# Statistical Analysis Plan

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|---|---|
| **Protocol Title:** | A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism |
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| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
|---|---|---|
| Original (v1.0) | 18SEP2017 | |
| [Amendment 1 (v2.0)] | 03FEB2020 | To address protocol amendment 3.0, specified 'measured at the central laboratory' for all cCa description and analysis language.<br>Section 6.3: replaced 'constant maintenance hemodialysis for at least three times a week' with 'maintenance hemodialysis three times a week for at least 3 months'.<br>Section 8.3: replaced 'concomitant medication of interest (section 6.3)' with 'concomitant medication'.<br>Section: 9.1: added 'For analyses performed on cCa and Ca, only central laboratory results will be used.'<br>Section 9.6.2: removed 'Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product and up to 30 days after the last administration of investigational product.' to avoid redundant definitions.<br>Section 9.6.3: added 'In this section, cCa refers to cCa measured by central laboratory, Ca refers to Ca measured by central laboratory. All cCa and Ca results from local laboratory testing will be excluded from analysis.'<br>Section 9.6.3: updated potential Hy's law lab criteria, to keep consistent with programming standard macro.<br>Removed 'Section 12. Prioritization of Analysis' due to no applicable. |
| [Amendment 2 (v3.0)] | 14APR2020 | Section 3.1: added study schema.<br>Section 6.4: replaced 'enrolled' with 'randomized'.<br>Section 6.4: added 'Subjects will be analyzed according to randomized treatment group.'<br>Added Section 6.5. to be consistent with protocol.<br>Section 9.5.2.2: added 'The difference of least square means between treatment groups will be presented with 95% CI'.<br>Section 9.5.2.2.: added 'and cCa completer set will be used for sensitivity analysis'.<br>Section 9.5.2.2: added 'The difference between treatments will be estimated and presented with a 95% confidence interval.' |

## Table of Contents

**List of Tables**



**List of Figures**

## List of Abbreviations and Definition of Terms

| Abbreviation or Term | Definition/Explanation |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| [redacted] | |
| cCa | Albumin corrected calcium concentration |
| CDM | Clinical data management |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CMH | Cochran-Mantel-Haenszel |
| CPE | Clinical Planned Event |
| CRF | Case report form |
| CSR | Clinical study report |
| CTCAE | Common terminology criteria for adverse events |
| [redacted] | |
| DM | Data management |
| EAP | Efficacy assessment phase: the period between Week 20 and Week 27, inclusive |
| ECG | Electrocardiogram |
| EOI | Adverse event of interest |
| EOS | End of Study |
| ESRD | End-stage renal disease |
| EVOLVE | Evaluation Of Cinacalcet Therapy to Lower Cardiovascular Events |
| FAS | Full analysis set |
| IP | Investigational product |
| IPD | Important protocol deviation |
| iPTH | Intact parathyroid hormone |
| IV | Intravenous |
| IXRS | Interactive voice/web response system<br>Technology that utilizes either telecommunications or is web based, which is linked to a central computer in real time as an interface to collect and process information. |
| LLOQ | Lower limit of quantification |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| LVCF | Last value carried forward |
| MedDRA | Medical dictionary for regulatory activities |
| Abbreviation or Term | Definition/Explanation |
| MI | Multiple imputation |
| P | Phosphorus |
| PCAS | PTH completer analysis set |
| PK | Pharmacokinetic |
| PPAS | Per protocol analysis set |
| PTH | Parathyroid hormone |
| Q1 | First quartile |
| Q3 | Third quartile |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SE | Standard error |
| SHPT | Secondary hyperparathyroidism |
| TBL | Total bilirubin |
| TEAE | Treatment-emergent adverse event |
| ULOQ | Upper limit of qualification |
| ULN | Upper limit of normal |

# 1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20150238, Etelcalcetide (AMG 416) dated 27 November 2018. The scope of this plan includes the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

# 2. Objectives, Endpoints and Hypotheses

## 2.1 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To demonstrate that treatment with etelcalcetide (AMG 416) is not inferior to treatment with cinacalcet for lowering serum intact parathyroid hormone (PTH) levels by > 30% from baseline among subjects with chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) who require management with hemodialysis | • Achievement of a > 30% reduction from baseline in mean predialysis serum PTH level during the EAP of the study (EAP is defined as weeks 20 to 27, inclusive) |
| **Key Secondary** | |
| • To assess whether treatment with etelcalcetide (AMG 416) is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline | • Achievement of a > 50% reduction from baseline in mean predialysis serum PTH during the EAP (superiority)<br>• Achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP (superiority) |
| **Secondary** | |
| • To assess percent change from baseline in mean predialysis albumin corrected calcium (cCa) measured at the central laboratory, and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dl measured at the central laboratory during the efficacy assessment phase (EAP) | • Percent change from baseline in mean predialysis measured by the central laboratory serum cCa during the EAP<br>• Achievement of mean predialysis measured by the central laboratory serum P ≤ 4.5 mg/dL during the EAP |

| Objectives | Endpoints |
|---|---|
| **Safety** | |
| • To assess the safety and tolerability of etelcalcetide compared to cinacalcet<br>• To evaluate antibody formation to etelcalcetide | • Incidence of cCa < 8.3 mg/dL measured by the central laboratory at any time during the study<br>• Incidence of cCa < 8.0 mg/dL measured by the central laboratory at any time during the study<br>• Incidence of cCa < 7.5 mg/dL measured by the central laboratory at any time during the study<br>• Incidence of treatment-emergent symptomatic hypocalcemia during the study<br>• Incidence of antibody formation to etelcalcetide<br>• Nature, frequency, severity, and relationship of treatment-emergent adverse events |
| **Exploratory** | |
| [redacted] | |

