, of immunoglobulin and complement at the site of injury in monkeys, consistent with immune complex deposition. However, high plasma concentrations of sotatercept (ACE-011) in monkeys likely interfered with the immunogenicity assay, so the true incidence of anti-drug antibodies is unknown in this species.

The no-observed-adverse effects levels (NOAELs) in rats and monkeys were 3 (3-month study) and 1 mg/kg (9-month study), respectively.

Summary of Clinical Experience

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

Sotatercept (ACE-011) was first studied in a randomized, phase 1a, single dose, dose escalation study in healthy, postmenopausal females (Ruckle, 2009). Sotatercept (ACE-011) was diluted in normal saline administered as an IV infusion (over approximately 1 hour) or as a SC injection on Day 1. Dose levels were 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg IV and 0.03 and 0.1 mg/kg SC. A total of 48 subjects were enrolled; 5 active and 1 placebo at each of the IV and SC dose levels. All subjects were followed for 4 months following a single dose administration.

The pharmacokinetics (PK) of sotatercept (ACE-011) was linear. The overall mean exposure (AUC) was proportional to doses (0.01-3 mg/kg IV, 0.03-0.1 mg/kg SC). Across IV doses ranging from 0.1 through 3.0 mg/kg, the mean clearance (CL) ranged from 0.092 to 0.128 mL/h/kg, the volume of distribution ranged from 73.7 to 110 mL/kg, and the mean terminal half life in serum ($t_{1/2,}$ z) ranged from 23.7 to 31.8 days, with no apparent dependence on dose. After SC administration of 0.03 and 0.1 mg/kg, sotatercept (ACE-011) was completely absorbed, and the mean $t_{1/2,}$ z was approximately 30 days, with no apparent dependence on dose.

The most commonly occurring treatment-emergent adverse events (AEs; i.e., those occurring in more than 1 subject in any treatment group) were headache, infusion site reaction, injection site hemorrhage, and toothache. The majority of the injection site reactions and injection site hemorrhages were in the first IV cohort and were related to infiltration of the IV site. The majorities of treatment-emergent AEs was mild in severity and were judged to be unrelated to sotatercept (ACE-011). No deaths, serious AEs (SAEs), or AEs leading to discontinuation were reported. Changes in RBCs, Hgb, reticulocytes, liver function tests, glucose, uric acid, amylase and lipase occurred in some subjects. Mild, transient elevations in pancreas enzymes, liver enzymes, or glucose were reported as AEs in five subjects.

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

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

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

Sotatercept (ACE-011) was studied in a phase 1b, single-center, randomized, double-blind, placebo-controlled, multi-dose, dose-escalating study to evaluate the safety, tolerability and pharmacodynamics of sotatercept (ACE-011) in healthy postmenopausal women. Four cohorts of 10 subjects each were planned at the following dose levels: 0.1, 0.3, 1.0, and 2.0 mg/kg administered SC. Within each cohort, subjects were to be randomized to either active or placebo treatment in an 8:2 ratio. Subjects were to receive one SC injection of sotatercept (ACE-011) or placebo every 28 days for a total of 4 doses. All subjects were to be followed for 12 weeks after the last dose.

The treatment phase of the study was terminated early after a dose-limiting pharmacodynamic effect was observed. While on study, one subject in the 1.0 mg/kg cohort experienced an SAE of

progressive and persistent hypertension that was attributed to a rapid and significant rise in Hgb levels, up to 20 g/dL and HCT levels, up to 57.3%. Due to symptoms of headaches, nausea, eye pain, dizziness and vomiting approximately one week following the second dose, the subject was hospitalized for monitoring and evaluation of her hypertension. The head MRI, fundoscopy, and ECG performed were reported as normal and headache symptoms resolved following corrective treatment by phlebotomy. The SAE resolved and the subject was discharged from the hospital the following day. The hypertension was monitored closely and managed initially with antihypertensive medication. The hypertension resolved by the end of the study without need of any antihypertensive medication. The subject received aspirin prophylactically until the end of the study and continued taking ibuprofen as needed for headaches. Further details can be found in the Investigator's Brochure.

Based on the magnitude of the hematopoietic response, the Sponsor suspended dose escalation to the 2.0 mg/kg dose level and further dosing in all cohorts as a result of this dose-limiting pharmacodynamic effect at the 1.0 mg/kg dose level. In total, 31 subjects were enrolled and treated. Dose levels of sotatercept (ACE-011) administered included 0.1, 0.3, and 1.0 mg/kg (Cohorts 1, 2, and 3 respectively). All subjects randomized to active treatment in Cohort 1 received all 4 planned doses of sotatercept (ACE-011). Due to early discontinuation of study drug, subjects randomized to active treatment in Cohort 2 received 3 doses of sotatercept (ACE-011), and subjects randomized to active treatment in Cohort 3 received 2 doses of sotatercept (ACE-011). Subjects randomized to placebo treatment received between 1 and 4 doses of study treatment.

In the analysis of the data, after the administration of the first dose, a dose and time dependent increase in Hgb, 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]	**Sotatercept (ACE-011) 0.1 mg/kg N=8**	**Sotatercept (ACE-011) 0.3 mg/kg N=8**	**Sotatercept (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

Other than the serious case of Hgb increase, no life-threatening events were reported. The most notable AEs were those related to increases in hematologic laboratory measures in the 1.0 mg/kg dose group: HCT, Hgb, and RBC count. The AEs of increased Hgb and/or HCT were reported for seven of the eight subjects in this dose group. These events were reported as mild or moderate elevations; all were considered probably related to study drug treatment. Three of the

subjects in the 1.0 mg/kg group with elevated Hgb levels underwent phlebotomies and all Hgb elevations were resolved by the end of the follow-up period. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups.

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

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

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

The PK of sotatercept (ACE-011) were linear after SC administration. Both AUC28d and Cmax were proportional to dose from 0.1 to 1 mg/kg following the first SC administration. The $t_{1/2,}$ z of sotatercept (ACE-011) following the last dose in all three dose groups was identical, with mean $t_{1/2,}$ z being approximately 23 days. Based on the one-compartmental modeling, the mean CL/F ranged from 3.05 to 3.90 mL/d/kg, the mean Vz/F ([apparent] volume of distribution) ranged from 97.47 to 103.03 mL/kg, with no apparent dependence on dose.

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

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

Study A011-04 is a phase 2a, multi-center, randomized, multiple-dose study to evaluate the safety, tolerability and efficacy of sotatercept (ACE-011) in subjects with osteolytic lesions of multiple myeloma (MM).

In this study, subjects were randomized in a 4:1 ratio to one of three dose levels of sotatercept (ACE-011) (0.1, 0.3 and 0.5 mg/kg) or placebo, administered to subjects every 28 days by SC injection, for up to four doses over a 3-month period. Sotatercept (ACE-011) was evaluated in combination with the anti-myeloma therapy of melphalan (4 mg/m^2 on days 1-7), prednisolone (40 mg/m^2 on days 1-7) and thalidomide (100 mg per day) (MPT). The sites, Sponsor and Sponsor representatives were blinded to treatment assignment.

Thirty subjects were randomized and received at least one dose of study medication: 6 subjects received placebo, 8 subjects received 0.1 mg/kg sotatercept (ACE-011), 8 subjects received 0.3 mg/kg sotatercept (ACE-011), and 8 subjects received 0.5 mg/kg sotatercept (ACE-011). Twenty six (86.7%) subjects completed the study. One subject in the 0.1 mg/kg dose group and one subject in the 0.5 mg/kg dose group discontinued due to AEs. One subject in the 0.1 mg/kg dose group withdrew consent and was discontinued, and one subject in the 0.3 mg/kg dose group was discontinued at the request of the investigator.

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

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

Fourteen out of 24 subjects (58%) who received study treatment (sotatercept [ACE-011]) did receive 3 doses or more (4 out of 8 subjects in the 0.5 mg/kg dose level, 5 out of 8 subjects in the 0.3 mg/kg dose level and 5 out of 8 subjects in the 0.1 mg/kg dose level).

Safety: Overall, 22 (91.7%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo reported at least one AE. Among subjects receiving sotatercept (ACE-011), AEs were reported in 87.5%, 87.5%, and 100% of subjects in the 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg dosing cohorts, respectively. Treatment-related AEs (i.e., those assessed by the Investigator as possibly, probably, or definitely related to treatment) were reported by 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) receiving placebo. Most subjects had AEs that were assessed as related to MPT: 21 (87.5%) subjects receiving sotatercept (ACE-011) and 4 (66.7%) subjects receiving placebo. No AEs were assessed by the Investigator as related to the study medication alone (sotatercept [ACE-011] or placebo). Two subjects had AEs assessed as possibly or probably related to study drug and possibly or probably related to MPT, one subject in the 0.1 mg/kg sotatercept (ACE-011) dose group (increased blood pressure; sudden death) and one subject in the 0.5 mg/kg sotatercept (ACE-011) dose group (hypertension). Four subjects had SAEs, 1 (12.5%) subject in the 0.1 mg/kg sotatercept (ACE-011) group and 3 (37.5%) subjects in the 0.5 mg/kg sotatercept (ACE-011) group. Three subjects had SAEs that were assessed as treatment-related. Of the 3 treatment-related SAEs, 2 SAEs were assessed as possibly related to MPT and unrelated to sotatercept (ACE-011), and 1 SAE (sudden death) was assessed as probably related to MPT and possibly related to sotatercept (ACE-011). One subject in the 0.5 mg/kg sotatercept (ACE-011) dose group discontinued study drug due to episodes of atrial fibrillation assessed as possibly related to MPT and unrelated to sotatercept (ACE-011).

Table 2 summarizes the most frequent AEs ≥ 5% in all treatment groups and Table 3 is a summary of SAEs reported.

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

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

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

* Indicates the adverse event was assessed by the investigator as related (possibly, probably, or definitely) to study drug, (sotatercept (ACE-011) or placebo).

Table 3: Summary of SAEs Reported

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

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

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

[b]Relative to first dose of study drug.

Following analysis of the central laboratory data, increases in Hgb values were observed within 28 days after administration of the first dose of sotatercept (ACE-011)/placebo and sustained for ≥ 28 days from baseline at any time as presented in Table 4.

