Official Protocol Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of ACE-011 for the Treatment of Chemotherapy Induced Anemia in Patients with Metastatic Breast Cancer
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STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER A011-08

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of ACE-011 for the Treatment of Chemotherapy Induced Anemia in Patients with Metastatic Breast Cancer

PHASE 2

SPONSOR:
Acceleron Pharma, Inc.
128 Sidney Street
Cambridge, Massachusetts 02139-4242

Final Version 2.0

Date**:** 27 October, 2009

1.1 APPROVAL SIGNATURES

Study Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of ACE-011 for the Treatment of Chemotherapy Induced Anemia in Patients with Metastatic Breast Cancer

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2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical classification
BMI	Body mass index
BMD	Body mineral density
BSAP	Bone specific alkaline phosphatase
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CIA	Chemotherapy induced anemia
CP	Concomitant procedure
CRF	Case Report Form
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Serum C-terminal type I collagen telopeptide
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
ESA	Erythropoiesis-stimulating agents
FACT	Functional Assessment of Chronic Illness
FSH	Follicle-stimulating hormone
ICH	International Conference on Harmonization
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat (population)
MRI	Magnetic resonance imaging
ORR	Objective response rate
PFS	Progression-free survival
PINP	Serum intact procollagen type I N terminal propeptide
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
PP	Per-protocol (population)
PT	Prothrombin time
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SRE	Skeletal-related event
TIBC	Total iron binding capacity
TRACP-5b	Serum tartrate-resistant acid phosphatase isoform-5b
WBC	White blood cell (count)

4.0 INTRODUCTION

The study is being conducted under the sponsorship of Acceleron Pharma, Inc. The clinical monitoring, data management and statistical analysis are being performed under contract with PPD, in collaboration with Acceleron Pharma, Inc.

This document contains detailed information regarding the statistical analysis to be performed for study A011-08. The table, appendix, and figure shells planned for this study will be maintained in a separate document. This is a Phase 2, double-blind, randomized, placebo controlled study to evaluate the efficacy, safety, and tolerability of ACE-011 for the treatment of chemotherapy induced anemia in patients with metastatic breast cancer.

The finalization of the SAP is made before the database hard lock.

This analysis plan was developed based on International Conference on Harmonization (ICH) E3 and E9 Guidelines, and with references to the following protocols:

- Protocol A011-08, dated March 13, 2009
- Protocol A011-08 Amendment #1, dated April 22, 2009
- Protocol A011-08 Amendment #2, dated May 21, 2009
- Protocol A011-08 Amendment #3, dated October 07, 2009

5.0 DATA QUALITY ASSURANCE

The Clinical, Data Management, and Biostatistics departments at PPD will work diligently and collaboratively, internally and with the Sponsor, to ensure that the data collected and analyzed for this study are of the highest quality possible. This will be accomplished in part by having thorough edit checks written, programmed, and updated as needed to guarantee high quality data. Edit checks will be reviewed by the statistician on an ongoing basis to evaluate whether any need to be added.

6.0 OBJECTIVES AND STUDY DESIGN

6.1 Study Objectives

The primary objective is to evaluate the proportion of patients in each ACE-011 dose regimen who achieve a hematopoietic response during the treatment period including up to 2 months after the last dose of ACE-011 treatment of chemotherapy induced anemia in patients with metastatic breast cancer. Hematopoietic response is defined as an increase in hemoglobin of ≥ 1.0 g/dL above the study baseline value for 28 consecutive days during the treatment period including up to 2 months after the last dose of ACE-011, in the absence of any RBC transfusions and/or ESAs.

The secondary objectives include:

1. To evaluate the safety and tolerability of ACE-011 for the treatment of chemotherapy induced anemia in patients with metastatic breast cancer.

2. To evaluate the percentage of patients who achieve an increase in hemoglobin of ≥ 2 g/dL and/or hemoglobin concentration ≥ 11 g/dL for a consecutive 28 day period during the treatment period including up to 2 months after the last dose of ACE-011 in the absence of any RBC transfusions and/or ESAs.

3. To estimate the duration of the hematopoietic response associated with each ACE-011 dose regimen.

4. To estimate the time to the hematopoietic response associated with each ACE-011 dose regimen.

5. To estimate the proportion of patients receiving red blood cell (RBC) transfusions and/or ESAs within each cycle of ACE-011 with each dose regimen.

6. To estimate the effect of each ACE-011 dose regimen on progression free survival (PFS) and objective response rate (ORR).

The exploratory objectives include:

1. To estimate the effect of each ACE-011 dose regimen on serum bone biomarkers (OC, BSAP, P1NP, CTX, TRACP-5b), urine bone biomarker (uNTX), bone mineral density (DXA scans of lumbar spine and hip) and incidence of skeletal related events (SREs).

2. To evaluate the quality of life in relation to the treatment of chemotherapy induced anemia in patients with metastatic breast cancer during the study.

6.2 Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, and tolerability of ACE-011 for the treatment of chemotherapy induced anemia in patients with metastatic breast cancer. A total of 105 patients will be enrolled.

Patients will be evaluated for study inclusion/exclusion criteria by the Investigator. Patients who meet the study entry criteria will be enrolled within 14 days of the screening visit. Local lab values for hemoglobin and central lab values will be utilized for the evaluation of patient eligibility. Central labs will also be used in the evaluation of patient safety throughout the study. Local lab values for hemoglobin and hematocrit will be collected and reported from screening (for eligibility) through the Day 281/Termination visit. Three cohorts of 30 patients each are planned at the following doses of ACE-011: 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg. Fifteen patients will be enrolled into the placebo cohort.

Each eligible patient will be randomized to one of the four cohorts to receive a dose administered as a subcutaneous injection every 28 days for up to 4 doses. Dosing will be administered on days 1, 29, 57, and 85. Concurrent treatment with a myelosuppressive chemotherapy regimen for metastatic breast cancer will also be administered per standard of care at the site. Patients will be stratified according to administration of either single agent weekly chemotherapy or less frequent chemotherapy regimens.

Blood samples will be collected at selected study sites from approximately one-third of patients for the evaluation of serum concentrations of ACE-011.

Patients will be assessed for safety by monitoring adverse events, clinical laboratory tests, assessment of quality of life (FACT- Fatigue), vital signs and physical examinations on an ongoing basis. ECGs will be performed during screening, prior to dosing on the first cycle, during the first, second and third cycle, Day 113 (28 days after the last dose of ACE-011) and at Day 281/ Termination visit to monitor safety. Blood pressure and lab values will be assessed at each study visit during the treatment and treatment follow up period.