## 2.2 Hypotheses and/or Estimations

Treatment of SHPT with etelcalcetide is not inferior to treatment with cinacalcet as measured by the proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP.

Treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease from baseline in mean predialysis serum PTH during the EAP, and by the proportion of subjects with > 30% decrease from baseline in mean predialysis serum PTH during the EAP.

# 3. Study Overview

## 3.1 Study Design

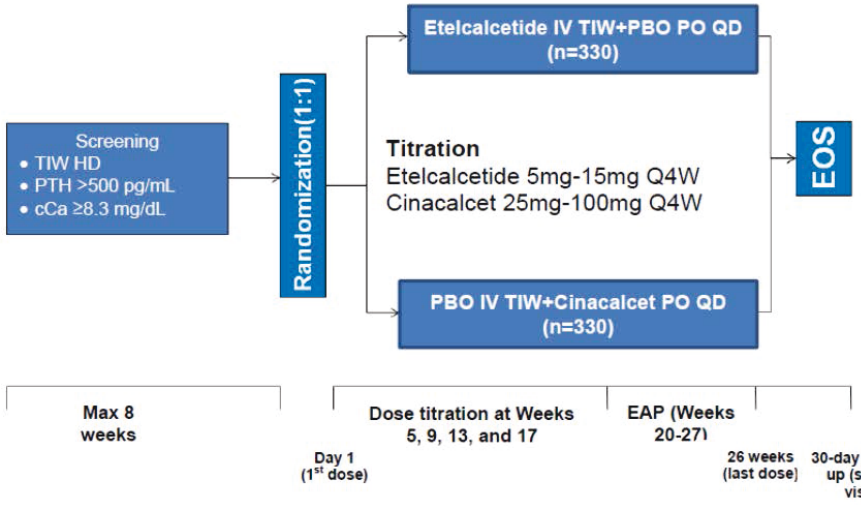
This is a phase 3, multicenter, randomized, active-controlled, double-blind, double-dummy, dose-titration, 26-week treatment period comparison of etelcalcetide and cinacalcet.

All subjects, regardless of treatment assignment, may receive standard of care as prescribed by the individual Investigator, with calcium supplements, phosphate binders, vitamin D sterols, and nutritional vitamin D supplements. If treatment with calcitriol or vitamin D analogs is ongoing when subjects are enrolled in the study, the doses of these agents should remain constant for the duration of study, unless treatment with vitamin D is initiated, interrupted, or adjusted for reasons of safety.

Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL), screening serum cCa (< 9.0 mg/dL, ≥ 9.0 mg/dL) measured by the central laboratory, and country (China and non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet.

The overall study design is described by a study schema in Figure 3-1.

**Figure 3-1 Study Schema**




cCa = corrected calcium, EAP = efficacy assessment phase, EOS = end of study, HD = hemodialysis, IV = intravenous, Max = maximum, PBO = placebo, PO = orally, PTH – parathyroid hormone, Q4W = every 4 weeks, QD = daily, TIW = three times/week

## 3.2 Sample Size

The planned sample size is 660 subjects (330 subjects per treatment arm).

The sample size calculations are based on the results of the global head-to-head study (20120360) and take into consideration sufficient power for both the primary and secondary endpoints. The non-inferiority margin is defined based on results from EVOLVE trial (Amgen Study 20050182), which was a randomized, placebo-controlled trial. Using a similar subject population in the EVOLVE trial as intended to be recruited in this study, rates of 25% and 60% in the placebo and cinacalcet arms, respectively, achieved > 30% reduction from baseline in iPTH at week 28 and the two-sided 95% CI

for the treatment difference based on the large sample normal approximation is (31%, 39%). Half of the lower limit of the CI for the treatment difference (compared to placebo) is 15.5%. Taking a conservative approach, the non-inferiority margin is defined as 12%.

Based on the global head-to-head study comparing etelcalcetide with cinacalcet (20120360), 58% of subjects randomized to cinacalcet and 68% of subjects randomized to etelcalcetide achieved a > 30% reduction from baseline in mean predialysis PTH during the EAP. Using this data, 300 subjects per treatment arm will provide over 99% power to demonstrate non-inferiority using a margin of 12% for the upper bound of the 95% 2-sided CI for the treatment difference between cinacalcet and etelcalcetide (cinacalcet - etelcalcetide).