Table 4: Number of Subjects with an Increase in Hgb from Baseline at Any Time and Sustained for Greater Than or Equal To 28 Days

Increase in Hgb	Dose Sotatercept (ACE-011)/Placebo				
	0.1 mg/kg N=8	0.3 mg/kg N=8	0.5 mg/kg N=8	Placebo N=6	Overall N=30
≥ 1.0 g/dL	4	3	7	2	16
≥ 1.5 g/dL	2	3	3	1	9
≥ 2.0 g/dL	1	3	2	0	6

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

Potential Risks for Human Use

Nonclinical studies to determine the safety of sotatercept (ACE-011) have been conducted in cynomolgus monkeys and Sprague-Dawley rats. Many of the observed effects in these studies

were as a result of the expected biologic activity of sotatercept 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 erythropoiesis.

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 sotatercept (ACE-011) treatment and is being targeted as a therapeutic intervention for conditions associated with anemia.
- In the 6- and 9-month monkey studies, glomerulonephritis and/or tubulointerstitial nephritis were observed in monkeys administered ≥ 10 mg/kg administered subcutaneously (SC) every 2 or 4 weeks. At 2.6 mg/kg administered SC every 4 weeks for 9 months, kidney findings were limited to a single incidence of tubulointerstitial nephritis. The NOAEL in the 9-month study was considered to be 1 mg/kg every 4 weeks. Serum exposure in monkeys at the 1 mg/kg dose is estimated to be ~1.4-fold greater than the projected serum exposure in humans at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject. Because sotatercept is a fully human molecule, immunogenicity and, by extension, kidney injury is not expected in humans. In the single- and multiple-dose studies in healthy postmenopausal women, there have been no changes in serum chemistry or urinalysis profiles suggestive of kidney injury. Subjects administered sotatercept (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. These changes were also considered related to the formation of anti-drug antibodies. Findings at 1 mg/kg were limited to mononuclear cell infiltrates and were not considered 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 sotatercept (ACE-011). There were no histological correlates in the liver, and often a dose-response relationship was not observed. The relevance of these findings to sotatercept (ACE-011) treatment is uncertain; however, liver enzymes will continue to be monitored in this study.

- Pregnancy and Lactation
  - 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 in rats at doses ≥ 15 mg/kg (2.8-fold greater exposure than the projected exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject). In addition, at 50 mg/kg (4.7-fold the exposure at the maximum proposed human dose), there was an increase in late fetal death coupled with an overall increase in post implantation loss and a reduction in live litter size, as well as an increase in the incidence of developmental variations of supernumerary ribs with corresponding increases and decreases in thoracic and lumbar vertebrae, respectively. No fetal malformations were observed in this study at dosages up to 50 mg/kg. The NOAEL for embryofetal development effects was 5 mg/kg (1.5-fold greater exposure than the exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject) based on reduced fetal weights and associated delays in ossification.
  - In an embryo-fetal development study in rabbits, post implantation loss was increased and average litter size and live fetuses were reduced at 15 and 50 mg/kg. In addition, fetal body weights were reduced in all sotatercept dosage groups. Abortions occurred in one rabbit in the 5 mg/kg dosage group and two rabbits in the 50 mg/kg dosage group. Based on these findings, an NOAEL was not identified in this study and was therefore less than 5 mg/kg (<1.2-fold greater exposure than the exposure at the maximum proposed human dose of 61 mg every 6 weeks in a 50 kg subject)
  - Precautions should be taken to protect females of childbearing potential. Nonclinical studies on breast milk have not been done.
  - If sotatercept (ACE-011) is taken during pregnancy, a teratogenic effect in humans cannot be ruled out. Therefore, all sotatercept (ACE-011) protocols describe pregnancy prevention requiring females of child-bearing potential to use highly effective methods of birth control. In addition, since it is unknown if sotatercept (ACE-011) is found in breast milk, breast feeding is prohibited in all protocols.
- Fertility
  - In male rats, sperm granulomas and testicular degeneration were observed histologically. In addition, sperm analysis revealed a reduction in sperm counts and motility as well as sperm fragmentation in isolated animals (2/10 males) at doses of 30 mg/kg IV. Sperm fragmentation was also noted in 2/5 males administered 10 mg/kg IV at the end of the recovery period. Overall, there was some evidence of recovery (motility similar to controls) at the end of the 4-week recovery period. There was no evidence of a treatment-related impact on reproductive organs (testes, ovary, uterus) of monkeys in the toxicity studies; however, the monkeys on these studies, were too immature to fully assess the potential impact on reproductive organs. The NOAEL for reproductive effects

(testicular or ovarian) was 1 mg/kg IV. Serum exposure (AUC_{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 61 mg every 6 weeks (estimated AUC_{28d} ~ 4248 µg·hr/mL in a 50 kg subject).

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

Because of the potential risks sotatercept (ACE-011) treatment has on fertility, sotatercept (ACE-011) was first studied in healthy postmenopausal in two completed phase 1 clinical trials. In addition, due to the potential for effects on hormones in the pituitary, levels of growth hormone, ACTH, and thyroid stimulating hormone (TSH) were monitored closely in the phase 1 studies.

Completed studies in humans carried out in postmenopausal females showed a dose-dependent decrease in circulating levels of FSH, with mean levels in the multi-dose study in the two higher dose groups remaining below baseline at study end. FSH will continue to be evaluated in ongoing studies. No abnormal effects of sotatercept (ACE-011) on growth hormone, ACTH, and TSH and kidney toxicities were observed.

Based on the safety data from the two completed phase 1 studies, single doses of sotatercept (ACE-011) up to 3.0 mg/kg IV and multiple doses of sotatercept (ACE-011) up to 0.3 mg/kg 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 sotatercept (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 sotatercept (ACE-011).

2. STUDY OBJECTIVES

2.1. Exploratory Objectives

- To explore doses of sotatercept (ACE-011) that result in a hematopoietic response for the treatment of CIA in subjects with advanced or metastatic solid tumors treated with platinum-based chemotherapeutic regimens, excluding those solid tumors treated with curative intent.
- To evaluate the safety and tolerability of sotatercept (ACE-011).
- To determine the PK of sotatercept (ACE-011) in subjects receiving platinum-based chemotherapy.
- To evaluate the hematopoietic response and its duration associated with sotatercept (ACE-011) treatment.
- To evaluate the effect of sotatercept (ACE-011) treatment on the quality of life (QoL).
- To estimate the effect of sotatercept (ACE-011) treatment on bone metabolism.
- To evaluate the expression of Activin A and other proteins/biomarkers (including myostatin and follistatin) related to sotatercept (ACE-011) mechanism of action in blood.
- To assess renal function biomarkers.

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

3. STUDY ENDPOINTS

3.1. Exploratory Endpoint(s)

Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs. In addition to the hematopoietic response, the safety profile, dose modifications and extent of exposure in each dosing level will be reviewed.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

- Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) current active minor version 4.0] of adverse events
- Duration of hematopoietic response
- Sotatercept (ACE-011) concentration in serum
- Non-compartmental PK parameters for sotatercept (ACE-011)
- QoL assessment (FACIT Fatigue Scale [Version 4]) and LCSS questionnaire (Hollen, 1993; Hollen, 1994a; Hollen, 1994b; Hollen, 1995, Hollen, 1999)
- Change in serum and urine bone biomarkers, including osteocalcin (OC), serum bone specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type 1 collagen telopeptide (CTX) and tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), the urine bone biomarker (urine N-telopeptide [uNTX]) related to activin or sotatercept (ACE-011) mechanism of action
- Change in BMD (DXA scans of lumbar spine and hip)
- Time to first symptomatic skeletal related event (SRE) defined as pathologic fracture, clinical need for radiation therapy, surgery to bone or spinal cord compression
- Expression of Activin A and other protein/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin)
- Change in renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic regimens. Subjects with advanced or metastatic solid tumor types will be randomized to one of two sotatercept (ACE-011) dose treatment arms. Continuous monitoring of safety data will be conducted.

The study is planned to be conducted in the United States.

Study treatment is defined as sotatercept (ACE-011).

Two sotatercept (ACE-011) dose levels, 15 and 30 mg, were selected for the study. Up to approximately 30 subjects with advanced or metastatic solid tumor types will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Each dose level will be administered every 42 days for a total of up to four doses.

The Treatment Period is approximately six months, which includes up to four doses of sotatercept (ACE-011) and a Post Treatment Follow-Up Visit. The Post Treatment Follow-Up Visit will occur approximately 42 days after the last dose of study treatment. The Post Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

At the time of randomization subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

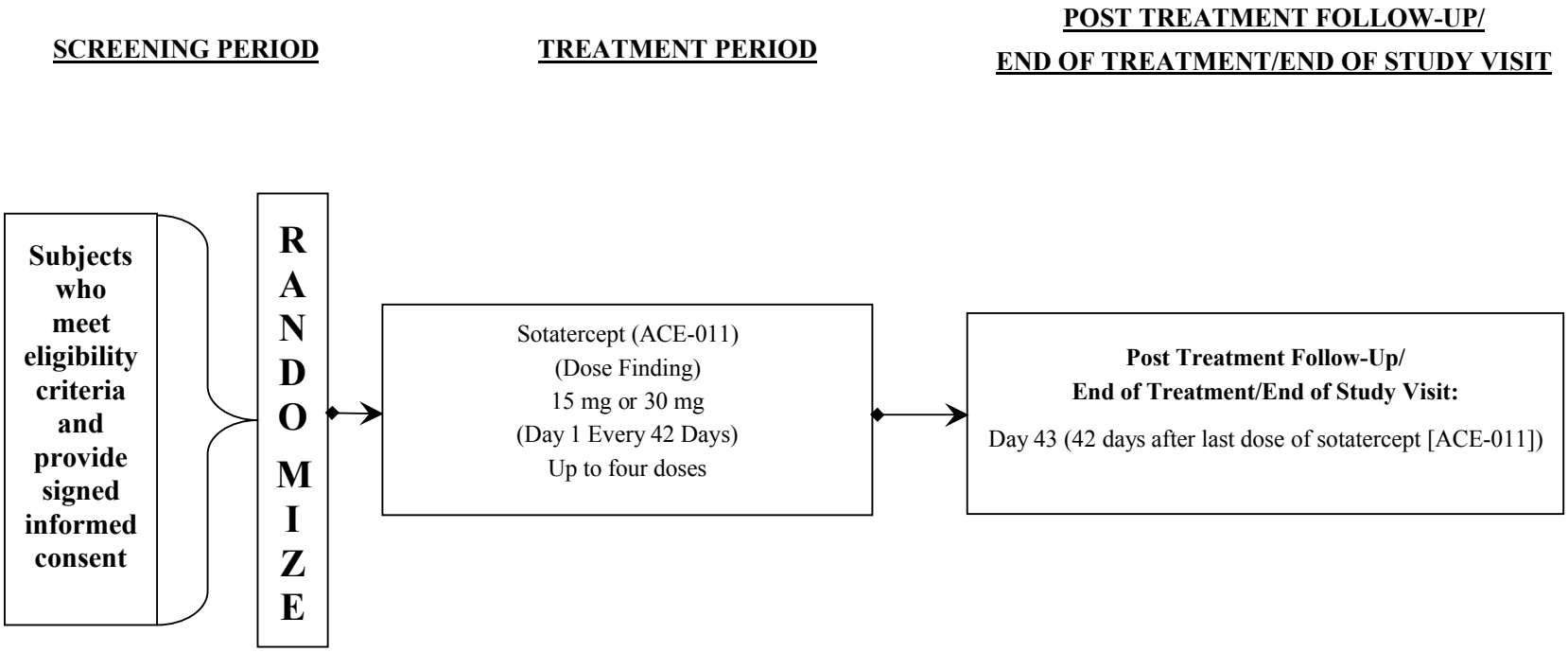
- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

Stratification and randomization will be performed utilizing a validated interactive voice response system (IVRS).