Local laboratory hemoglobin values and blood pressure values will be evaluated prior to dosing per the dose modification criteria, as applicable.

Patients will be followed for a minimum of 7 months following their last dose of ACE-011/placebo. Study participation for each patient is approximately 10.5 months (14 day screening period, 3 month treatment period with a 2 month treatment follow up period, and a 5 month post treatment follow-up period). If a patient discontinues the study due to progression of disease (metastatic breast cancer) and/or begins another chemotherapy regimen, the patient will discontinue ACE-011/placebo treatment, complete the Day 281/Termination visit procedures, and be followed for survival only (a minimum 7 months from the last dose of ACE-011/placebo).

Anti-drug antibody testing will be performed at Day 281/Termination visit and if positive, the patient may be asked to return to the clinical site for additional monthly anti-drug antibody testing for up to 12 months, after their last dose.

7.0 ANALYSIS ENDPOINS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the hematopoietic response rate at each dose level. It is defined as the proportion of patients who have a hematopoietic response of an increase in hemoglobin of ≥ 1 g/dL for 28 consecutive days during the treatment period including up to 2 months after the last dose of ACE-011/placebo, in the absence of any RBC transfusions and/or ESAs. The ACE-011/placebo treatment period is defined as the time period from the first ACE-011/placebo dose to up to 2 months after the last dose of ACE-011/placebo treatment.

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of patients achieving an increase in hemoglobin of ≥ 2 g/dL for 28 consecutive days during the treatment period and up to 2 months after the last dose of ACE-011/placebo in the absence of any RBC transfusions and/or ESAs.

- Proportion of patients achieving hemoglobin concentration ≥ 11 g/dL for 28 consecutive days during the treatment period and up to 2 months after the last dose of ACE-011/placebo in the absence of any RBC transfusions and/or ESAs

- Duration of hematopoietic response (days) defined as the time period from the first time hemoglobin increases at least ≥ 1 g/dL from baseline to the last time there is hemoglobin ≥ 1 g/dL increase from baseline. Duration of response is only calculated for a responder and will be at least 28 days. The duration of response is only calculated for a patient who meets the primary efficacy endpoint.

- Duration of hematopoietic response (days) defined as the time period from the first time hemoglobin increases at least ≥ 2 g/dL from baseline to the last time there is hemoglobin ≥ 2 g/dL increase from baseline. Duration of response is only calculated for a responder and will be at least 28 days. The duration of response is only calculated for a patient who meets the primary efficacy endpoint.

- Duration of hematopoietic response (days) defined as the time period from the first time hemoglobin concentration ≥ 11 g/dL to the last time there is hemoglobin concentration ≥ 11 g/dL. Duration of response is only calculated for a responder and will be at least 28 days. The duration of response is only calculated for a patient who meets the primary efficacy endpoint.

- Duration of hematopoietic response (days) defined as the time period from the first time to achieve at least ≥ 1 g/dL, ≥ 2 g/dL and/or hemoglobin concentration ≥ 11 g/dL to the last time there is the same response.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time a hemoglobin result at least ≥ 1 g/dL increase from baseline and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time a hemoglobin result at least ≥ 2 g/dL increase from baseline and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time hemoglobin concentration ≥ 11 g/dL and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time period the first time hemoglobin increases at least ≥ 1 g/dL, ≥ 2 g/dL from baseline and/or hemoglobin concentration ≥ 11 g/dL for a period of at least 28 consecutive days.

- Proportion of patients receiving red blood cell (RBC) transfusions and/or ESAs in each dose group as well as within each cycle of each ACE-011/placebo dose level.

- Objective tumor response rate for each dose level using RECIST criteria v1.1.

- Progression-Free Survival is defined as the time from the start date of current chemotherapy regimen into the study to the first observation of documented disease progression or death due to any cause. If the patient has not progressed or died at the time of final analysis, PFS will be censored at the time of last tumor assessment.

7.3 Safety Analysis Endpoints

The safety analysis endpoints include:

- Incidence of adverse events.

- Change and shift from baseline in clinical laboratory parameters including iron studies, nutritional tests, coagulation, serum chemistry, hematology, LH, FSH, testosterone, progesterone, and estradiol, and urinalysis, and 12-lead ECG.

7.4 Exploratory Analysis Endpoints

- Change or percent change in serum bone biomarkers (OC, BSAP, P1NP, CTX, TRACP-5b), urine bone biomarker (uNTX), bone mineral density (DXA scans of lumbar spine and hip) from baseline.

- Incidence of skeletal related events (SREs).

- Change in the FACT-Fatigue.

8.0 DETERMINATION OF SAMPLE SIZE

With an anticipated dropout rate of 20%, a sample size of 30 patients per dose level is estimated to achieve at least 80% power with 2 sided significance level of 0.05 to differentiate targeted response rate of p1=0.45 from null hypothesis p0=0.20. An additional 15 patients will be enrolled to the placebo group for safety comparison. A total of 105 patients will be randomized to three ACE-011 dose groups (0.1, 0.3, and 0.5 mg/kg) and placebo with a ratio of 2:2:2:1.

9.0 INTERIM ANALYSIS

There is no planned interim analysis for this study.

10.0 METHODS OF ANALYSIS AND PRESENTATION

10.1 General Principles

A blind data review of tables, appendices, and figures presented with surrogate treatment codes will be conducted prior to database freeze. This review will assess the accuracy and completeness of the study database, patient evaluability (including definition of analysis populations), and appropriateness of the planned statistical methods.

10.1.1 Analysis Data Sets

The data from all centers that participate in this protocol will be combined for the analysis. Missing data will not be imputed in any of the analysis.

Derived analysis data sets will be produced as appropriate from the case report form (CRF) data and laboratory data (including central lab, ECG, bone biomarker, anti-drug antibody test, and DXA) to assist with analysis and summary of both efficacy and safety variables. Derived data sets will identify observations selected according to the study window convention described in section 10.1.3. For details regarding the derived variables and derived analysis data sets, see the Study Derived Database and Technical Programming Specifications document.

10.1.2 Definition of Study Day 1 and Baseline

Study Day 1 is defined as the date of the first dose of ACE-011/placebo administered on or after the date of randomization. Other study days are defined relative to Study Day 1, and are numbered as …, -2, -1, 1, 2, …, with Day 1 defined as Study Day 1 and Day -1 defined as the day prior to Study Day 1. The baseline value for a variable is defined as the last observation collected on or before Study Day 1, prior to the first dose of ACE-011/ Placebo (including a screening value, if necessary).