For the key secondary endpoint of achievement of > 50% reduction from baseline in mean predialysis PTH during the EAP, 300 subjects per treatment group will provide approximately 84% power to detect a statistically significant difference between the treatment groups at the 5% significance level (two-sided), assuming a 52% and 40% response rate in subjects randomized to etelcalcetide and cinacalcet, respectively.

For the key secondary endpoint of achievement of > 30% reduction from baseline in mean predialysis PTH during the EAP (superiority analysis), 300 subjects per treatment group will provide about 72% power to detect a statistically significant difference between the treatment groups at the 5% significance level (two-sided), assuming a 68% and 58% response rate in subjects randomized to etelcalcetide and cinacalcet, respectively.

Considering the 10% dropout rate, the estimated sample size in each group is 330 subjects.

### 3.3 Adaptive Design

Adaptive design is not planned for this study. One of the goals of this study is to replicate a previously completed trial. Therefore, the study will continue to its expected completion without adaptive design elements.

## 4. Covariates and Subgroups

### 4.1 Planned Covariates

The planned covariates include the baseline stratification factors as well as other important baseline factors:

- Screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL)

- Screening serum cCa level (< 9.0 mg/dL, ≥ 9.0 mg/dL)
- Country (China and non-China)
- Dialysis vintage (0 -≤ 1 yr, > 1-≤ 5 yr, > 5 yr)
- Dialysate calcium (< 3.0 mEq/L vs. ≥ 3.0 mEq/L)
- Baseline vitamin D sterol use (yes/no)
- Baseline calcium containing phosphate binder or calcium supplement use (yes/no).
- Previous cinacalcet use (yes/no)
- Sex (male/female)
- Age (< 65 years, ≥ 65 years)

All of these covariates will be used in the Multiple Imputation Method to be implemented in sensitivity analyses of the key secondary endpoint of achievement of > 50% and > 30% reduction from baseline in mean predialysis serum PTH during EAP, respectively.

### 4.2 Subgroups

The secondary efficacy endpoints will be analyzed in the subgroups defined by baseline covariates listed in Section 4.1.

## 5. Definitions

### 5.1 Study Time Points

Informed Consent Date

The informed consent date for each subject is the date the subject signs the original informed consent for this study.

Screening Phase

The period after a subject has provided written informed consent and prior to randomization. This period may last up to 8 weeks and it is during this period when eligibility is determined, based on all screening tests and procedures.

Enrollment Date

The date a subject is randomized to a treatment group by the interactive voice/web response system (IXRS) after they have satisfied all enrollment criteria.

Randomization Date

The randomization date is the same as the enrollment date.

Study Week

The 7-day periods beginning with Study Day 1.

Study Day 1

The first day that investigational product is administered to the subject. For subjects who did not receive any investigational product during the study, Study Day 1 will be the randomization day.

Study Day

For each subject and for a given study visit date, study day is defined as the number of days since Study Day1:

Study day = (study visit date – Study Day 1 date) + 1

If the date of interest is prior to study day 1, study day will be calculated as

Study day = (study visit date – Study Day 1 date).

Efficacy Assessment Phase (EAP)

The period between Week 20 and Week 27, inclusive.

Date of Last Dose IP Received

For each subject, the last investigational product dose date is defined as the date when the last non-missing dose of investigational product is administered (zero dose is still counted).

Subject-level End of Study Date

End of study for each subject is defined as the date of the subject last study assessment in the study. The date subject ended the study is recorded on the End of Study electronic case report form (CRF).

Study-level End of Study Date

End of study for the study is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie. last subject last visit), following any additional parts in the study (ie, long-term follow-up) as applicable.

Follow-up

The 30-day period that occurs after a subject receives the last dose of investigational product during which safety information will be collected.

## 5.2 Demographics and Baseline Related Definitions

Age

Age is calculated as the subject's (floor) integer age in years at the enrollment date. If the date of birth is not available, collected age will be used in the analyses.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by baseline height in meters squared ($kg/m^2$).

Dialysis Vintage (years)

Dialysis vintage is defined as the duration in years from the dialysis start date (recorded on the end-stage renal disease (ESRD) history CRF) to the randomization date.

Baseline Values

Baseline values of PTH, cCa, and serum phosphorus are defined as the average of the last pre-dialysis assessment done during the screening period and the pre-dialysis assessment done on Study Day 1.

All other baseline laboratory values are using the last non-missing assessment taken prior to or on Study Day 1 (Study Day 1 assessment if available, otherwise the last screening assessment prior to Study Day 1).

Baseline vital sign and weight will be the last post-dialysis assessment values prior to or on Study Day 1.

The use of vitamin D, including nutritional vitamin D (vitamin D supplement) and vitamin D sterol (active vitamin D), is defined as use of vitamin D during the 7 days period prior to Study Day 1, inclusive.

The use of other concomitant medication of interest at baseline is defined as use of each concomitant medication on Study Day 1. This includes medication use that starts prior to Study Day 1 and ends on Study Day 1 or duration of use covers Study Day 1.