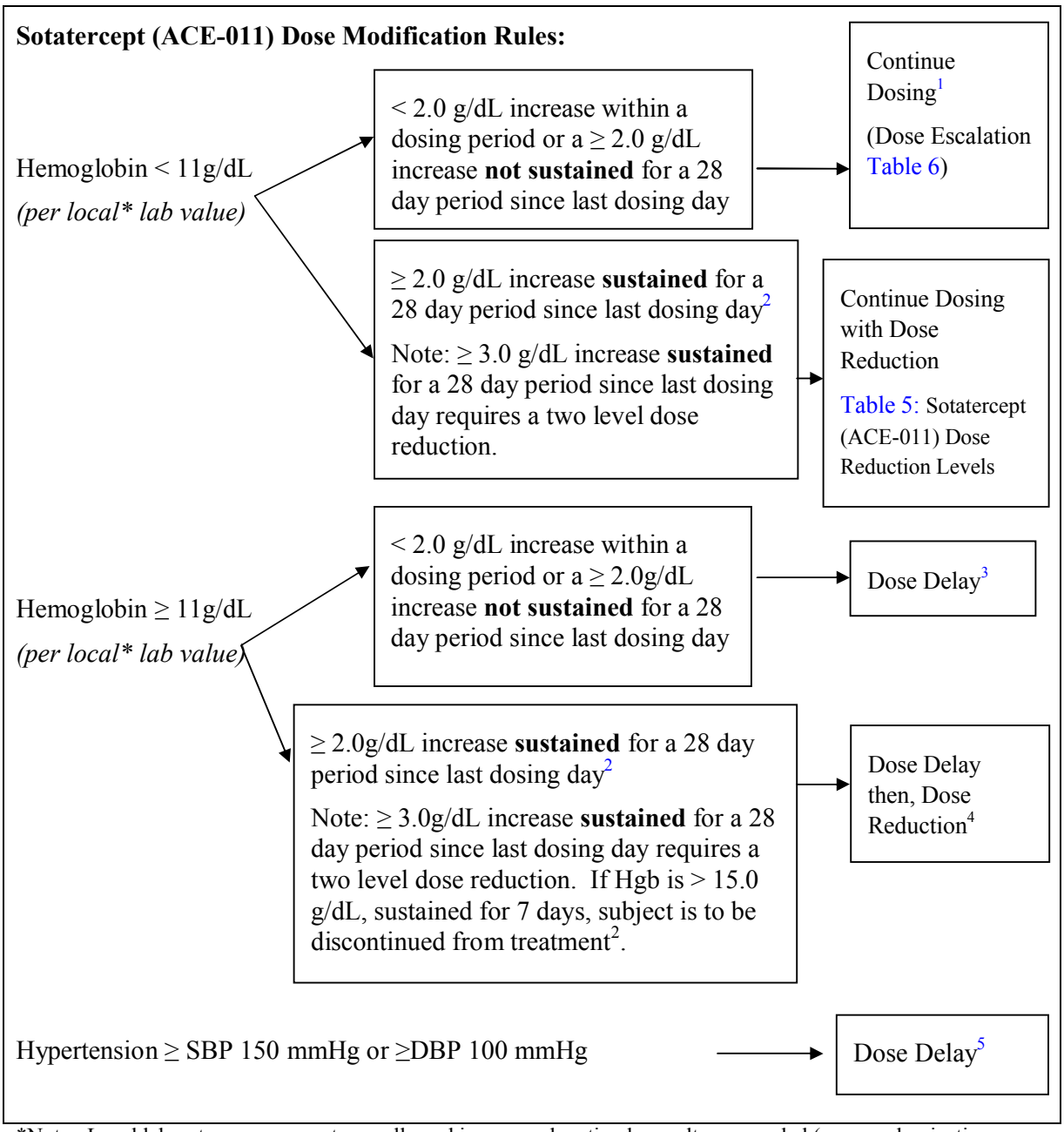
- Subjects will be randomized to one of two sotatercept (ACE-011) dose levels and will be stratified by:
  1. Baseline Hgb level
     - 6.5 to < 9.0 g/dL
     - 9.0 to < 11.0 g/dL
  2. Type of platinum-based chemotherapy (cisplatin versus other non-cisplatin chemotherapy)

Figure 1: Study Design



4.1.1. Sotatercept (ACE-011) Dose Modification, Reduction and Escalation Rules

Subjects should have Hgb and blood pressure measured (confirmed by two measurements obtained at least five minutes apart) prior to each dose of study drug. The Investigator must adhere to the following Hgb and blood pressure-based dose modification rules for sotatercept (ACE-011) for the subject's **second** dose of study treatment and beyond.



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

[1]If Hgb increase ≥ 1.0 but < 2.0 g/dL, dose remains the same.

If the RBC transfusion was given > 7 days following the previous dose of sotatercept (ACE-011), the subsequent dose of sotatercept (ACE-011) will be **increased** one dose level (Refer to sotatercept (ACE-011) Dose Escalation Levels- Table 6). Hemoglobin level must be < 11 g/dL AND hypertension < SBP 150 mmHg and < DBP 100 mmHg on the day of dosing. Sotatercept (ACE-011) should not be administered ≤ 7 days post RBC transfusion.

[2]Hemoglobin increases of ≥ 2 g/dL sustained for a 28 day period since last dosing day should be confirmed on the dosing day, 7, 14 , 21 (after first dose of study treatment) and 28 days after dosing, **and reviewed** in comparison to Hgb level on previous dosing day. Any Hgb increase of ≥3.0 g/dL sustained for 28 days will require a subsequent sotatercept (ACE-011) dose reduction of two dose levels (Refer to sotatercept [ACE-011] Dose Reduction Levels [Table 5]). A second Hgb increase of ≥ 3.0 g/dL sustained for 28 days, following a two level dose reduction, will require the subject discontinue from study treatment. If Hgb is > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment) subject is to be discontinued from treatment. (See Section 8.2.3 Discontinuation)

[3]Sotatercept (ACE-011) should be **delayed** until Hgb is < 11g/dL and hypertension < SBP 150mm Hg and < DBP 100 mm Hg. Dosing can commence at ≥7 days after the originally planned sotatercept (ACE-011) dose that was **delayed**. Subsequent sotatercept (ACE-011) doses will then begin 42 days following this revised treatment dose date.

A **delayed** sotatercept (ACE-011) dose is defined as a dose administered > 4 days from the planned dosing date (due to Hgb ≥ 11.0 g/dL, hypertension > SBP 150 mmHg or > DBP 100 mmHg and/or sotatercept [ACE-011] related toxicity).

[4]Sotatercept (ACE-011) should be delayed as above in foot note ([3]), a reduced dose as above in foot note ([2]) of sotatercept (ACE-011) will be administered based on the evaluation of the Hgb and blood pressure at that time.

[5]Sotatercept (ACE-011) should be held until hypertension resolves to < SBP 150mmHg and < DBP 100 mmHg and may then be resumed beginning seven days after the previous planned scheduled treatment visit as above in foot note ([3]).

Table 5: Sotatercept (ACE-011) Dose Reduction Levels

When required, per dose modification rules above, sotatercept (ACE-011) dose(s) should be reduced as follows:

Dose Schedule Sotatercept (ACE-011)	Dose Reduction* #1	Dose Reduction* #2	Dose Reduction* #3
Every 42 days- 30 mg	26 mg	22 mg	18 mg
Every 42 days- 15 mg	13 mg	11 mg	9 mg

*Note: Any Hgb increase of ≥3.0 g/dL sustained for a 28 day period since last doing day will require a subsequent sotatercept (ACE-011) dose reduction of two dose levels. A second Hgb increase of ≥3.0 g/dL, sustained for 28 days, following a two-level dose reduction will require the subject discontinue from study treatment.

Dosing visits are on Day 1 and repeated every 42 days, for up to four doses.

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (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. A dose level may not be increased following a dose reduction.

Sotatercept (ACE-011) Dose Escalation Levels:

The following dose escalation rules apply for sotatercept (ACE-011) dose(s):

- Less than 1.0 g/dL increase in Hgb in response to prior sotatercept (ACE-011) dose
- Hgb level must be < 11.0 g/dL and hypertension < SBP 150mmHg and < DBP 100 mmHg
- Dose escalation to begin at next treatment visit
- Sotatercept (ACE-011) should not be administered ≤ 7 days from the date of RBC transfusion.

Subjects who have received an RBC transfusion should receive a one level dose increase of Sotatercept (ACE-011) at the subsequent visit per the escalation table below.

Table 6: Sotatercept (ACE-011) Dose Escalation Levels

Dose Schedule Sotatercept (ACE-011)	Dose Increase #1	Dose Increase #2	Dose Increase #3
Every 42 days- 30 mg	33 mg	36 mg	40 mg
Every 42 days- 15 mg	17 mg	20 mg	23 mg

Blood pressure (confirmed by two measurements obtained at least five minutes apart) and Hgb values must be evaluated prior to dosing at each dosing day for consideration in administration of sotatercept (ACE-011).

4.2. Study Design Rationale

The A011-01, A011-02 and A011-04 studies have shown that dosing with sotatercept (ACE-011) resulted in a rapid, sustained and dose-dependent increases in hematopoietic parameters, (Hgb, HCT and RBC counts) which occurred earlier than would be expected from a stimulation of erythropoiesis by an ESA. This observation, coupled with nonclinical data demonstrating some level of erythrocyte stimulatory effect in the presence of anti-erthyropoietin (EPO) antibodies, suggests that the hematopoietic effect of sotatercept is different from that of ESAs. Treatment of subjects with metastatic lung cancer with myelosuppressive platinum-based chemotherapy is frequently associated with anemia. Chemotherapy induced anemia is a significant problem for subjects with cancer, causing fatigue and reduced quality of life (Groopman, 1999). Subjects with CIA are currently treated with blood transfusion and/or ESAs (NCCN Guidelines, 2009). However, with these treatment options CIA is still an area of major medical morbidity. Erythropoiesis-stimulating agents can successfully mitigate transfusion need in a proportion of these subjects, but concerns have emerged regarding apparent negative effects on survival and/or tumor progression in certain patient populations.