10.1.3 Study Dates and Visit Windows

Durations (e.g., treatment duration) will be measured in days and calculated as: End Date – Start Date + 1. All scheduled study visit days will be defined relative to Study Day 1.

A windowing convention will be used to determine the analysis value for a given study visit and will be applicable for all by-visit summaries.

The visit window convention will be used for the analyses of efficacy and safety laboratory variables, as well as vital signs, ECG, FACT-Fatigue, DXA, and LH, FSH, Testosterone, Progesterone and Estradiol.

For efficacy variables, the visit windows are based on the windows defined in the protocol Schedule of Events. For safety variables, visit windows are exhaustive.

One or more results for a particular efficacy or safety variable may be obtained in the same visit window. In such an event, the result with the date closest to the scheduled visit date will be used.

10.1.4 Analysis Considerations

All confidence intervals, statistical tests, and resulting p-values will be reported as 2-sided and will be assessed at the 0.05 significance level. Unless otherwise specified, no Type 1 error adjustments for multiple comparisons will be made.

Alternative methods of analysis may be considered prior to unblinding should some of the underlying model assumptions not be met (e.g. normality, missing values and lost to follow-up). The reason for any changes to the planned approach and methods will be fully documented.

10.1.5 Table and Appendix Presentation

Frequency distributions (number and percentage of patients) will be used to summarize categorical variables. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. Unless otherwise specified, the denominator for percentages will be the number of patients in a given ACE-011/placebo group within the population of interest. Descriptive statistics (number of patients with non-missing values, mean, median, SD, minimum, and maximum) will be used to summarize continuous variables unless otherwise noted.

In summary tables for categorical data, all categories will be presented if they are specified on the CRF (e.g., discontinuation reason), or if categories are ordered intervals (e.g., age groups), regardless of whether or not a patient is found in a given category. For other categorical data (e.g., adverse events and medications), only categories with at least 1 patient will be presented.

When no data are available for a table or appendix, an empty page with the title will be produced with suitable text (e.g., “There are no observations for this table/appendix.”).

Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SDs) and standard errors (SEs, if applicable) will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Confidence intervals will be presented using the same number of decimal places as the parameter estimate (e.g., mean). Percentages will be presented to 1 decimal place.

All p-values will be rounded to 3 decimal places. If a p-value is less than 0.001, it will be reported as “<0.001”. If a p-value is greater than 0.999, it will be reported as “>0.999”.

The tables will be accompanied by data appendices sorted by treatment, study center, and patient number. Patients are uniquely identified by a concatenation of study center number and patient number. All data available from the CRFs along with some derived

variables will be listed. For relevant dates, the actual day relative to start of ACE-011/ placebo will also be listed. Dates will be presented in the format of "DDMONYYYY."

10.1.6 Analysis Software

SAS® Version 8.2 or higher (Cary, NC: SAS Institute) will be used for all statistical analyses.

10.2 Analysis Sets

The following 4 analysis sets will be used: the Randomized Set, the modified Intent-To-Treat Set (MITT), the Safety Set, and the Per Protocol Set (PP).

The Randomized Set includes all enrolled patients who have been randomized.

The modified Intent-To-Treat Set includes all randomized patients who received at least one dose of ACE-011/placebo.

The Safety Set includes all patients who received at least one dose of ACE-011/placebo.

The Per Protocol Set includes all patients randomized who have confirmed chemotherapy induced anemia, received at least one dose of ACE-011/ placebo and on study (treatment) for at least 2 months (57 days).

The number and percentage of patients in each analysis set will be summarized in Table 14.1.1.

10.3 Patient Disposition

Patient disposition will be summarized (frequency, percentage) by dose groups or placebo and overall for each patient sample, as will incidence of discontinuation of investigational drug, reason for discontinuation of investigational drug, incidence of discontinuation of study follow-up and reason of discontinuation of study follow-up. Overall disposition summaries will be presented in Table 14.1.1. Disposition information will be listed in Appendix 16.2.1

A summary of patients enrolled by sites will be provided in Table 14.1.2.

Inclusion/Exclusion criteria and randomization details will be listed in Appendices 16.2.2 and 16.1.7, respectively.

10.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by dose groups or placebo and overall. Demographic and baseline characteristics include age (years), race, ethnicity, height (cm), weight (kg), body mass index (BMI) (kg/m^2), breast cancer

history such as stage of breast cancer at diagnosis, histological subtype at diagnosis, histological grade, molecular subtype, estrogen and progesterone receptor status, HER-2/neu status and sites of metastatic breast cancer. Summaries of demographic and baseline characteristics will be based on the MITT Set.

Age in years is calculated as the integer part of the formula (Date of informed consent – Date of Birth + 1) /365.25 and will be summarized using descriptive statistics.

The number and percentage of patients in each race category (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White and Other) will be presented.

The number and percentage of patients in each ethnicity category (Hispanic or Latino and Others) will be presented.

BMI will be calculated using weight and height collected at Screening as follows: [(weight in kg) / ((height in cm) / 100)^2].

These data will be listed in Appendices 16.2.4.1 and 16.2.4.2 and summarized in Tables 14.1.3.1 and 14.1.3.2.

10.5 Medical History

Summaries of medical history will be based on the MITT Set. No inferential statistics will be presented.

Medical history will consist of any significant conditions or diseases including relevant surgical, therapeutic and diagnostic procedures that started prior to first dosing (Day 1).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 11.1) coding system. Each diagnosis is mapped to a lower level term, and then to a preferred term, which is then mapped to a system organ class.

The number and percentage of patients with any reported medical history will be summarized for each system organ class and preferred term in Tables 14.1.4. For the tables, if a patient reports the same preferred term multiple times, then that preferred term will be counted only once for that patient. Similarly, if a patient reports multiple conditions within the same system organ class, then that system organ class will be counted only once for that patient in the tables. System organ classes and preferred terms will be sorted in decreasing frequency based on the total number of reports. Medical history will be presented in Appendix 16.2.4.3.

10.6 Concomitant Diagnostic, Surgical, and Therapeutic Procedures

Any diagnostic, surgical, and therapeutic procedures that are conducted during the study i.e., from Day 1 to Day 281/Termination visit, will be considered as concomitant

procedures. Concomitant diagnostic, surgical, and therapeutic procedures will be listed in Appendix 16.2.4.4.1.

10.7 Prior and Concomitant Medications

Summaries of prior and concomitant medications will be based on the MITT Set. No inferential statistics will be presented.