Change from Baseline

The arithmetic difference between a post-baseline value and baseline value for a given time point:

Change from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

For each subject, percent change from baseline in a given variable at a given time point is defined as:

100 x [(value at given time point – baseline value) / baseline value]

### 5.3 Other Study Related Definitions

Protocol Scheduled Visits

The clinical planned event (CPE) assigned in the clinical database will be used as protocol scheduled visits. If the value at a scheduled visit is missing, an unscheduled assessment can be used provided the unscheduled assessment occurs within the window for that study week, ie

ceiling (study day of the unscheduled visit / 7) = study week number

All missing scheduled assessments will be replaced using the above method, if possible, prior to deriving any study endpoints.

If the value at a scheduled visit is missing and multiple unscheduled assessments occurs within the window of this visit, or there are multiple values at a scheduled visit, then the first record will be used for the visit.

Mean Value of Efficacy Endpoints during the EAP

The mean of the scheduled (including the missing scheduled assessments replaced by unscheduled assessments as described above) pre-dialysis assessments taken during week 20 to week 27, inclusive.

Efficacy Endpoints Based on the Percent Changes

Percent change from baseline to the mean value during the EAP for the corresponding endpoint.

Corrected Total Serum Calcium (cCa)

Corrected calcium (mg/dL) = Total calcium (mg/dL) + (4 – albumin [g/dL]) x 0.8

Total serum calcium will be corrected using above formulae if the serum albumin is < 4 g/dL or 40 g/L, otherwise cCa equals total serum calcium.

Low Calcium Based on Corrected Calcium Values

cCa values measured by central laboratory will be used to identify cases of low calcium of different severities using the following three categories:
< 7.0 mg/dL, 7.0 - < 7.5 mg/dL, and 7.5 - < 8.3 mg/dL.

Exposure Period

For each subject who received at least one dose of IP, the number of weeks of IP exposure is calculated as:

Exposure period (weeks) = [(date of last dose received – date of first dose) + 1]/7

Compliance to Investigational Product (%)

Compliance = number of actual treatments taken / number of prescribed treatments *100

For the Intravenous (IV) treatment, the number of actual treatments taken is defined as the actual number of IV doses a subject received, and the number of prescribed treatments is defined as the number of IV doses prescribed.

For the oral treatment, the number of actual treatments taken is defined as the number of days that a subject took the oral dose, and the number of prescribed treatment is defined as the number of days that oral treatment was prescribed.

The treatment compliance calculation only considers the periods when a subject was supposed to receive IP and it will exclude the dose withholding periods due to protocol specified reasons on CRF.

Treatment Emergent Adverse Events (TEAE)

Adverse events (AEs) starting on or after the Study Day 1 as determined by the flag indicating if the adverse event started prior to the first dose of IP on the Adverse Events Summary CRF and up to 30 days after the last dose date. Serious adverse events (SAEs) starting on or after the Study Day 1 as determined by the flag indicating if the adverse event started prior to the first dose of IP on the Adverse Events Summary CRF and up to 30 days after the last dose date.

Adverse Event Subject Incidence

Defined as the number and percentage of subjects with a reported event(s). For subjects with multiple reports of the same event during the study, the subject will be counted only once. For adverse event tabulations involving severity, the highest severity of the particular adverse events will be used for each subject.

Adverse Events of Interest (EOI)

Adverse events of interest are defined by the most current standardized product-level event of interest list. Unless otherwise specified, the narrow search scope will be used for all EOIs.

Concomitant Medications of Interest

The selected medications of interest are: nutritional vitamin D (vitamin D supplement), vitamin D sterol (active vitamin D), calcium supplements, and phosphate binders, as identified in the concomitant medication CRFs.

## 6. Analysis Sets

### 6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects. Subjects will be analyzed according to the randomized treatment group assigned by the IXRS. Primary analysis for the primary and key secondary endpoints will be performed using the FAS.

### 6.2 Safety Analysis Set

The Safety Analysis Set consists of all randomized subjects who receive at least one dose of investigational product. Subjects will be analyzed by their randomized group unless an incorrect treatment was administered throughout the study, in which case the actual received treatment group will be used for analysis. Safety analyses will be performed using the Safety Analysis Set.

### 6.3 Per Protocol Set(s)

The Per Protocol Analysis Set (PPAS) is defined as all randomized subjects who have no major protocol violations (as defined below) and have at least one post-dose PTH value and had at least 16 weeks exposure of IP. Subjects with the following eligibility deviations will be excluded from the PPAS:

- Less than 18 years at screening
- Not receiving maintenance hemodialysis three times a week for at least 3 months
- Not meeting either calcium concentration or PTH eligibility criteria at screening
- Received cinacalcet within 3 months prior to screening or underwent a parathyroidectomy within 6 months prior to dosing
- Currently enrolling in another study or less than 30 days since ending another study
- Having known sensitivity to either cinacalcet or etelcalcetide

Moreover, subjects who have the following deviations during study period will also be excluded in this analysis set:

- Had parathyroidectomy or kidney transplant before EAP
- Received commercialized cinacalcet during the study
- Missed > 14 consecutive days of intravenous (IV) IP or oral IP, excluding the withholding of IP for protocol-specific reasons

For the subjects who undergo parathyroidectomy or kidney transplantation during EAP, only the PTH values before the surgery will be used.