4.2.1. Fixed Dose

Sotatercept (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 sotatercept (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 sotatercept (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 sotatercept (ACE-011) exposure. Because the Hgb response is dependent on sotatercept (ACE-011) exposure and because body weight is not a major source for the intersubject variability of sotatercept (ACE-011) exposure, a fixed dosing approach is considered to be appropriate for the current study.

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 by taking into consideration the rapid and prolonged Hgb response to sotatercept (ACE-011) as well as the dosing schedule for the platinum-based chemotherapies. The Hgb-increasing effect of sotatercept (ACE-011) was usually evident approximately 1 week after a SC dose and remained detectable through 6-8 weeks. In addition, as platinum-based chemotherapy is often administered once every 3 weeks, a once every 6 week dosing schedule allows administration of sotatercept (ACE-011) at the same visit for the chemotherapy, which is convenient to both subjects and study sites.

4.2.3. Dose Levels

Two dose levels, 15 and 30 mg, were chosen for the study. Selection of these doses is primarily based on the safety and exposure-response data observed in MM subjects under the standard MPT chemotherapy, who received up to four doses of sotatercept (ACE-011) at 0.1, 0.3, or 0.5 mg/kg (Study A011-04). In these subjects, sotatercept (ACE-011) had an acceptable safety profile and caused exposure-dependent Hgb response. Further, there was no relationship observed between an increase in blood pressure and the maximal sotatercept (ACE-011) concentration or the maximal Hgb rise within 28 days of the first dose (Report A011-04-CP). The two dose levels approximate the average doses received by a 70 kg subject over a 6-week interval (10.5 mg and 31.5 mg respectively) in the A011-04 study.

In Study A011-04, four MM subjects received at least three sotatercept (ACE-011) doses at 0.5 mg/kg every 4 weeks without a dose interruption, and none of them was reported to have an AE related to sotatercept (ACE-011).

4.3. Study Duration

To evaluate sequence and study timelines, please see the Table of Events (see Section 5). Approximately 30 subjects with advanced or metastatic solid tumor types will be randomized prior to receiving the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy. Each subject will be on the study for approximately 6 months (including the Screening Period, the Treatment Period, and the Post

Treatment Follow-Up Visit). The Treatment Period is approximately 6 months (up to four doses of sotatercept [ACE-011] every 42 days) with a Post Treatment Follow-Up Visit occurring at 42 days after the subjects' last dose of sotatercept (ACE-011). Subjects who discontinue treatment early will still continue to the Post Treatment Visit. The Post-Treatment Follow-Up Visit will also serve as the End of Treatment / End of Study Visit.

5. TABLE OF EVENTS

Table 7: Sotatercept (ACE-011) Schedule of Assessments

Assessments	Screening Period	Treatment Period									
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 4 Schedule (± 3 days)				
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Treatment Follow-Up/End of Treatment / End of Study Visit[t]
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Complete Medical History	X										
Cancer History and Prior Therapies[a]	X										
Prior ESA and RBC transfusion history[a]	X	X									
Clinical visits (*study treatment visit)	X	X*	X	X			X*		X		X
ECOG Performance Status	X	X		X			X		X		X
Vital Signs / Blood Pressure[b]	X	X	X	X		X	X		X	X	X
Height (at randomization only)/Weight	X	X		X		X	X		X	X	X
12-Lead Electrocardiogram (ECG) [c]	X	X	X				X				X
Pregnancy Testing[d]	X	X					X				X

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period									
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 4 Schedule (± 3 days)				
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Treatment Follow-Up/End of Treatment / End of Study Visit[t]
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X
Absolute Reticulocyte Count[e]	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[f]	X	X		X		X	X		X	X	X
Serum Creatinine and Creatinine Clearance[g]	X	X		X		X	X		X	X	X
Serum Iron, TIBC, Transferrin and Serum Ferritin, Vitamin B12 and RBC Folate Levels[h]	X						X[h]				X
Serum Erythropoietin (**Full PK subjects post first dose only)[i]	X	X	X**	X	X**	X**	X		X[i]		X
Urinalysis and Renal Biomarkers[j]	X	X		X			X		X		X
FSH and LH – Males and Females	X	X	X				X		X		X
Dihyroepiandosterone and Testosterone (Free & Total) - Males Only	X	X	X				X		X		X
Estrogen and Estradiol & Menstrual Status - Females Only	X	X	X				X		X		X
TSH[k]	X	X					X[k]				X

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period									
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 4 Schedule (± 3 days)				
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Treatment Follow-Up/End of Treatment / End of Study Visit[t]
Sotatercept (ACE-011) drug antibody test (pre-dose)[t]		X		X			X				X[t]
Bone Biomarkers (BSAP, OC, P1NP, CTX, TRACP-5b and uNTX)[f] (**Full PK subjects post first dose only)		X	X**	X**	X**	X**	X				X
Bone Imaging (DXA)[m] (Optional in Selected Centers)	X										X
Activin A and other proteins/biomarkers in blood (serum) (pre-dose study treatment in a subset of subjects)		X	X				X				X
Pharmacokinetics–		Refer to Table 8 – Schedule of Pharmacokinetic Assessments									
Tumor Assessments[o]	X[o]	≤ Every 9 weeks or as per standard of care at study site									
QoL Assessment (LCSS and FACIT Fatigue Scale)[p]	X	X	X	X			X		X		X
Adverse Events	X	All AEs regardless of causality up to 6 weeks (42 days) post last dose of study treatment, after day 43 of last dose – Post Treatment Follow-Up /End of Treatment / End of Study Visit- only SAEs assessed as related to study treatment are to be reported									
Concomitant Medications (including ESAs and transfusions)	X	X		X			X		X		X

Table 7: Sotatercept (ACE-011) Schedule of Assessments (Continued)

Assessments	Screening Period	Treatment Period									
		Sotatercept (ACE-011) Dose 1 Schedule (± 3 days)					Sotatercept (ACE-011) Subsequent Doses 2 through 4 Schedule (± 3 days)				
	Day -28 to Day -1	D1	D8	D15	D22	D29	D43/ D1	D8	D15	D29	D43 Post Treatment Follow-Up/End of Treatment / End of Study Visit[t]
Concomitant Procedures	X	X		X			X		X		X
Hospitalizations (Record)	X	X		X			X		X		X
Randomization		X									
Administer Sotatercept (ACE-011)/Perform Drug Accountability[q]		X					X				
Platinum-based Chemotherapy[r]	X	Dosing of allowed regimen(s) per standard practice									
Targeted/Maintenance Therapy[s]		Dosing of allowed regimen(s) per standard practice									
Overall Survival[t]											X
Post Treatment Anti-Neoplastic Therapy[t]											X

[a]Include cancer history, date of original diagnosis, clinical stage at Screening and date of metastases and advanced or metastatic site involvement. Record prior ESA history, starting at solid tumor diagnosis. Record RBC transfusion history, starting from diagnosis of advanced or metastatic disease, at a minimum of two months prior to randomization.

[b]Vital signs (including heart rate, seated blood pressure, and temperature) will be measured at Screening and all subsequent clinical visits, on Day 29 post sotatercept (ACE-011), and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit. Blood pressure should be confirmed by two measurements obtained at least five minutes apart Investigators are to report any clinically significant abnormal findings as adverse events.

[c]ECG to be performed as follows: At Screening, Day 1 Dose 1 pre and post sotatercept (ACE-011) dose, Day 8 post dose 1, every sotatercept (ACE-011) dosing Visit (post-dose) and at Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

[d]Females of childbearing potential (FCBP) only: 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 with a minimum sensitivity of 25mIU/ml must be performed within 3 days **prior** to the start of sotatercept (ACE-011) administration (Day 1) once the subject has been on effective contraception for at least 28 days and be performed within 3 days **prior** to dose administration of sotatercept (ACE-011) during the Treatment Period. Subjects must agree to use highly effective birth control measures (e.g., oral contraceptives or two forms of barrier method birth control) during study participation and for at least 112 days following the last dose of sotatercept (ACE-011).

[e]Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, ANC, MCV, platelet count and reticulocyte count). Hemoglobin should be tested prior to dosing with sotatercept (ACE-011) to ensure levels are within normal limits and that sotatercept (ACE-011) dose modification rules are followed as outlined in Section 4.1.1. Any laboratory evaluations may be repeated more frequently if clinically indicated. In addition, RBC, Hgb, and reticulocyte counts will be included at each timepoint within the full PK assessment).

[f]Serum chemistry laboratory evaluations (sodium, potassium, chloride, CO2 [bicarbonate], calcium, magnesium, phosphorus, BUN, creatinine, glucose, amylase, lipase, albumin, total protein, alkaline phosphatase, bilirubin [total and direct], AST/SGOT, ALT/SGPT, LDH and uric acid) if clinically significant any or all laboratory evaluations may be reported as AE and repeated more frequently.

[g]Creatinine clearance (per Cockcroft-Gault formula) every 2 weeks during the Treatment Period and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

Note: Footnotes [e], [f], [g]: Hematology, absolute reticulocyte count, serum chemistry and creatinine clearance are to be assessed ≤ 14 days prior to randomization.

[h]Serum Iron, TIBC, Transferrin, Serum Ferritin, Vitamin B12 and RBC Folate to be performed at Screening, pre-last dose of sotatercept (ACE-011) and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

[i]Erythropoietin – collected at day 15 following first 2 doses of sotatercept (ACE-011). For full PK assessment, weekly after first dose of sotatercept (ACE-011).

[j]Urine collection for: Urine albumin, urine albumin creatinine ratio, urine protein creatinine ratio and other renal biomarkers of glomerular and/or tubular injury.

[k]TSH – collected at screening, on Day 1 of only the first and second dose of sotatercept (ACE-011) and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

[l]Bone Biomarkers- Collected for **full** PK subjects prior to dose 1, weekly following dose 1, prior to dose 2 and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit. For all other subjects collected prior to dose 1, prior to dose 2 , and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose). Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

[m]Dual Energy X-ray Absorptiometry (DXA) scan of lumbar spine and hip to evaluate overall health at selected US site(s). Performed at Screening, and at the Post Treatment Follow-Up / End of Treatment / End of Study Visit (day 43 post last dose).