Any medication that was taken within 28 days prior to Day 1 and through 90 days from the last dose of ACE-011/placebo will be recorded in the CRF as prior and concomitant medication.

Prior and concomitant medications will be coded using the World Health Organization Drug dictionary (Version March 2009) and classified into the default anatomical therapeutic chemical classification system (ATC) code provided by the system (the first ATC code by alphabetic order). The level 2 code will be used for analyses.

Prior and concomitant medication will be summarized by dose groups or placebo and overall in Table 14.1.5. The table will present the number and percentage of patients by preferred term within each class sorted by decreasing frequency based on the total number of reports. The total number and percentage of patients receiving at least 1 medication will also be presented. Prior and concomitant medications will be listed in Appendix 16.2.4.5.

10.8 Prior and Current Chemotherapy for Breast Cancer

Summaries of prior chemotherapy agents and current chemotherapy agents for breast cancer will be based on the MITT Set. No inferential statistics will be presented.

Any chemotherapy agents that were stopped at or prior to Screening will be considered prior chemotherapy. Chemotherapy agents taken at any time from Screening through Day 281/Termination visit will be considered current chemotherapy.

Prior and current chemotherapy agents will be coded using the World Health Organization Drug dictionary (Version March 2009) and classified into the default anatomical therapeutic chemical classification system (ATC) code provided by the system (the first ATC code by alphabetic order). The level 2 code will be used for analyses.

Prior chemotherapy agents will be summarized by dose groups or placebo and overall in Table 14.1.6.1. Current chemotherapy agents will be summarized by dose groups or placebo and overall in Table 14.1.6.2. The tables will present the number and percentage of patients by preferred term within each class sorted by decreasing frequency based on the total number of reports. The total number and percentage of patients receiving at least 1 chemotherapy agent will also be presented. Prior and current chemotherapy agents will be listed in Appendices 16.2.4.6.1 and 16.2.4.6.2 respectively.

10.9 Prior Radiation Therapy

Any radiation therapy prior to Day 1 will be recorded in the CRF. Radiation therapy will be summarized by dose groups or placebo and overall in Table 14.1.7. The table will present the number and percentage of patients by body sites. The total number and percentage of patients receiving at least 1 radiation therapy will also be presented. Prior radiation therapy will be listed in Appendix 16.2.4.7.

10.10 Investigational Drug Exposure and Dose Modification

ACE-011/placebo will be administered as a SC injection at the clinical site by the study staff, approximately every 28 days, on days 1, 29, 57, and 85 of the treatment period.

The summaries of drug exposure and dose modification will be based on the Safety Set. No inferential statistics will be presented.

The number of doses received (i.e., 1 – 4), skipped and/or modified (i.e., 0 – 3) during the study will be summarized in Table 14.1.8.1 using frequencies and percentages for each dose group. The total dosage received, which is defined as the sum of dosage received during the treatment period will be summarized using descriptive statistics for each dose group.

The local hemoglobin values and blood pressure values will be evaluated on each ACE-011/placebo dosing day (Appendix 16.2.5.2). The hemoglobin values 28 days prior to each ACE-011/placebo dosing day and blood pressure will be reviewed and evaluated for dose modifications. The rules for dosing modifications have been specified in protocol section 9.5.2.2. A patient may have up to 3 dose reductions in the study. The total number of dose modifications (i.e., 0, 1, 2 and 3) and reason of dose modification at Days 29, 57 and 85 will be summarized by dose groups or placebo and overall (all three doses together) in Table 14.1.8.2.

The investigational drug exposure and dose modification will be listed in Appendix 16.2.5.1.

10.11 Efficacy Analysis

10.11.1 Primary Efficacy Analysis

The primary efficacy endpoint is the hematopoietic response rate at each dose level or placebo. It is defined as the proportion of patients who have a hematopoietic response of an increase in hemoglobin of $\geq$ 1 g/dL for 28 consecutive days during the treatment period including up to 2 months after the last dose of ACE-011/placebo, in the absence of any RBC transfusions and/or ESAs. The ACE-011/placebo treatment period is defined as the time period from the time of first ACE-011/placebo dose to up to 2 months after the last dose of ACE-011/placebo treatment. To be considered as a responder, all hemoglobin measurements during a 28 consecutive day period or longer must have an

increase of ≥ 1 g/dL from baseline. If RBC transfusions and/or ESAs are required, no hemoglobin measurements within 28 days of the RBC transfusion of ESA administration will be used to determine the hemoglobin response.

Primary efficacy analysis will be based on the PP Set. Primary efficacy analysis will also be conducted on the MITT Set as supportive to the PP based analysis. Patients who do not receive ACE-011/placebo will be excluded from primary efficacy analysis. Patients who discontinue the ACE-011/placebo treatment prematurely will be counted as non-responder in the calculation of response rate unless the patients can be determined as responder using available hemoglobin measurements.

An exact 95% confidence interval (CI) for the response rate for each dose level or placebo as well as overall (all three doses levels analyzed together) will be provided to assess whether 95% CI of response rate contains null hypothesis response rate, p0=0.20 (Clopper and Pearson, 1934). The response rate and 95% CI will also be provided for patients with chemotherapy on weekly basis versus those with chemotherapy on a less frequent basis for each dose level or placebo as well as overall (all three doses levels analyzed together).

An exploratory analysis with the Kaplan Meier approach will be considered to account for those patients who discontinue the ACE-011/placebo treatment prematurely if the drop out rate is greater than 20%. Exploratory analysis of comparing hematopoietic response rates between active and placebo will be performed using Fisher's exact test. Due to the nature of the study (phase 2 dose determination study), no multiplicity adjustment will made for the multiple comparisons.

Primary efficacy analysis of hematopoietic response in the PP Set and MITT Set will be based on central lab hemoglobin values and summarized in Table 14.2.1.1 and Table 14.2.1.2 respectively. The values of hemoglobin and hematocrit will be listed in Appendix 16.2.6.1.

10.11.2 Secondary Efficacy Analyses

All secondary efficacy analyses will be conducted under both MITT and PP analysis sets. The following secondary efficacy endpoints will be analyzed in the SAP.

- Proportion of patients achieving an increase in hemoglobin of ≥ 2 g/dL for 28 consecutive days during the treatment period and up to 2 months after the last dose of ACE-011/placebo in the absence of any RBC transfusions and/or ESAs.

- Proportion of patients achieving hemoglobin concentration ≥ 11 g/dL for 28 consecutive days during the treatment period and up to 2 months after the last dose of ACE-011/placebo in the absence of any RBC transfusions and/or ESAs.