Subjects in the PPAS will be analyzed according to randomized treatment assignment. PPAS will be used in the sensitivity analysis of the primary endpoint.

### 6.4 iPTH Completer Analysis Set

The iPTH Completer Analysis Set (PCAS) includes all randomized subjects with at least 1 predialysis iPTH value during the EAP. Subjects will be analyzed according to randomized treatment group.

### 6.5 cCa Completer Analysis Set

The cCa Completer Analysis Set (CCAS) includes all randomized subjects with at least one predialysis cCa value, measured by the central laboratory, during the EAP. Subjects will be analyzed according to randomized treatment group.

## 7. Planned Analyses

The planned analysis is described as below:

### 7.1 Interim Analysis and Early Stopping Guidelines

Interim analysis or early stopping rule are not planned for this study.

### 7.2 Primary Analysis

The primary analysis will be the same as final analysis.

### 7.3 Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

## 8. Data Screening and Acceptance

### 8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

### 8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

### 8.3 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point at a particular point in time. Sites will be queried for missing or non-conformant data that are required or considered critical. All efforts will be made to capture complete critical data prior to the database lock.

The following imputation rules will be implemented for critical data if the missing or incomplete data cannot be resolved after the query process:

Only missing or partially missing start dates for adverse events will be imputed with the exception of adverse events occurring prior to the first dose date. Stop dates for AEs will not be imputed. Adverse events with a partially missing start date that is conclusively prior to the date of first IP administered (as indicated by 'Did event start before first dose of IP' on the AE CRF page) will be considered pre-treatment adverse events and excluded from safety analyses. All other partially missing adverse event start dates will be handled as described below, with the reference date being Study Day 1:

- If the year is available and the day and month are missing, the day and month will be set to the 1st of January of the onset year
- If the year and month are available and the day is missing, the day will be set to the 1st of the onset month
- If the day and month are available and the year is missing, the year will be set to the year of the reference date
- If the year and day are available and the month is missing, the month will be set to January of the onset year
- If the resulting date is prior to the reference date, the date will be reset to the reference date (this applies to AE start date imputation only)

Partial/missing start dates for concomitant medications will be imputed using the algorithm above with the reference date being Study Day 1. Partial/missing stop dates for concomitant medications will be imputed using the following logic:

- If the medication stop date is completely missing, then the stop date is set as the end of the study date. Otherwise,

- If the stop year is available and stop month and day are missing, the month and day will be reset to 31st of December of the stop year
- If the stop year and month are available and the stop day is missing, the stop day will be set to the last day of the month of the stop year
- If the stop year and day are available and stop month is missing, the stop month will be set to December of the stop year
- If the stop month and day are available and stop year is missing, the stop year will be reset to the year of the start date
- If any of the resulting dates are prior to the start date, the stop date will be reset to the start date

If any of the resulting dates are after the end of study (EOS) date, the stop date will be reset to the EOS date. Handling of missing laboratory values is described in section 9.5.1 and 9.5.2.

### 8.4 Detection of Bias

This is a randomized, active-controlled, double-blind and double-dummy study. Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL), screening serum cCa (< 9.0 mg/dL, ≥ 9.0 mg/dL) measured by central laboratory, and country (China and non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet. Blinding and randomization minimize bias. It is not expected that any study conduct procedures or statistical analysis will incur bias in the study results or conclusions. The potential sources of bias in this study are:

a) Inadvertent breaking of the blind

Break of blind should be rare and anticipated only if it is necessary for safety and treatment reasons. Should this happen in more than 5% of the subjects in the study, a sensitivity analysis may be conducted for the primary endpoint by excluding those patients who were unblinded.

b) Withdrawal

If there is a differential dropout rate between the treatment groups over the course of the study, the sensitivity of the conclusions on the primary and secondary endpoints due to drop out will be explored.

c) Protocol deviations

A subject list of important protocol deviations will be finalized prior to the database lock and unblinding. The impact of protocol deviations on the study results will be investigated and a sensitivity analysis may be conducted if deemed necessary by

comparing the results of the primary endpoint analysis on subjects with and without protocol deviations.

Should any sensitivity analyses be required for potential bias in the study results and conclusions, the source and results of the sensitivity analyses will be documented in the CSR.

### 8.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with CDM to ensure accuracy. Extreme data points will be included in the analyses.

Pharmacokinetic (PK) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

### 8.6 Distributional Characteristics

The percent change endpoints will be analyzed using a repeated measures mixed effects model, which assumes that the data are normally distributed. The normality assumption will be assessed using the graphical methods such as the normal quantile-quantile plot (Q-Q plot) along with the Shapiro-Wilk test. If the normality assumption does not hold, data transformation will be considered.