[n]Pharmacokinetics: Blood samples will be collected to evaluate the blood or serum concentrations of sotatercept (ACE-011). Approximately 10 subjects at each sotatercept (ACE-011) dose level, 15 and 30 mg, will have full PK sampling. In addition, RBC, Hgb, and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 after the first dose within the full PK assessment. Subjects not participating in the optional full PK assessment may participate in the sparse PK assessment.

REFER TO Table 8, SCHEDULE OF PHARMACOKINETIC ASSESSMENTS.

[o]Tumor assessments: Screening Period tumor assessments may be performed within six weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the Screening Period, will be collected. Following randomization, tumor assessments will be performed ≤ every 9 weeks or per standard of care at the study site, starting from the date of the previous (screening period) tumor assessment and following the chemotherapy schedule.

[p]QoL assessments- FACIT Fatigue Scale (Version 4) – to be completed by all subjects and LCSS questionnaire – to completed by only subjects with NSCLC. NOTE: The LCSS consists of two scales: one scale for the subject (Patient Scale) and a counterpart scale for health professionals acting as observers (Observer Scale). All QoL assessments should be completed by the subject upon arrival at clinic and prior to any study procedures or testing at all visits, as indicated in the Schedule of Assessments.

[q]Sotatercept (ACE-011) dosing repeats every 42 days and will start after the subject begins a platinum-based chemotherapy regimen. The **first dose** of sotatercept (ACE-011) **may be given at any time following the first dose of platinum-based chemotherapy. Subsequent doses** of Sotatercept (ACE-011) can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) administration does not need to be delayed until start of next chemotherapy cycle.

[r]Platinum-based chemotherapy is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice. Type of chemotherapy and dosing will be recorded.

[s] Targeted/maintenance therapy (e.g. pemetrexed, erlotinib, etc.) is to be administered based on guidelines for administration according to manufacturer's recommendations and standard clinical practice.

[t]Day 43 (6 weeks) post last dose sotatercept (ACE-011) corresponds to the Post Treatment Follow-Up / End of Treatment / End of Study Visit. Subjects who discontinue the sotatercept (ACE-011) Treatment Period early will continue to the Post Treatment Follow-Up / End of Treatment / End of Study Visit. Survival Data and Post Treatment Anti-Neoplastic Therapy should be captured at this Visit. For subjects with a positive sotatercept (ACE-011) drug antibody assessment at the Post Treatment Follow-Up / End of Treatment / End of Study Visit, sotatercept (ACE-011) drug antibody assessments will be repeated every two months or as appropriate for up to one year or until the results are negative, whichever occurs first.

Table 8: Schedule of Pharmacokinetic Assessments

Scheduled Time	Time relative to Sotatercept (ACE-011)	PK Sampling[a,b]		Collection Window[e]
		Full PK[c]	Sparse PK[d]	
Dose 1, D1	pre-Dose 1	X	X	-2 to 0 hour
Dose 1, D1	4 hours after Dose 1	X	X	±1 hour
Dose 1, D5	4 days after Dose 1	X	-	± 1 day
Dose 1, D8	7 days after Dose 1	X	X	± 1 day
Dose 1, D11	10 days after Dose 1	X	-	± 1 day
Dose 1, D15	14 days after Dose 1	X	X	± 1 day
Dose 1, D22	21 days after Dose 1	X	-	± 1 day
Dose 1, D29	28 days after Dose 1	X	X	± 1 day
Dose 1, D36	35 days after Dose 1	X	-	± 1 day
Dose 1, D43 (Dose 2, D1)	pre-Dose 2	X	X	± 2 days
Dose 2, D8	7 days after Dose 2	X	-	± 2 days
Dose 2, D15	14 days after Dose 2	X	-	± 2 days
Dose 2, D43 (Dose 3, D1)	pre-Dose 3	X	X	± 2 days
Dose 3, D8	7 days after Dose 3	X	-	± 2 days
Dose 3, D15	14 days after Dose 3	X	-	± 2 days
Dose 3, D43 (Dose 4, D1)	pre-Dose 4	X	X	± 2 days
Dose 4, D8	7 days after Dose 4	X	-	± 2 days
Dose 4, D15	14 days after Dose 4	X	-	± 2 days
Dose 4, D29	28 days after Dose 4	X	-	± 3 days
Last Dose, D43	42 days after final dose	X	X	± 3 days

[a] Notes about PK sampling times:

- For subjects participating in full PK sampling, RBC, Hgb and reticulocyte counts will be collected at each time point (excluding the 4-hour time point on Day 1) from Day 1 to Day 43 post first sotatercept (ACE-011) dose. Erythropoietin and bone biomarkers will be collected at D1, D8, D15, D22, D29, and D43 post first sotatercept (ACE-011) dose. If the time points for RBC, Hgb, reticulocyte, erythropoietin, and bone biomarkers overlap with the time points defined in Table 7, only one sample is required.
- For subjects who discontinue the treatment early, PK blood sample collection will be continued during the follow-up period.

[b] At each time point, collect approximately 2 mL of blood. After collection, allow the blood to clot at room temperature for approximately 1 hour and then centrifuge the blood sample at room temperature for 10 min (1100-1300 g) to obtain serum.

[c] To be collected for approximately 20 subjects (approximately 10 subjects in each dose group).

[d] To be collected in subjects participating in sparse PK sampling and not participating in full PK sampling.

[e] For subjects who participate in full PK sampling only. The collection window for sparse PK samples will be the same as the visit window defined in Table 7.

6. PROCEDURES

Screening Period (Day -28 to Day -1)

Prior to screening, subjects must sign an informed consent. Potentially protocol-eligible subjects will be evaluated for the inclusion and exclusion criteria for the Treatment Period of this study. All screening assessments must be completed ≤ 28 days prior to randomization. Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1) (Appendix A), must be performed within 6 weeks prior to randomization or as per study site standard of care. Historical tumor assessment data, from prior to the initiation of platinum-based chemotherapy through the screening period, will be collected. Hematology and chemistry laboratory assessments should be performed ≤ 14 days of randomization.

The assessments and procedures that will be performed during the Screening Period are outlined in the Table of Events (see Section 5) and include:

- Informed consent
- Assessment of inclusion / exclusion criteria
- Complete medical history including history of cardiac, renal and thromboembolic events
- Cancer history, including date of original diagnosis, histopathology, clinical stage at screening, date of advanced or metastatic stage and site involvement
- Prior ESA treatment history starting from the initial solid tumor diagnosis
- RBC transfusion history starting from diagnosis of advanced or metastatic disease at a minimum of up two months prior to randomization
- 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, with a minimum sensitivity of 25 mIU/ml, for females of childbearing potential (FCBP) to be assessed within 3 days prior to sotatercept (ACE-011) administration
- Serum chemistry, hematology, absolute reticulocyte count to be assessed ≤ 14 days prior to randomization
- Creatinine clearance (per Cockroft-Gault formula) to be assessed ≤ 14 days prior to randomization
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin
- Vitamin B12 and RBC folate levels
- Serum erythropoietin

- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total) – males only
- Estrogen and estradiol – females only
- TSH
- Bone imaging – DXA scan (optional at selected sites)
- Tumor Assessment - Screening period tumor assessments and tumor evaluation documentation, as per RECIST criteria (Version 1.1), must be performed within 6 weeks or as per study site standard of care prior to randomization. Also, historical tumor assessment data, from prior to the initiation of platinum based chemotherapy through the screening period, will be collected.
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Documentation of concomitant medications / procedures / hospitalizations
- Documentation of concomitant platinum-based chemotherapy

Treatment Period (Day 1/Dose 1 of study treatment to Day 43 post last study treatment dose)

Results from screening evaluations must be reviewed prior to randomization to confirm subject eligibility.

Subjects who meet all eligibility criteria will be randomized utilizing IVRS to receive one of the following sotatercept (ACE-011) dose levels, with approximately 10-15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Each dose level will be administered every 42 days for up to four doses.

- A subject will be considered randomized once a unique multi-digit subject identification number has been assigned by IVRS.

Following randomization, subjects will receive SC doses of sotatercept (ACE-011) on Day 1 and every 42 days for up to four doses during the Treatment Period, as specified in the Table of Events (see Section 5).

The assessments and procedures that will be performed during the Treatment Period are outlined in the Table of Events (see Section 5).

- Updated prior ESA and RBC transfusion history which may have occurred between the screening visit and randomization
- ECOG performance status

- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG
- Medically supervised pregnancy test, with a minimum sensitivity of 25 mIU/ml, for FCBP within 3 days **prior** to sotatercept (ACE-011) administration.
- Serum chemistry, hematology, absolute reticulocyte count.
  - Hematology laboratory evaluations (RBC count, Hgb, HCT, WBC count and differential, mean corpuscular volume [MCV], absolute neutrophil count [ANC], platelet count and reticulocyte count) will be collected weekly after the first dose of sotatercept (ACE-011) and at subsequent sotatercept (ACE-011) doses collected at 7, 14 days and 28 days post-dose.
  - Within full PK assessment, RBC, Hgb and reticulocyte counts are collected at each time point; erythropoietin and bone biomarkers at weekly intervals post first dose of study treatment.
- Creatinine clearance will be assessed every 14 days.
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin at last dose and 42 days after last dose of study treatment
- Vitamin B12 and RBC folate levels at last dose and 42 days after last dose of study treatment
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for premenopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and Testosterone (free and total)– males only
- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (**pre-dose** on the day of sotatercept [ACE-011] administration)
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Activin A and other sotatercept (ACE-011)-related proteins/biomarkers
  - in blood, including myostatin and follistatin:
    - **pre-dose** on Day 1 and Day 8 after first dose of sotatercept (ACE-011)
    - pre-dose on Day 1 subsequent dosing visits
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or per standard of care at the study site, starting from the previous [screening] tumor assessment) and following the chemotherapy schedule

- Pharmacokinetics
- QoL Assessment (FACIT Fatigue Scale [Version 4]) – all subjects
- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Evaluation and all AE/SAE reporting (regardless of causality)
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Documentation of concomitant platinum-based chemotherapy and/or targeted/maintenance therapy
- Administration of sotatercept (ACE-011) on: Day 1 every 42 days

Subjects who discontinue from the Treatment Period early will continue to the Post Treatment Follow-Up / End of Treatment / End of Study Visit 42 days (6 weeks) after their last dose of sotatercept (ACE-011).