- Proportion of patients achieving an increase in hemoglobin of ≥ 2 g/dL and/or hemoglobin concentration ≥ 11 g/dL for 28 consecutive days during the treatment

period and up to 2 months after the last dose of ACE-011/placebo in the absence of any RBC transfusions and/or ESAs.

For the above endpoints, patients who discontinue the ACE-011/placebo treatment prematurely will be counted as non-responder in the calculation of response rate unless the patients can be determined as responder using the available hemoglobin measurements. An exact 95% confidence interval (CI) for the response rate for each dose level as well as overall (all three doses levels analyzed together) will be provided (Clopper and Pearson, 1934). The response rate and 95% CI will also be provided for patients with chemotherapy on weekly basis versus those with chemotherapy on a less frequent basis for each dose level as well as overall (all three doses levels analyzed together). P–value will be calculated based on Fisher's exact test to compare the response rate between each dose level and placebo. No multiplicity adjustment will made for the multiple comparisons. The results will be presented in Tables 14.2.2.1 – 14.2.2.6.

- Duration of hematopoietic response (days) defined as the time period the first time hemoglobin increases at least ≥ 1 g/dL from baseline to the last time there is hemoglobin ≥ 1 g/dL increase from baseline.

- Duration of hematopoietic response (days) defined as the time period the first time hemoglobin increases at least ≥ 2 g/dL from baseline to the last time there is hemoglobin ≥ 2 g/dL increase from baseline.

- Duration of hematopoietic response (days) defined as the time period the first time hemoglobin concentration ≥ 11 g/dL to the last time there is hemoglobin concentration ≥ 11 g/dL.

- Duration of hematopoietic response (days) defined as the time period the first time hemoglobin increases at least ≥ 1, ≥ 2 g/dL and/or hemoglobin concentration ≥ 11 g/dL from baseline to the last time when the same response is maintained.

For the above endpoints, duration of response is only calculated for a responder and will be at least 28 days. The duration of response is only calculated for a patient who meets the primary efficacy endpoint. Duration of hematopoietic response in days will be summarized by each dose group or placebo as well as overall (all three doses together) using descriptive statistics in Tables 14.2.2.7 and 14.2.2.8.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time a hemoglobin result at least ≥ 1 g/dL increase from baseline and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time a hemoglobin result at least ≥ 2 g/dL increase from baseline and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time from first dose of ACE-011/placebo to the first time hemoglobin concentration ≥ 11 g/dL and maintained for a period of at least 28 consecutive days.

- Time to achieve hematopoietic response (days) defined as the time period the first time hemoglobin increases at least ≥ 1, ≥ 2 g/dL and/or hemoglobin concentration ≥ 11 g/dL and maintained for a period of at least 28 consecutive days.

For the above endpoints, patients who die before the event was reached will be right censored at the date of death. Patients who discontinue the study or who are lost to follow up and for whom the event was not reached before premature discontinuation will be right censored at the last date of follow up. Patients who complete the required follow up but do not reach the event will also be right censored at the last date of follow up. Time to achieve hematopoietic response after the first dose of ACE-011/placebo will be analyzed using Kaplan-Meier method to estimate the survival curve and median time to event. The 95% Confidence Interval (CI) for the estimated median time will be based on the sign test (Brookmeyer and Crowley 1982). Time to hematopoietic response will be summarized in Tables 14.2.2.9 and 14.2.2.10 and plotted in Figures 14.2.2.9.1 – 14.2.2.9.5 and Figures 14.2.2.10.1 – 14.2.2.10.5.

- Proportion of patients receiving red blood cell (RBC) transfusions and/or ESAs in each dose group as well as within each cycle of each ACE-011 dose level.

The RBC transfusion and ESA will be captured and coded in the Concomitant Medication page. The treatment cycles are defined as from Day 1 to prior to Day 29, Day 29 to prior to Day 57, Day 57 to prior to Day 85 and Day 85 to prior to Day 141. For each treatment cycle and overall for all treatment cycles, the number and percentage of patients who have received any RBC transfusion, any ESA, and any RBC transfusion and/or ESA will be presented by dose groups or placebo as well as overall (all three doses together) in Tables 14.2.2.11 and 14.2.2.12.

- Objective tumor response rate for each dose level using RECIST criteria v1.1.

The objective tumor response evaluated using RECIST criteria will be recorded at Days 64 and 113. The tumor (both target and non-target) responses will be summarized in Tables 14.2.2.13 and 14.2.2.14 for dose groups or placebo and overall (all three doses together). The unscheduled tumor response evaluations will not be summarized in the tables but be presented in Appendix 16.2.6.2. The tumor lesions assessed by CT/MRI scans recorded at Screening, Days 64 and 113 and Unscheduled will be presented in Appendix 16.2.6.3.

- Progression-Free Survival (PFS) is defined as the time from the start date of current chemotherapy regimen to the first observation of documented disease progression or death due to any cause. If the patient has not progressed or died at the time of end of follow-up, PFS will be censored at the time of last tumor

assessment. The number and percentage of patients who have progressed, died and censored as well as the median PFS (95% CI) will be presented in Tables 14.2.2.15 and 14.2.2.16. The median PFS will be estimated using Kaplan – Meier method and the 95% CI will be calculated using the sign test (Brookmeyer and Crowley 1982).

10.12 Safety and Exploratory Analyses

10.12.1 Adverse Events

All adverse events will be summarized using the Safety Set. No inferential statistics will be provided.

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational drug, whether or not it is considered to be investigational drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of investigational drug (treatment-emergent).

A treatment-emergent adverse event will be defined as any adverse event, regardless of relationship to investigational drug occurring after ACE-011/placebo administration up to 90 days from the last dose of ACE-011/placebo.

Adverse events with missing onset dates will be considered treatment-emergent. If an onset date or end date is partial, the event will be considered treatment-emergent unless the partial date eliminates the possibility that the event is treatment-emergent. Specifically, if a day is missing, the month and year will be used to determine treatment emergence. If a day and month is missing, the year will be used to determine treatment emergence.

All adverse events will be coded using the MedDRA (Version 11.1) coding system. In this dictionary, each diagnosis is mapped to a lower level term, and then to a preferred MedDRA term, which is then mapped to system organ class.

Adverse events will be summarized by dose groups or placebo and overall (three doses levels combined). The following sections describe the summaries that will be presented.