### 8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4.

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

This is a phase 3 study to evaluate the efficacy of etelcalcetide as compared to cinacalcet. The primary objective is to determine if etelcalcetide is non-inferior to cinacalcet on achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP. Etelcalcetide will be considered non-inferior if the upper

bound of the two-sided 95% CI of the treatment difference (cinacalcet – etelcalcetide) is smaller than 12%. If this criterion is met, the 2 key secondary endpoints will be tested sequentially. The testing for the endpoint of achievement of a > 50% reduction from baseline in mean predialysis serum PTH during the EAP will be carried out first. Only if the result achieves statistical significance, the secondary endpoint of achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP will be tested. The other secondary endpoints will be formally tested for superiority if both key secondary endpoints are statistically significant. To control for the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used for testing of the other secondary endpoints. The primary analysis of all primary and secondary endpoints will be conducted on the FAS.

For the efficacy endpoints using laboratory measurements (predialysis PTH, cCa, and P), values based on averaging over the EAP will be used in the analyses where applicable.

Baseline values for PTH, cCa, and P will be based on the mean of the last screening value and the day 1 value.

For analyses performed on cCa and Ca, only central laboratory results will be used.

Descriptive statistics include number of observations (n), mean, standard deviation (SD) or standard error (SE), median, 1st (Q1) and 3rd (Q3) quartiles, minimum and maximum will be used to summarize continuous variables. The number and percent of subjects will be used to summarize the categorical variables.

### 9.2 Subject Accountability

The number (percentage) of subjects randomized, received IP, completed IP, and completed the study will be summarized by randomized treatment group based on the FAS. Reasons for study discontinuation and IP discontinuation will also be summarized separately by randomized treatment group.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of study, and last subject's end of IP will be presented.

### 9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined

in the protocol. A table and a list of eligibility deviations will be generated for the Full Analysis Set.

### 9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristic will be summarized by treatment group and overall using descriptive statistics based on the FAS.

Sex, age, weight, height, BMI, race, ethnicity, stratification factors, iPTH, corrected total serum calcium, serum phosphorous, cCa x P, vital signs, selected concomitant medications, and selected medical history (history of hemodialysis, parathyroidectomy history, ESRD history, cardiovascular/social/other history).

### 9.5 Efficacy Analyses

All analyses of efficacy endpoints will be performed according to their randomized treatment group. The analyses of primary efficacy endpoint and key secondary efficacy endpoint are summarized in the following table and subsequent sections.

**Table 9-1. Primary and Key Secondary Endpoints Summary Table**

| Endpoint | Primary Summary and Analysis Method | Sensitivity Analysis |
|---|---|---|
| Primary Endpoint | | |
| Achievement of a > 30% reduction from baseline in mean predialysis serum PTH level during the efficacy assessment phase (EAP) (non-inferiority) | Mantel-Haenszel (M-H) estimation method adjusting for the three randomization stratification factors to estimate 95% CI based on the FAS. Multiple imputation under the non-inferiority null method will be applied to the subjects who do not have data during the EAP. | 1. iPTH Completer Case analysis (PCAS): similar to primary analysis method but only subjects who meet the criteria for inclusion in the PCAS are included.<br>2. Last value carried forward (LVCF): similar to primary analysis but using LVCF to impute missing data during the EAP. For subjects without PTH data during the EAP, the mean of the last 2 pre-dialysis PTH values obtained after Study Day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. A similar imputation approach as the primary analysis (non-inferiority null method) will be applied to subjects without a post-baseline PTH value after applying LVCF approach.<br>3. Per Protocol: similar as primary analysis method but using PPAS. |

**Table 9-1. Primary and Key Secondary Endpoints Summary Table**

| Endpoint | Primary Summary and Analysis Method | Sensitivity Analysis |
|---|---|---|
| Key Secondary Endpoints | | |
| Achievement of a > 50% reduction from baseline in mean predialysis serum PTH during the EAP (superiority) | A Cochran-Mantel-Haenszel (CMH) test adjusting for the three randomization stratification factors based on FAS. Subjects will be considered as not achieving the endpoint if they do not have data during the EAP (non-responder imputation). | Multiple Imputation (MI): for subjects without PTH data during the EAP, the multiple imputation method using SAS® PROC MI will be used to impute the PTH value during EAP. Treatment group, stratification factors, baseline covariates (as detailed in Section 4.1) will be considered for inclusion in the model as auxiliary variables. Full Analysis Set will be used for the analysis. |
| Achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP (superiority) | A Cochran-Mantel-Haenszel (CMH) test adjusting for the three randomization stratification factors based on FAS. Subjects will be considered as not achieving the endpoint if they do not have data during the EAP (ie. non-responder imputation). | Multiple Imputation (MI): for subjects without PTH data during the EAP, the multiple imputation method using SAS® PROC MI will be used to impute the PTH value during EAP. Treatment group, stratification factors, baseline covariates (as detailed in Section 4.1) will be considered for inclusion in the model as auxiliary variables. Full Analysis Set will be used for the analysis. |

Page 2 of 2

### 9.5.1 Analyses of Primary Efficacy Endpoint(s)

The analysis of the primary efficacy endpoint is to assess if the treatment of SHPT with etelcalcetide is not inferior to treatment with cinacalcet as measured by the proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP. Etelcalcetide will be considered non-inferior to cinacalcet if the upper bound of the two-sided 95% confidence interval of the treatment difference (cinacalcet - etelcalcetide) is smaller than 12%.