Post Treatment Follow-Up / End of Treatment / End of Study Visit (Day 43 post last dose of study treatment)

Following completion or early discontinuation from the Treatment Period, subjects will have a **Post Treatment Follow-Up / End of Treatment / End of Study Visit.** The assessments and procedures that will be performed during this period are outlined in the Table of Events (see Section 5) and include:

- ECOG performance status
- Vital signs including weight, heart rate, seated systolic and diastolic blood pressure, and temperature
- ECG – end of study treatment (day 43 post last dose)
- Medically supervised pregnancy test, with a minimum sensitivity of 25mIU/ml, for FCBP
- Serum chemistry, hematology, absolute reticulocyte count
- Creatinine clearance
- Serum iron, total iron binding capacity (TIBC), transferrin and serum ferritin – end of study treatment (at day 43 post last dose)
- Vitamin B12 and RBC folate levels – end of study treatment (at day 43 post last dose)
- Serum erythropoietin
- Urinalysis
- FSH (include current menstrual cycle status for pre-menopausal female subjects) and LH – both males and females
- Dihyroepiandosterone and testosterone (free and total)– males only

- Estrogen and estradiol – females only
- TSH
- Serum for sotatercept (ACE-011) drug antibody test (pre-sotatercept (ACE-011) dose). For subjects with a positive sotatercept (ACE-011) drug antibody assessment at the Post Treatment Follow-Up / End of Treatment / End of Study Visit, sotatercept (ACE-011) drug antibody assessments will be repeated every two months or as appropriate for up to one year or until the results are negative, whichever occurs first.
- Bone or other potential mechanistic or disease-related proteins/biomarkers
- Bone imaging – DXA scan (optional at selected sites)
- Activin A and other sotatercept (ACE-011) related proteins/biomarkers, including myostatin and follistatin, in blood
- Pharmacokinetics
- Tumor Assessment and Response Evaluation, as per RECIST criteria (Version 1.1), (performed ≤ every 9 weeks or as per standard of care at the study site, and following the chemotherapy schedule)
- QoL Assessment (FACIT Fatigue Scale (Version 4)) – all subjects
- LCSS questionnaire (consisting of Patient Scale and Observer Scale) – only subjects with NSCLC
- Evaluation and reporting of all AEs regardless of causality (up to 6 weeks) after last dose of sotatercept (ACE-011).
- Documentation of concomitant medications / procedures (including use of ESAs and all transfusions) / hospitalizations
- Post-Treatment Anti-Neoplastic Therapy
- Overall survival

Additional Procedure Descriptions:

Central ECG

ECGs will be performed and read per Central ECG vendor.

Please refer to vendor manual for procedures.

Clinical Laboratory Evaluations

Clinical laboratory evaluations (serum chemistry, hematology, absolute reticulocyte count, creatinine clearance, serum iron, total iron binding capacity, transferrin and serum ferritin, serum erythropoietin, vitamin B12, serum RBC folate levels, urinalysis, FSH, LH, dihyroepiandosterone, estrogen, estradiol, testosterone and serum thyroid-stimulating hormone) will be performed by a central laboratory.

Please refer to vendor manual for procedures.

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

Exploratory Biomarkers

Analyses will be undertaken to evaluate the expression of Activin A and other proteins/biomarkers related to sotatercept (ACE-011) mechanism of action in blood (including myostatin and follistatin).

Renal function biomarkers via urinalysis measuring urine albumin / creatinine ratio, urine protein / creatinine ratio and other biomarkers of glomerular and/or tubular injury - urine kidney injury molecule-1 (KIM-1), urine trefoil factor 3 (TTF3), urine cystatin C and + or – urine β2-microglobulin will be evaluated in all subjects.

Pharmacokinetics

- Blood samples will be collected to evaluate the full PK profile of sotatercept (ACE-011) from approximately 20 subjects at select centers (approximately 10 subjects for each sotatercept [ACE-011] dose group).

For subjects who do not participate in either full or sparse PK assessments, the ACE-011 (sotatercept) concentration may be determined in their anti-sotatercept antibody samples to assist in the evaluation of immunogenicity, as well as PK.

Detailed PK sampling schedule is presented in Table 8: Schedule of Pharmacokinetic Assessments.

- PK samples must be collected **predose** on the day of sotatercept (ACE-011) administration. PK samples may be collected at any time on non-dosing days. After collection, allow the blood to clot at room temperature for approximately one hour and then centrifuge the blood sample at room temperature for 10 minutes (1100-1300g) to obtain serum. At each time point, approximately 2 mL or less blood will be collected.

Bone Biomarkers

Bone biomarkers will be evaluated in all subjects. The serum and urine bone biomarkers will include BSAP, OC, P1NP, CTX, TRACP-5b and uNTX. Both serum and urine samples will be collected.

Biomarker serum samples should be consistently collected early morning. The urine sample should **not** be from the first morning void.

Bone Imaging - optional

DXA scan to evaluate overall bone health will be performed at select site(s).

Quality of Life Assessments

The QoL Assessment (FACIT Fatigue Scale [Version 4]) will be completed by all subjects and LCSS questionnaire will be completed for subjects with NSCLC. Each assessment will be completed by the subject upon arrival at clinic and prior to any study procedures or testing.

NOTE: The LCSS consists of two scales: one scale for the patient (Patient Scale) and a counterpart scale for health professionals acting as observers (Observer Scale).

7. STUDY POPULATION

At the time of randomization, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

7.1. Number of Subjects

This platinum-based CIA study will enroll approximately 30 subjects with advanced or metastatic solid tumor types.

Up to approximately 30 subjects will be randomized to receive one of the following sotatercept (ACE-011) dose levels, with 10-15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

and will be stratified by:

1. Baseline Hgb level
   - 6.5 to < 9.0 g/dL
   - 9.0 to < 11.0 g/dL
2. Type of platinum-based chemotherapy (cisplatin versus other non-cisplatin chemotherapy)

7.2. Inclusion Criteria

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

1. Men and women ≥ 18 years of age at the time of signing the informed consent document.
2. Histologically confirmed (cytology or biopsy) solid tumor malignancy, excluding those solid tumors treated with curative intent.
3. Documented advanced or metastatic disease.
4. Measurable or non-measurable disease evaluable by RECIST criteria (Version 1.1) (Appendix A).
5. All of the following laboratory values:
   - Hemoglobin ≥ 6.5 to < 11.0 g/dL (≥ 65 to < 110 g/L), due to chemotherapy-induced anemia
   - Absolute neutrophil count ≥ 500/mm^3
   - Platelet count ≥ 75,000/mm^3 (> 72 hours since prior platelet transfusion)
   - Adequate renal function:
     - creatinine clearance ≥ 40mL/min or ≥ 50 mL/min if cisplatin is concomitantly administered

       and
     - urine protein / creatinine ratio ≤ 1.0; or ≤ 2.0 if bevacizumab (Avastin®) is concomitantly administered
   - Hepatic function (bilirubin ≤ 1.5 x ULN; AST and ALT ≤ 3.0 x ULN and ≤ 5.0 ULN for subjects with liver metastases)
   - Corrected calcium within normal limits (WNL) or ≤ Grade 1. Previous hypercalcemia treatment is allowed
6. Subjects must:
   - have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

     OR
   - have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

     OR
   - currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

   Any platinum-based regimen approved for the specific indication
7. ≥ 28 days must have elapsed since previous treatment with ESA

8. ≥ 14 days must have elapsed (prior to Day 1) since the last RBC transfusion and receipt of ≤ 2 units of blood in the past 30 days (prior to Day 1)
9. ECOG Performance status of 0 – 2 (Appendix B)
10. 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 at least 112 days following the last dose of sotatercept (ACE-011).

    Some highly effective methods of birth control include:

    - Oral contraceptives, intrauterine device, tubal ligation or a partner with a 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 negative pregnancy test, with a minimum sensitivity of 25 mIU/ml, within 3 days **prior** to sotatercept (ACE-011) administration (Day 1). In addition, subjects must be educated concerning measures to be used to prevent pregnancy and potential toxicities. (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).
11. Males must agree to use a latex condom or non-latex condom NOT made of natural (animal) membrane during any sexual contact with females of childbearing potential or a pregnant female while participating in the study and for at least 112 days following the last dose of sotatercept (ACE-011), even if he has undergone a successful vasectomy.
12. Life expectancy of ≥ 3 months.
13. Is willing to adhere to the study visit schedule, understand and comply with all protocol requirements.
14. Understand and voluntarily sign a written informed consent document prior to any study related assessments/procedures are conducted.

7.3. Exclusion Criteria

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

1. Subjects who have any Grade ≥ 3 toxicity (according to the currently active minor version of the NCI National Cancer Institute Common Terminology for Adverse Events [CTCAE] version 4.0 [Appendix C]) at the time of screening, including Grade ≥ 3 residual adverse events related to either chemotherapy or underlying disease. Exception: Grade ≥ 3 hematotoxicity (e.g., asymptomatic anemia, neutropenia and thrombocytopenia) occurring during the chemotherapy nadir period and resolving or non-hematological events (e.g., nausea, vomiting, fatigue, or muscle or bone/joint pain), occurring during the chemotherapy period and resolving.

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 subject participation in the study, at the discretion of the Investigator.
3. CNS metastases **(exception: subjects with CNS metastases treated with whole brain radiotherapy, gamma knife radiosurgery and/or surgery and stable for at least 2 weeks prior to randomization)**.
4. Clinically significant pulmonary, endocrine, neurologic, gastrointestinal, hepatic or genitourinary disease unrelated to underlying malignancy.
5. Subjects with classification of 3 or higher heart failure as classified by the New York Heart Association (NYHA) (Appendix D).
6. History of thrombosis, deep vein thrombosis (DVT), pulmonary emboli (PE), or embolic stroke if not stable on anticoagulants and/or one of these events occurring within the past 6 months. Local central line thrombosis is allowed.
7. Diagnosis of a myeloid malignancy or known history of myelodysplasia.
8. Subjects with a recent history (within 14 days of Day 1) of administration of IV antibiotics or oral antibiotics (due to post septic episode). Subjects should be free of infection at least 14 days after the last dose of systemic antibiotic treatment (prior to Day 1).
9. Uncontrolled hypertension. Controlled hypertension is considered clinically stable and systolic blood pressure (SBP) must be < 150 mmHg and diastolic blood pressure (DBP) must be < 100 mmHg.
10. Known infection with human immunodeficiency virus (HIV).
11. Known active hepatitis B or C antibody defined by positive serology.
12. Deficiency in iron (transferrin saturation < 20%), vitamin B_{12}, or RBC folate. Subjects may be re-screened following treatment with supplements and normalization of levels.
13. History of anemia as a result of inherited hemoglobinopathy such as sickle cell anemia or thalassemia.
14. History of anemia due to autoimmune or hereditary hemolysis; or gastrointestinal bleeding occurring within the past 6 months.
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 sotatercept (ACE-011).
17. Pregnant or lactating females or females planning to become pregnant.
18. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational product (Refer to the Investigator's Brochure for further information).