10.12.1.1 Incidence of Adverse Events

A high-level summary of treatment-emergent adverse events will be presented in Table 14.3.1.1. This table will include the number and percentage of patients who have experienced any treatment-emergent adverse event and any treatment-emergent adverse events that lead to investigational drug discontinuation. The table will also present the

event count of each CTCAE grade and related or not related to investigational drug by dose groups or placebo and overall (three doses levels combined).

Treatment-emergent adverse events will be presented by system organ class and preferred term in Table 14.3.1.2. The table will include only one occurrence of a preferred term per patient. If a patient reports the same preferred term multiple times, then that preferred term will be counted only once for that patient. Similarly, if a patient reports multiple adverse events within the same system organ class, then that system organ class will be counted only once for that patient. System organ class terms and preferred terms will be sorted in decreasing frequency based on the total number of adverse event reports. All adverse events will be presented in Appendix 16.2.7.1.

10.12.1.2 Relationship of Adverse Events to Investigational drug

An overview of treatment-emergent adverse events by relationship to investigational drug will be presented in Tables 14.3.1.3.1. The overview presents by the relationship with the investigational drug (none, unlikely, possibly, probably and definitely) the number of treatment-emergent adverse events and the number and percentage of patients who have experienced at least one treatment-emergent adverse event.

Drug-related adverse events will be defined as any adverse events that are considered by the investigator to be either possibly, probably, or definitely related to investigational drug. A summary of treatment-emergent adverse events related to investigational drug will be presented by system organ class and preferred term in Table 14.3.1.3.2.

A patient is counted once for most related event if the patient reports more than one event. If relationship to investigational drug is missing, no imputation will be implemented for the missing relationship (Appendix 16.2.7.1).

10.12.1.3 CTCAE Grade of Adverse Events

An overview of treatment-emergent adverse events by CTCAE grades will be presented in Table 14.3.1.4.1. The overview presents by the CTCAE grades (1-5) the total number of treatment-emergent adverse events and the number and percentage of patients who have experienced at least one treatment-emergent adverse event.

The grades 3, 4 and 5 AEs will be summarized by system organ class and preferred term in Table 14.3.1.4.2. A patient is counted once for most severe event if the patient reports more than one event.

10.12.1.4 Adverse Events Leading to Treatment Discontinuation

All treatment-emergent adverse events collected with an investigational drug action taken as “Permanently Discontinued” will be presented by system organ class and preferred term in Table 14.3.1.5.

10.12.1.5 Serious Adverse Events

All treatment-emergent SAEs will be presented in Table 14.3.1.6 and Appendix 16.2.7.2. Treatment-Emergent serious adverse event is defined as any serious adverse event that starts on or after date of first dose through Day 281/Termination visit. If a patient reports the same SAE preferred term multiple times, then that preferred term will be counted only once for that patient. Similarly, if a patient reports multiple SAEs within the same system organ class, then that system organ class will be counted only once for that patient. If a patient reports multiple occurrences of the same SAE, only the most related occurrence will be presented.

10.12.1.6 Skeletal Related Events

Skeletal Related Events (SREs) are defined as pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression that starts on or after the date of first dose through Day 281/Termination visit.

The overall number of SREs reported in both AE and Concomitant Diagnostic, Surgical, and Therapeutic Procedures (CP) pages will be summarized in Table 14.3.2 by dose groups or placebo and overall (three doses levels combined). The number of patients with at least one SRE will be summarized in this table as well. In addition, the number and percentage of patients within each SRE category (i.e., pathologic fracture, radiation therapy to bone, surgery to bone, and spinal cord compression) will also be summarized in Table 14.3.2. All SREs in AE and CP pages will be presented respectively in Appendices 16.2.7.1 and 16.2.4.4.1. A summary of all SREs will be listed in Appendix 16.2.4.4.2.

10.12.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be assessed using the Safety Set. No inferential statistics will be presented.

All iron studies, nutritional tests, coagulation studies, serum chemistry, hematology, urinalysis and LH, FSH, testosterone, progesterone, and estradiol will be sent to the central laboratory. Central laboratory results will be used for assessment of the study outcomes. Hemoglobin and hematocrit will be also evaluated by the local laboratory in the evaluation of ACE-011/placebo dose modifications. Urine pregnancy test will be conducted in local laboratories.

Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Change from baseline in continuous safety laboratory variables will be summarized by dose groups or placebo and overall (three doses levels combined) as described below. Conventional units will be reported for all analytes.

In addition, shift tables will be presented showing the number of patients with low, normal, or high values at baseline and each post-baseline visit according to the central laboratories' reference ranges.

For the relationship to normal reference range and shift table summaries, if a patient has multiple tests available in a particular visit window, the most abnormal result will be selected for summary (if applicable). All descriptive statistics will be based on data selected according to the window convention outlined in Section 10.1.3.

Laboratory tests with character results that cannot be analyzed by change from baseline or shift table analysis will be listed in their respective data appendices 16.2.8.1 – 16.2.8.8.

10.12.2.1 Iron Studies

Iron studies will be collected at Screening, Days 1, 29, 57, 85 and 281. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.3.1.1 will present descriptive statistics of iron studies for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.1.2 will present the shift from baseline to each post-baseline visit. The following laboratory tests will be included:

- serum iron (mcg/dL)
- total iron binding capacity (TIBC) (mcg/dL)
- transferrin(g/L)
- serum ferritin (ng/dL)

For all parameters, mean values (±SE) over time will be graphed in Figures 14.3.3.1.3.1 – 14.3.3.1.3.4. Appendix 16.2.8.1 will list all iron studies values for all patients.

10.12.2.2 Nutritional Tests

Nutritional tests include serum folate (ng/mL) and vitamin B12 (pg/mL). Vitamin B12 will be collected only at Screening. Serum folate will be collected at Screening, Days 36, 113 and 281. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.3.2.1 will present descriptive statistics of nutritional tests for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.2.2 will present the shift from baseline to each post-baseline visit. For serum folate, mean values (±SE) over time will be graphed in Figure 14.3.3.2.3. Appendix 16.2.8.2 will list all nutritional tests values for all patients.

10.12.2.3 Coagulation

Coagulation profile will be collected at Screening, Days 1, 8, 15, 22, 29, 36, 43, 57, 64, 71, 85, 99, 113, 141 and 281. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.3.3.1 will present descriptive statistics of coagulation for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.3.2 will present the shift from baseline to each post-baseline visit. The following laboratory tests will be included:

- prothrombin time (PT) (sec)

- partial thromboplastin time (PTT) (sec)
- fibrinogen (mg/dL)

For all parameters, mean values (±SE) over time will be graphed in Figures 14.3.3.3.3.1 – 14.3.3.3.3.3. Appendix 16.2.8.3 will present coagulation profile for all patients.