#### 9.5.1.1 Primary Analysis

The primary endpoint will be analyzed using Mantel-Haenszel (M-H) estimation method [Agresti and Hartzel, 2000] stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL), screening serum cCa (< 9.0 mg/dL, ≥ 9.0 mg/dL) measured by the central laboratory, and country (China versus non-China) based on the FAS. The M-H estimator will be used to estimate the difference in the proportion of subjects who achieve the primary efficacy endpoint between two treatment groups and the standard error of the M-H estimator will also be estimated. The 95% two-sided confidence interval will be provided.

For the subjects who have at least one PTH value during EAP, the available data will be used to calculate the mean. For the subjects who have no PTH values during EAP, including subjects who discontinue the study, the missing primary endpoint will be imputed using non-inferiority null method [Koch, 2008]. The presumed response rate is 60% for the cinacalcet group. This response rate is based on the assumption that the cinacalcet group in study 20120360 resembles that studied in a previous cinacalcet clinical trial (Amgen EVOLVE trial 20050182) in which a response rate of 60% was observed for this endpoint in the cinacalcet arm. The response rate for the etelcalcetide group is assumed to be 12% lower than that of the cinacalcet group (ie, 48%), with 12% being the pre-specified non-inferiority margin [Koch, 2008]. The imputation will be performed 5 times. The combination of estimating result for the M-H estimator and its standard error from each imputed data set will follow the method used in SAS® PROC MIANALYZE.

#### 9.5.1.2 Sensitivity Analysis

The following sensitivity analyses will be conducted using the same M-H method as in primary analysis:

- PCAS: similar to primary analysis method but only subjects who meet the criteria for inclusion in the PCAS are included.
- LVCF: similar as primary analysis method but using LVCF to impute missing data during the EAP. For subjects without PTH data during the EAP, the mean of the last 2 pre-dialysis PTH values obtained after Study Day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. The same imputation strategy for primary analysis will be employed for subjects without a post baseline PTH value.
- PPAS: similar as primary analysis method but only the subjects who meet the criteria for inclusion in the PPAS are included.

### 9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Sequential testing of the following two key secondary efficacy endpoints will be performed in this order if non-inferiority is demonstrated on the primary endpoint.

- achievement of > 50% reduction in mean predialysis serum PTH during the EAP from baseline (superiority)
- achievement of > 30% reduction in mean predialysis serum PTH during the EAP from baseline (superiority)

#### 9.5.2.1 Primary Analysis

The endpoint of achievement of > 50% reduction in mean predialysis serum PTH during the EAP from baseline will be analyzed using the CMH test stratified by the randomization stratification factors and based on the FAS. The non-responder

imputation strategy will be used for subjects with no PTH value during the EAP. The endpoint of achievement of > 30% reduction in mean pre-dialysis serum PTH during the EAP from baseline for superiority will be analyzed similarly using CMH test with non-responder imputation strategy applied for subjects who have no PTH value during EAP. Subgroup analysis for both endpoints will be performed based on baseline covariates listed in section 4.1.

#### 9.5.2.2 Sensitivity Analysis

The sensitivity analysis for the key secondary endpoint of proportion of subjects who have achievement of > 50% reduction from baseline in mean pre-dialysis serum PTH during EAP will be performed based on the FAS. The multiple imputation method will be used to carry out the multiple imputation using SAS® PROC MI. The Fully Conditional Specification (FCS) method (SAS/STAT® 9.3 User's Guide) will be used to carry out the multiple imputation using SAS® PROC MI. PTH values from all post Study Day 1 scheduled visits will be included in the imputation model. The mean PTH value over the EAP is treated as a single time point. Treatment group, stratification factors, baseline covariates (as detailed in Section 4.1), will be considered for inclusion in the model as auxiliary variables. With FCS method, the missing PTH values are imputed sequentially in the order specified in the VAR statement (chronological order). Each imputed dataset will be analyzed using stratified CMH method. Final result of CMH estimate and odds ratio are based on combined inference from each of the imputed datasets.

The same sensitivity analyses will be repeated for the key secondary endpoint of proportion of subjects who have achievement of > 30% reduction from baseline in mean pre-dialysis serum PTH during EAP for superiority in the same manner with the same group of auxiliary variables when imputing the mean of PTH value over the EAP. Each imputed dataset will be analyzed using stratified CMH method. Final result of CMH estimate and odds ratio are based on combined inference from each of the imputed datasets.