19. Major surgery within 30 days prior to Day 1 (subjects must have completely recovered from any previous surgery prior to Day 1).

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 sotatercept (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 sotatercept (ACE-011) lyophilized drug product is 2°C to 8°C.

Prior to administration, the lyophilized drug product is reconstituted with 1 mL sterile water for injection (WFI) in the closed product vial using sterile needles and syringes following institutional standards for reconstitution of sterile products. The reconstituted drug product consists of a 50 mg/mL solution of sotatercept (ACE-011). The solution must be refrigerated at 2°C to 8°C upon reconstitution.

The reconstituted sotatercept (ACE-011) should be used immediately after reconstitution, and if not used immediately, the reconstituted sotatercept, in its original package, may be held for up to 6 hours at 2°C to 8°C.

8.2. Treatment Administration and Schedule

Sotatercept (ACE-011) will be administered as a SC injection to subjects by the study staff at the clinical site and will be documented in the study source record. Subcutaneous injections will be given in the upper arm, abdomen, or thigh.

At the time of randomization, subjects must:

- have already received at least one cycle and up to 4 cycles (q3w schedule) of platinum-based chemotherapy and be randomized prior to receiving Cycle 5

OR

- have already received at least one cycle and up to 3 months (depending upon regimen) of platinum-based chemotherapy

OR

- currently be receiving maintenance therapy following treatment with platinum-based chemotherapy

Subjects must have an advanced or metastatic solid tumor treated with ≥ first–line platinum–based chemotherapy, excluding those solid tumors treated with curative intent.

Allowed concomitant platinum-based chemotherapy regimens are:

- any platinum-based regimen approved for the specific indication

Investigative sites will utilize commercial supply of these medications.

Concomitant or maintenance therapy with chemotherapeutic and/or targeted agents (e.g., pemetrexed, anti-EGFR agents, anti-VEGF agents), which are approved for a given tumor type, are allowed in addition to platinum-based chemotherapy.

Platinum-based tumor therapy may be revised at the discretion of the Investigator for toxicity reasons only.

Sotatercept (ACE-011) dosing may occur on different weeks of the chemotherapy cycle due to the subjects' Hgb levels. Dose delays of sotatercept (ACE-011) and/or dose delays of chemotherapy may occur.

8.2.1. Selection of Dose for the Study

Subjects will be randomized to one of the following sotatercept (ACE-011) dose levels, with 10-15 subjects per arm:

- Sotatercept (ACE-011) 15 mg SC
- Sotatercept (ACE-011) 30 mg SC

Each dose level will be administered every 42 days for up to four doses.

Hematopoietic response is defined as an increase in Hgb of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks, in the absence of RBC transfusions and/or ESAs.

The effective dose of sotatercept (ACE-011) is defined as follows:

> An increase in hemoglobin (Hgb) of ≥ 1.0 g/dL above the study baseline value for 4 consecutive weeks.

Hematopoietic response will be determined by laboratory analysis of hemoglobin levels.

8.2.2. Selection and Timing of Dosing for Each Subject

Subjects will be randomized to receive sotatercept (ACE-011) starting on Day 1 (one SC dose every 42 days) and continuing during the six-month Treatment Period, as outlined in the Table of Events (see Section 5).

Subjects will be randomized to receive one of two dose levels of sotatercept (ACE-011), with 10-15 subjects per arm.

Each subject will return to the site on each scheduled clinic visit. During the Treatment Period, subjects will receive sotatercept (ACE-011) every 42 days as determined by Hgb levels and randomization schedule. Hemoglobin levels and reticulocyte counts will be repeated weekly after the first dose of sotatercept (ACE-011) and then at 7, 14 and 28 days after each subsequent dose of sotatercept (ACE-011).

The **first dose** of sotatercept (ACE-011) can be administered **at any time after the first cycle and prior to the fifth cycle (q3w regimen) OR prior to starting the fourth month (depending upon regimen) of platinum-based chemotherapy OR during maintenance therapy following treatment with platinum-based chemotherapy.**

Subsequent doses of sotatercept (ACE-011) can be administered at any time point during a chemotherapy cycle or maintenance therapy.

Administration of subsequent cycles of chemotherapy, including dose reductions and dose delays, should not affect the sotatercept (ACE-011) dosing schedule, unless determined to be necessary by the Investigator. If there is a chemotherapy dose delay, sotatercept (ACE-011) administration does not need to be delayed until start of next chemotherapy cycle.

Following completion of the Treatment Period, subjects will continue to the Post Treatment Follow-Up / End of Treatment / End of Study Visit to occur 42 days (6 weeks) after the subjects' last dose of sotatercept (ACE-011).

Subjects will be discontinued from the study treatment for reasons listed in Section 8.2.3 of the protocol, for unacceptable toxicity, or for progression of advanced or metastatic disease that requires the initiation of another treatment.

8.2.3. Discontinuation

Treatment Discontinuation

Subjects will be discontinued from Study Treatment due to the following:

- Adverse events(s)
  - Hypertension ≥ Grade 3 – defined as Stage 2 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100mmHg) confirmed by two measurements obtained at least five minutes apart; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or medically significant hypertension which cannot be adequately controlled with antihypertensive therapy
  - Any AE > Grade 2 assessed to be related to sotatercept (ACE-011) therapy.
  - Any persistent AE > Grade 1 considered to be related to sotatercept (ACE-011) treatment and causing a subject to miss three months sotatercept (ACE-011) therapy
  - Any thromboembolic event > Grade 2
  - Elevated Hgb > 15.0 g/dL (sustained for a 7 day period, confirmed by laboratory assessment)
  - Urine protein / creatinine ratio > 1.0; or > 2.0 if bevacizumab (Avastin®) is concomitantly administered
  - Persistent hematuria ≥ Grade 2 - defined as symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental activities of daily living, and persisting for one week
- Lack of sotatercept (ACE-011) therapeutic effect, defined as < 1.0 g/dL increase in Hgb from baseline following three dose escalations.
- Concomitant use of ESAs if administered at any time.
- Sotatercept (ACE-011) Dose Modifications:
  - A second Hgb increase of ≥3.0 g/dL following a two level dose reduction due to a Hgb increase ≥3.0 g/dL

- Disease Progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation – as determined by the Sponsor

The reason for treatment discontinuation should be recorded in the eCRF 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 (subject has completed approximately six month Treatment Period including a 42 day [6-week] Post-Treatment Follow-Up/End of Treatment/End of Study Visit).
- Withdrawal of consent
- Death
- Lost to follow-up

The following events **may be** considered sufficient reasons for discontinuing a subject from the study, as determined by the Sponsor:

- Adverse events(s)
- Disease progression
- Protocol violation

The reason for study discontinuation should be recorded in the eCRF 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.

8.3. Method of Treatment Assignment

All subjects who qualify for the study will be randomly enrolled into the study and receive up to four doses of sotatercept (ACE-011). A unique multi-digit subject identification number will be assigned by IVRS to each subject entering the Treatment Period.

8.4. Packaging and Labeling

The label(s) for investigational product (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 sotatercept (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 secured location. The investigational site must maintain accurate records demonstrating dates and amounts of sotatercept (ACE-011) received, to whom it was administered (subject-by-subject accounting), and accounts of any sotatercept (ACE-011) accidentally or deliberately destroyed or returned. Unless otherwise notified, all vials of sotatercept (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 sotatercept (ACE-011) to the Sponsor at the end of the study, or the sotatercept (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 investigational medicinal product.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF 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

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 and 7.3 Inclusion Criteria and 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 eCRF throughout the course of the study.

Concomitant therapies considered as supportive care are acceptable while participating in this study, including growth colony stimulating factors (G-CSF); anti-emetics to limit chemotherapy-related nausea and vomiting; palliative radiation; bisphosphonates and denosumab therapy for bone metastases. Additionally, the study site should use its standard of care regarding hydration and the minimization of nephrotoxicity prior to/following the administration of platinum-based regimens.

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.

Iron supplementation

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

Erythropoiesis-stimulating agents (ESAs)

The use of an ESA is not allowed in the study. The use of ESAs will need to result in immediate notification to the study Sponsor and Medical Monitor, as well as to the clinical site pharmacist, so that **no further dosing with sotatercept (ACE-011) in that study subject will occur** If treatment with ESAs is required in the opinion of the Investigator, the ESA label instructions are to be strictly followed.

Any subject who receive an ESA will be discontinued from the study Treatment Period and continue to the Post Treatment Follow-Up / End of Treatment / End of Study Visit.

RBC transfusions

Concurrent treatment for CIA with blood transfusions is recommended when Hgb value is < 8 g/dL or at the discretion of the Investigator if the Hgb value is ≥ 8 g/dL and associated with anemia symptoms such as hemodynamic or pulmonary compromise requiring treatment. If an

RBC transfusion is given to a subject during the Treatment Period, sotatercept (ACE-011) should be administered >7 days from the date of the RBC transfusion.

9.2. Prohibited Concomitant Medications and Procedures

No concurrent treatments with any other investigational agent are allowed. Bisphosphonate therapy (other than for the treatment of hypercalcemia), and denosumab therapy for bone metastases can be started prior to randomization but should not be started on study.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

10.1. Overview

This is an open-label randomized, phase 2a, dose-ranging study of sotatercept (ACE-011) therapy for chemotherapy-induced anemia (CIA) in subjects with advanced or metastatic solid tumor types treated with platinum-based chemotherapeutic regimens. An IVRS will be utilized to ensure an equal weight central randomization based on a permuted-block randomization method according to stratification factors defined in Section 4.1 Study Design. Subjects will be randomized to one of two doses of sotatercept (ACE-011).

Analyses will be exploratory.

10.2. Study Population Definitions

Three study populations will be used for analyses.

- The Intent-to-Treat (ITT) Population – All randomized subjects.
- Safety Population – All subjects who take at least one dose of study medication.
- Efficacy Evaluable (EE) Population – All ITT subjects who take at least one dose of study medication and have baseline and at least one post-baseline efficacy assessment without major protocol deviation.

10.3. Sample Size and Power Considerations

Up to 30 subjects will be randomized among two dosing groups. Enrollment was limited and there are no power considerations due to study closure.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics by treatment arm, 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 by treatment arm. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

The hematopoietic response is defined as an increase in Hgb of $\geq$ 1.0 g/dL above the study baseline value for 28 consecutive days, in the absence of RBC transfusions and/or ESAs.