10.12.2.4 Hematology

Hematology will be collected at every visit including Screening, Days 1, 8, 15, 22, 29, 36, 43, 57, 64, 71, 85, 99, 113, 141, 169, 197, 225, 253 and 281. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Peripheral blood smear will be conducted only on dosing days (i.e., Days 1, 29, 57, and 85) and Day 281. Reticulocyte will be done on days 1, 8, 15, 22, 29, 36, 57, 64, 85, and at the termination visit. Table 14.3.3.4.1 will present descriptive statistics of hematology values for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.4.2 will present the shift from baseline to each post-baseline visit. The following laboratory tests will be included:

- red blood cell (RBC) count (10^6/mm^3)
- hemoglobin (g/dL)
- hematocrit (%)
- platelet count (10^3/mm^3)
- white blood cell (WBC) count (10^3/mm^3)
- total neutrophils (10^3/mm^3)
- eosinophils (K/mm^3)
- basophils (K/mm^3)
- monocytes (K/mm^3)
- lymphocytes (K/mm^3)
- mean corpuscular volume (fl)
- mean corpuscular hemoglobin (pg)
- mean corpuscular hemoglobin concentration (g/dL)
- erythropoietin (mIU/mL)
- reticulocyte (absolute count)
- reticulocyte (%)

For all parameter, mean values (±SE) over time will be graphed in Figures 14.3.3.4.3.1 – 14.3.3.4.3.16. Appendix 16.2.8.5 will list all hematology values for all patients.

10.12.2.5 Serum Chemistry

Serum chemistry will be collected at visits including Screening, Days 1, 8, 15, 22, 29, 36, 43, 57, 64, 71, 85, 99, 113, 141 and 281. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.3.5.1 will present descriptive statistics of serum chemistry for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.5.2 will present the shift from baseline to each post-baseline visit. The following laboratory tests will be included:

- blood urea nitrogen (mg/dL)
- calcium (mg/dL)
- creatinine (mg/dL)
- sodium (mEq/L)
- alkaline phosphatase (U/L)
- aspartate aminotransferase (AST) (U/L)
- alanine aminotransferase (ALT) (U/L)
- chloride (mEq/L)

- potassium (mEq/L)
- total bilirubin (mg/dL)
- uric acid (mg/dL)
- glucose (fasting) (mg/dL)
- phosphorus (mg/dL)
- lipase (U/L)
- indirect bilirubin (mg/dL)
- total protein (g/dL)
- albumin (g/dL)
- carbon dioxide (mEq/L)
- amylase (U/L)
- lactate dehydrogenase (LDH) (U/L)

For all parameters, mean values (±SE) over time will be graphed in Figures 14.3.3.5.3.1 – 14.3.3.5.3.20. Appendix 16.2.8.4 will present serum chemistry values for all patients.

10.12.2.6 Urinalysis

Urinalysis will be collected at Screening, Days 1, 85 and 281. Urinalysis laboratory parameters including protein, glucose, blood, ketone, leukocyte esterase and nitrite will be categorically summarized as shift from baseline to each post-baseline visit in Table 14.3.3.6.2. Urinalysis PH values and specific gravity will be presented in Table 14.3.3.6.1. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Descriptive statistics for baseline, each post-baseline visit and change from baseline to each post-baseline visit will be presented. Microscopy results such as crystals, casts, WBCs, and red blood cells (if applicable) will not be summarized, only listed using categorical results provided directly by the laboratory (Appendix 16.2.8.6).

Appendix 16.2.8.6 will include all urinalysis laboratory values for all patients.

10.12.2.7 LH, FSH, Testosterone, Progesterone, and Estradiol

The parameters of LH (mIU/mL), FSH (mIU/mL), testosterone (ng/dL), progesterone (ng/mL), and estradiol (pg/dl) will be evaluated at Screening, Days 1, 29, 57, 85, 113 and 141. Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.3.7.1 will present descriptive statistics for LH, testosterone, progesterone and estradiol for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Table 14.3.3.7.2 will present descriptive statistics for FSH for baseline, each post-baseline visit, and change and percent change from baseline to each post-baseline visit. Table 14.3.3.7.3 will present the shift from baseline to each post-baseline visit.

For all parameters as well as percent change from baseline in FSH, mean values (±SE) over time will be graphed in Figures 14.3.3.7.3.1 – 14.3.3.7.3.6. Appendix 16.2.8.8 will include all results for all patients.

10.12.2.8 Local Hematology

Local hematology will include hemoglobin and hematocrit that are collected at every visit from Screening to Day 281. These local lab results will be listed in Appendix 16.2.5.2.

10.12.2.9 Urine Pregnancy Test

Urine pregnancy test will be conducted for females of child bearing potential only at dosing days (Days 1, 29, 57 and 85, prior to dosing) and Day 281.The urine pregnancy test will be listed in Appendix 16.2.9.5.

10.12.3 Vital Signs

Vital sign measurements (seated systolic and diastolic blood pressure in mmHg, heart rate in beats/minute, oral temperature in °C, and weight in kg) will be collected at Screening, Days 1, 8, 15, 22, 29, 36, 43, 57, 64, 71, 85, 99, 113, 141 and 281. Measurements will be made prior to dosing on dosing days. Height in cm will be collected at Screening. Height and weight at screening will be summarized with Demographics and Baseline Characteristics in Table 14.1.4.

Vital signs will be summarized using the Safety Set. No inferential statistics will be presented.

Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.4 will display descriptive statistics for vital signs at baseline, each post-baseline visit, and change from baseline to each post-baseline visit by dose groups or placebo and overall (three doses levels combined).

All vital sign measurements will be presented by patient in Appendix 16.2.9.1.

10.12.4 Physical Examinations

All physical examination results will be presented in Appendix 16.2.9.2.

10.12.5 12-Lead ECGs

Triplicate twelve-lead ECGs (3 minute intervals) will be performed at Screening, Days 1, 8, 36, 64, 113 and 281. On Screening and Day 1, ECGs will be performed at two different time intervals (approximately 1 hour apart). On Day 1, ECGs are to be performed prior to dosing of ACE-011/placebo. ECG data will be interpreted by both local readers and central readers and the results will be presented separately.

ECGs will be summarized using the Safety Set. The endpoints that will be collected include ventricular rate (beats/min), PR interval (msec), QRS duration (msec), QT interval (msec) and QTc interval.

For each ECG parameter, the arithmetic mean will be calculated at each visit for all replicates. Baseline is defined as the last nonmissing mean value prior to the first dose of ACE-011/placebo. Descriptive statistics of mean ECG values will be presented for baseline, 8, 36, 64, 113 and 281 and change from baseline by dose groups or placebo and overall (three doses levels combined) in Tables 14.3.5.1 for local ECG and 14.3.5.3 for central ECG.

In addition, shift tables showing the number of patients with normal, non-clinically significant abnormal, or clinically significant abnormal ECG interpretation results from baseline to Days 8, 36, 64, 113 and 281 will be provided in Tables 14.3.5.2 for local ECG. For the ECG interpretation summaries, if a patient has multiple interpretations at a particular visit, the most significant result will be selected for summary (if applicable).

For QTc (QTcB and QTcF) from central readers, baseline adjusted QTc (post-dose – baseline) at each post-dose visit for ACE-011/placebo patients will be calculated for each patient. Descriptive statistics of the baseline adjusted QTc data will be present for Days 8, 36, 64, 113 and 281 by dose groups or placebo and overall (three doses levels combined) in Tables 14.3.5.4. In addition, the mean difference of the baseline adjusted QTc as well as its upper bound of one-sided 95% confidence interval will be calculated for each dose group and overall (three doses levels combined) comparing to the placebo.

QTc interval (QTcB and QTcF) from the central readers will also be categorized as ≤ 450 msec, > 450 but < 480 msec and ≥ 480 msec. Table 14.3.5.5 presents the number and percentage of patients for each category for baseline, Days 8, 36, 64, 113 and 281 by dose groups or placebo and overall (three doses levels combined).

Local and central ECG data will be presented in Appendices 16.2.9.3.1, 16.2.9.3.2, 16.2.9.4.1 and 16.2.9.4.2.

10.12.6 Anti-drug Antibody

The results of anti-drug antibody will be listed in Appendix 16.2.8.10.

10.13 Pharmacokinetic Analysis

The PK analysis will be analyzed separately by the sponsor.

10.14 Pharmacoeconomic Analysis

Not applicable.

10.15 Bone Biomarker Analysis

Bone biomarkers (serum) including osteocalcin (OC), procollagen type 1 N-terminal propeptide (P1NP), serum bone specific alkaline phosphatase (BSAP), C-terminal type 1 collagen telopeptide (CTX), tartrate-resistant acid phosphatase isoform-5b (TRACP-5b), and urine N-telopeptide (uNTX) will be collected prior to dosing on dosing days 1, 29, 57 and 85, as well as Days 113, 141 and 281.

Bone biomarker data will be summarized using the MITT Set. No inferential statistics will be presented.

Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Table 14.3.6 will display descriptive statistics for each bone biomarker at baseline, each post-baseline visit, and change and percent change from baseline to each post-baseline visit by treatment group.

For each parameters as well as percent change from baseline, mean values (±SE) over time will be graphed in Figures 14.3.6.1 – 14.3.6.12. All bone biomarker data will be presented by patient in Appendix 16.2.8.7.

10.16 Quality of Life Analysis

FACT-Fatigue questionnaire (version 4, Appendix) will be administered at Screening, prior to dosing on Days 1, 29, 57 and 85 and Day 281. FACT-Fatigue subscale has 13 Likert scale items with response categories of "Not at all", "A little bit", "Somewhat", "Quite a bit" and "Very much" coded as 0, 1, 2, 3 and 4. The total score of the subscale will be calculated by summing up all items with range from 0 – 52. The scoring algorithm is listed as below:

1. Reverse coding for items HI7, HI12, An1, An2, An3, An4, An8, An12, An14, An15 and An16 by subtracting the response from "4" to reflect the higher score means better quality of life,

2. Sum individual items to obtain a score,

3. Multiply the sum of the item scores by the number of items in the subscale (i.e., 13), then divide by the number of items answered. This produces the subscale score.

The total score requires more than 50% of the items are answered (i.e., a minimum of 7 of 13 items). The total score will be considered as missing when there are less than 50% item endorsed.

Baseline FACT-Fatigue total score is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Descriptive statistics for the total score will be presented for baseline, Days 29, 57, 85 and 281 and change from baseline by treatment group in Table 14.3.7.

FACT-Fatigue total score will be summarized using the MITT Set.

FACT-Fatigue item data will be presented in Appendix 16.2.9.7.

10.17 DXA Analysis

Bone Mineral Density (BMD) of lumbar spine and hip will be assessed using DXA scan at Screening, Days 113 and 281. The analyzed parameters include BMD (g/cm^2) for spine regions L1-L4 and hip total.

Baseline is defined as the last nonmissing value prior to the first dose of ACE-011/placebo. Tables 14.3.8.1 and 14.3.8.2 will display descriptive statistics for each parameter at baseline, each post-baseline visit, change from baseline and percent change from baseline to each post-baseline visit by treatment group.

BMD will be summarized using the MITT Set. Percent change from baseline in BMD will be compared to placebo group using ANOVA Dunnett's test.

The BMD and percent change from baseline for spine regions and hip total will be graphed by mean values (±SE) over time in Figures 14.3.8.3.1 - 14.3.8.3.4. DXA data will be presented by patient in Appendices 16.2.8.9.1 and 16.2.8.9.2.

10.18 Changes in the Statistical Analysis Plan from the Protocol Analysis Plan

The statistical analysis plan does not deviate from the analysis specified in the protocol.

11.0 REFERENCES

1. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29-41.

2. Clopper C., Pearson E. S. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; 26: 404-413.

3. Functional Assessment of Chronic Illness, FACT-Fatigue Version 4. http://www.facit.org/qview/qlist.aspx. 2003.

4. Hosmer DW, Lemeshow S. Applied Survival Analysis. New York: Wiley 1999.

5. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95 – adopted December 1995).

6. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 - adopted March 1998).

12.0 APPENDIX

FACT-Fatigue Subscale

Item Number	Item Description
HI7	I feel fatigued.
HI12	I feel weak all over.
An1	I feel listless (“washed out”).
An2	I feel tired.
An3	I have trouble starting things because I am tired.
An4	I have trouble finishing things because I am tired.
An5	I have energy.
An7	I am able to do my usual activities.
An8	I need to sleep during the day.
An12	I am too tired to eat.
An14	I need help doing my usual activities.
An15	I am frustrated by being too tired to do the things I want to do.
An16	I have to limit my social activity because I am tired.