10.7. Safety Analysis

All safety subjects will be used for safety analyses. Sotatercept (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 treatment arm. The incidence of AEs will be summarized by severity grade based on the NCI CTCAE version 4.0 (current active minor version). Serious adverse events (SAE), deaths and AEs leading to dose modifications and study treatment discontinuation will be summarized. Safety information obtained during through the Post Treatment Follow-Up / End of Treatment / End of Study Visit segment will be incorporated into these analyses.

10.8. Interim Analysis

There will be no interim analysis.

10.9. Other Topics

Pharmacokinetic Analysis

Approximately 5 - 10 subjects will be enrolled for full PK sampling in each treatment cohort.

Noncompartmental PK parameters for sotatercept (ACE-011), such as t_{max}, C_{max}, AUC, and $t_{1/2}$,z, may be estimated for subjects providing full PK samples. Descriptive statistics may be provided for plasma concentrations and PK parameters.

The relationship between sotatercept (ACE-011) exposure and response (hematology, biomarkers, and other clinical outcomes as appropriate) may be explored if data are sufficient.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

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

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 42 days after the last dose of IP. The AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately 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 42 days post last dose, only AEs assessed as related to study treatment are to be reported.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

11.2.1. Seriousness

An 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of 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 (delay) 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 an SAE.

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

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

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

The female subject should be referred to an 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 investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Immediate 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/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety immediately within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

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

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

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (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.

11.6. 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.

11.7. Expedited Reporting of Adverse Events

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

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics

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

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

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (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

Please refer to Section 8.2.3.

Stopping Rules

Celgene routine pharmacovigilance surveillance will review data on a regular basis (mainly grade 3 or 4 toxicities, SAEs and subject deaths). Any relevant imbalance in toxic deaths, related SAEs or detrimental survival would be considered for study discontinuation.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

15.2. Data Management

Data will be collected via an electronic data capture (EDC) system rather than paper. Data will be entered into the clinical database as per Celgene SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. The Clinical team and investigational site personnel will be alerted of discrepant data by the functionality of the system. 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMEA, 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

Aapro M, Vaupel P. Erythropoietin: effects on life expectancy in patients with cancer-related anemia. *Curr Med Res Opin.* 2006; 22(suppl 4):5-13.

Carlos JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer.* 2001; 91:2214-2221.

Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue, and quality of life in anemic cancer patients: results from five randomized clinical trials. *Ann Oncol.* 2004; 15:979-986.

Chantry A, Heath D, Mulivor A, Coulton L, Evans H, Abdul N, Werner ED, Bouxsein ML, Pearsall RS, Seehra J, Vanderkerken K, and Croucher PI. Inhibiting activin-A signalling stimulates bone formation, prevents tumor-induced osteolytic bone destruction and blocks bone metastasis. J Bone Miner Res 2010; 25 (12), 2633-46, Erroatum in J Bone Miner Res 2011; 26 (2), 439

Chen Y-G, Lui HM, Lin S-L, Lee JM, and Ying S-Y. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. *Exp Biol Med* 2002; 227: 75-87.

Dang TP, Carbone DP: Cancer of the Lung, in DeVita, VT, Hellman S, Rosenberg SA (eds): Cancer: Principles & Practice of Oncology, 8th edition, Philadelphia, PA. Lippincott Williams & Wilkens, 2008, 887-971.

Functional Assessment of Chronic Illness Therapy-Fatigue, FACIT-F Version 4. *http://www.facit.org/qview/qlist.aspx*, last accessed 21Jul2010.

Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer.* 1999; 86:1528-1536.

Groopman JE, Itri LM. Chemotherapy-Induced Anemia in Adults: Incidence and Treatment. *Journal of the National Cancer Institute* 1999, 91, 1616-1634.

Hollen, PJ, Gralla, RJ, Kris, MG, and Potanovich, LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). European Journal of Cancer, 1993; 29A, S51-S58.

Hollen, PJ, Gralla, RJ, Kris, MG, & Cox, C. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1994a; 2, 213-222.

Hollen, PJ, Gralla, RJ, Kris, MG, Cox, C, Belani, CP, Grunberg, SM, Crawford, J, and Neidhart, JA. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer, 1994b; 73, 2087-98.

Hollen PJ, Gralla RJ, Kris MG 'Lung Cancer Symptom Scale (LCSS)', *Administration, Scoring and Procedures Manual*, (1995) Ver.1.1.

Hollen, PJ, Gralla, RJ, Kris, MG, Eberly, SW, and Cox, C. Normative data and trends in quality of life from the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer, 1999; 7, 140-148.

Hong WK, Tsao AS, in Lung Carcinoma: Tumors of the Lungs: Merck Manuals Online Medical Library for Healthcare Professionals, 2008.
http://www.merck.com/mmpe/print/sec05/ch062/ch062b.html

Laurie SA, Jeyabalan N, Nicholas G, Dahrouge S. Association between anemia arising during therapy and outcomes of chemoradiation for limited small-cell lung cancer. *J Thorac Oncol.* 2006;146-151.

Lotinun S, Fajardo RJ, Pearsall RS, Bouxsein ML, and Baron R. A soluble activin receptor type IIA fusion protein, ACE-011, increases bone mass by stimulating bone formation and inhibiting bone resorption in cynomolgus monkeys. ASBMR 30th annual meeting, 2008.

MacRae R, Shyr Y, Jonson D, Choy H. Declining hemoglobin Turing chemoradiotherapy for locally advanced non-small cell lung cancer is significant. *Radiother Oncol.* 2002;64:37-40.

Mathews LS. Activin receptors and cellular signaling by the receptor serine kinase family. *Endocr Rev* 1994; 15: 310-25.

Murata M, Onomichi K, Eto Y, Shibai H, and Muramatsu M. Expression of erythroid differentiation factor (EDF) in Chinese hamster ovary cells. *Biochem Biophys Res Commun* 1988; 151: 230-5.

Nakao K, Kosaka M and Saito S. Effects of erythroid differentiation factor (EDF) on proliferation and differentiation of human hematopoietic progenitors. *Exp Hematol* 1991; 19: 1090-5.

National Heart, Lung, and Blood Institute, National Institutes of Health. New York Heart Association Classification. 2008.

NCCN Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy Induced Anemia, V.2. 2010 http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf; 2009.

Non-small Cell Lung cancer Collaborative Group 'Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials', *British Medical Journal* 1995 vol. 311, no.7010, 899-909.

Obermair A, Cheuk R, Horwood K, et al. Anemia before and during concurrent chemoradiotherapy in patients with cervical carcinoma: effect on progression-free survival. *Int J Gynecol Cancer.* 2003; 13:633-639.

Oken, MM., Creech, R.H., Tormey, D.C., et. al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982; 5:649-655.

Parker SL, Tong T, Bolden S, et. al. Cancer statistics, 1997. *CA Cancer J Clin*, 1997, 47, no. 1, 5-27.

Pearsall RS, Canalis E, Cornwall-Brady M, Underwood KW, Haigis B, Ucran J, Kumar R, Pobre E, Grinberg A, Werner ED, Glatt V, Stadmeyer L, Smith D, Seehra J, and Bouxsein ML. A soluble activin type IIA receptor induces bone formation and improves skeletal integrity. Proc Natl Acad Sci USA 2008, 105: 7082-7.

Perrien DS, Akel NS, Edwards PK, et. al. Inhibin A is an endocrine stimulator of bone mass and strength. *Endocrinology* 2007; 148: 1654-65.

Rivier J, Spiess J, McClintock R, Vaughan J and Vale W. Purification and partial characterization of inhibin from porcine follicular fluid. *Biochem Biophys Res Commun* 1985; 133: 120-7.

Rossi A, Maione P, Gridelli C Cetuximab in advanced non-small cell lung cancer. *Critical Reviews in Oncology/Hematology*, 2006 59, 139-149.

Ruckle J, Jacobs M, Kramer W, et. al. A single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res* 2009; 24 (4): 744-52.

Sandler A, Gray R, Perry M, et al Paclitaxel-Carboplatin alone or with Bevacizumab for Non Small Cell Lung Cancer, *NEJM*, 2006 vol.355, no.24, 2542-50.

Scagliotti G, Parikh P, von Pawel J, et al Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve patients With Advanced-Stage Non-Small-Cell Lung Cancer, JCO, 2008, 26 (21): 3543-51.

Schiller J, Harrington D, Belani C, et al Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2002; 346:92-98.

Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. *Am J Health Syst Pharm.* 2007; 64 (suppl 2):S5-S13.

Seder C, Hartojo W, Lin L, et al Upregulated INHBA Expression May Promote Cell Proliferation and Is Associated with Poor Survival in Lung Adenocarcinoma, Neoplasia, 2009, 11: 388-396.

Shedden K, Taylor J, Enkemann S, et al Gene Expression-Based Survival prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validation Study: Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma, Nat Med, 2008, 14 (8): 822-827.

Shiozaki M, Sakai R, Tabuchi M, et. al. Evidence for the participation of endogenous activin A/erythroid differentiation factor in the regulation of erythropoiesis. *Proc Natl Acad Sci USA* 1992; 89: 1553-6.

Shiozaki M, Sakai R, Tabuchi M, et. al. In vivo treatment with erythroid differentiation factor (EDF/activin A) increases erythroid precursors (CFU-E and BFU-E) in mice. *Biochem Biophys Res Commun* 1989; 165: 1155-61.

Vansteenkiste J, Pirker R, Massuti B, et. al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute, 2002, 94: 16: 1211-1220.

Woodruff TK. Regulation of cellular and system function by activin. *Biochem Pharmacol* 1998; 55: 953-63.

Ying S-Y. Inhibins, activins, and follistatins: gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine Rev* 1988; 9: 267-93.

19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Terms	**Definition**
Measurable disease	The presence of at least one measurable lesion by CT or MRI. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions	Lesions that can be accurately measured in least one dimension by CT scan with longest diameter $\geq$ 10 mm (CT scan thickness no greater than 5 mm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
Non-measurable lesion	All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

RECIST Criteria-Response Evaluation

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
***Partial Response (PR)*:**	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
***Stable Disease (SD)*:**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
***Progressive Disease (PD)*:**	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

RECIST Criteria-Response Evaluation (continued)

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of best overall response	The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (2009). European Journal of Cancer 45, 228-247.

Appendix B: 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 9: 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 C: 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 D: New York Heart Association - Classification of Heart Failure

Table 10: 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