The following other secondary endpoints will be evaluated for superiority if the above key secondary endpoints are considered statistically significant. To control the experiment-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used for the following:

- percent change from baseline in mean pre-dialysis measured by central laboratory serum cCa during the EAP
- achievement of mean pre-dialysis serum P ≤ 4.5 mg/dL during the EAP

A repeated measures mixed effects model will be used to compare treatment groups with respect to the percent change from baseline in serum cCa levels during the EAP, and will include the treatment group, randomization stratification factors, study week and study week by treatment as fixed effects. The difference of least square means between treatment groups will be presented with 95% CI. The FAS will be used for these analyses, and cCa completer set will be used for sensitivity analysis. Only central laboratory measured cCa will be used.

The secondary endpoint of proportion of subjects with mean pre-dialysis measured by central laboratory P ≤ 4.5 mg/dL during the EAP will be analyzed using the CMH test stratified by the randomization stratification factors. The difference between treatments will be estimated and presented with a 95% confidence interval. These analyses will be performed on the FAS using the non-responder method of imputation for those subjects without laboratory values during the EAP. The mean pre-dialysis P will be derived based on all central laboratory measured of P during EAP.

#### 9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

## 9.6 Safety Analyses

### 9.6.1 Analyses of Primary Safety Endpoint(s)

All analyses of safety endpoints will be performed using the Safety Analysis Set according to the actual treatment received.

### 9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version at the time of data base lock will be used to code all adverse events (AEs).

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order by treatment group.

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term by treatment group.

In addition, summaries of treatment-emergent and serious adverse events by preferred term will be provided in descending order of frequency in etelcalcetide arm.

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and severity by treatment group.

### 9.6.3 Laboratory Test Results

Laboratory values below the parameter-specific the lower limit of quantification (LLOQ) or above the parameter-specific upper limit of quantification (ULOQ) will be imputed as the LLOQ or ULOQ value, respectively.

In this section, cCa refers to cCa measured by central laboratory, Ca refers to Ca measured by central laboratory. All cCa and Ca results from local laboratory testing will be excluded from analysis.

Laboratory parameters including corrected calcium, PTH, P and Ca x P will be summarized by treatment group and the protocol-specified scheduled visit. Summaries of the absolute value change from baseline, and percent change from baseline will also be provided.

Shift tables will be provided for albumin, corrected calcium, potassium, phosphorus, magnesium, hemoglobin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL) by summarizing the most

extreme changes in toxicity grade from baseline (increase and/or decrease as appropriate) to any visit during the study while the subjects are receiving IP. The toxicity grading will be based on common terminology criteria for adverse events (CTCAE) version 4.0.

Number and percentage (with 95% confidence interval) of subjects with low calcium as defined by cCa < 7.0 mg/dL, < 7.5 mg/dL, < 8.0 mg/dL, < 8.3 mg/dL, 7.0 - < 7.5 mg/dL, and 7.5 - < 8.3 mg/dL during the study will be summarized by treatment group. Each subject's lowest corrected calcium value during the study (post-baseline) will be used in this analysis.

Number and percentage of subjects with 2 consecutively low corrected calcium, defined by 2 consecutive post-baseline corrected calcium < 7.5 mg/dL, < 8.0 mg/dL and < 8.3 mg/dL during the study will be summarized by treatment group.

A summary of potential Hy's law cases meeting lab criteria will be provided. Subject incidence meeting the following criteria will be provided at baseline and post-baseline:

ALT or AST > 3 x ULN and TBL ≥ 2 x ULN and ALP < 2 x ULN within ± 7 days

For subjects who meet the Hy's law lab criteria, information on their medical history and concomitant medication will be provided to further evaluate whether these are true Hy's law cases.

#### 9.6.4 Vital Signs

Vital signs will be summarized by treatment group at each protocol-specified time point.

#### 9.6.5 Physical Measurements

Physical measurements will be summarized by treatment group at each protocol-specified time point.

#### 9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

### 9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-etelcalcetide antibodies at any time, at baseline and post baseline will be tabulated for the etelcalcetide arm.

### 9.6.8 Exposure to Investigational Product

Descriptive statistics will be calculated to describe the exposure to IP for etelcacetide and cinacalcet separately.

Summary statistics will be provided for: number of days on IP, the minimum and maximum weekly dose, the cumulative total dose, average weekly dose during EAP, and the number and percentage of subjects receiving each dose level (5 mg, 10 mg, 15 mg etc for etelcalcetide and 25 mg, 50 mg, 75 mg, 100mg etc for cinacalcet) of IP at each visit during the study. Compliance to each IP will also be summarized.

### 9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving the following selected medications: nutritional vitamin D (vitamin D supplement), vitamin D sterol (active vitamin D), calcium supplements, and phosphate binder, will be summarized by treatment group at baseline and during the study.

Weekly dose of vitamin D sterol will be summarized by treatment group during the study. The dose will be presented as IV paricalcitol equivalent.

Summary of changes in dialysate calcium concentration over the course of the study will be provided.

## 9.7 Analyses of Pharmacokinetic Endpoints

Descriptive statistics for plasma etelcalcetide concentration at each visit collected will be summarized.

## 10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

## 11. Literature Citations / References

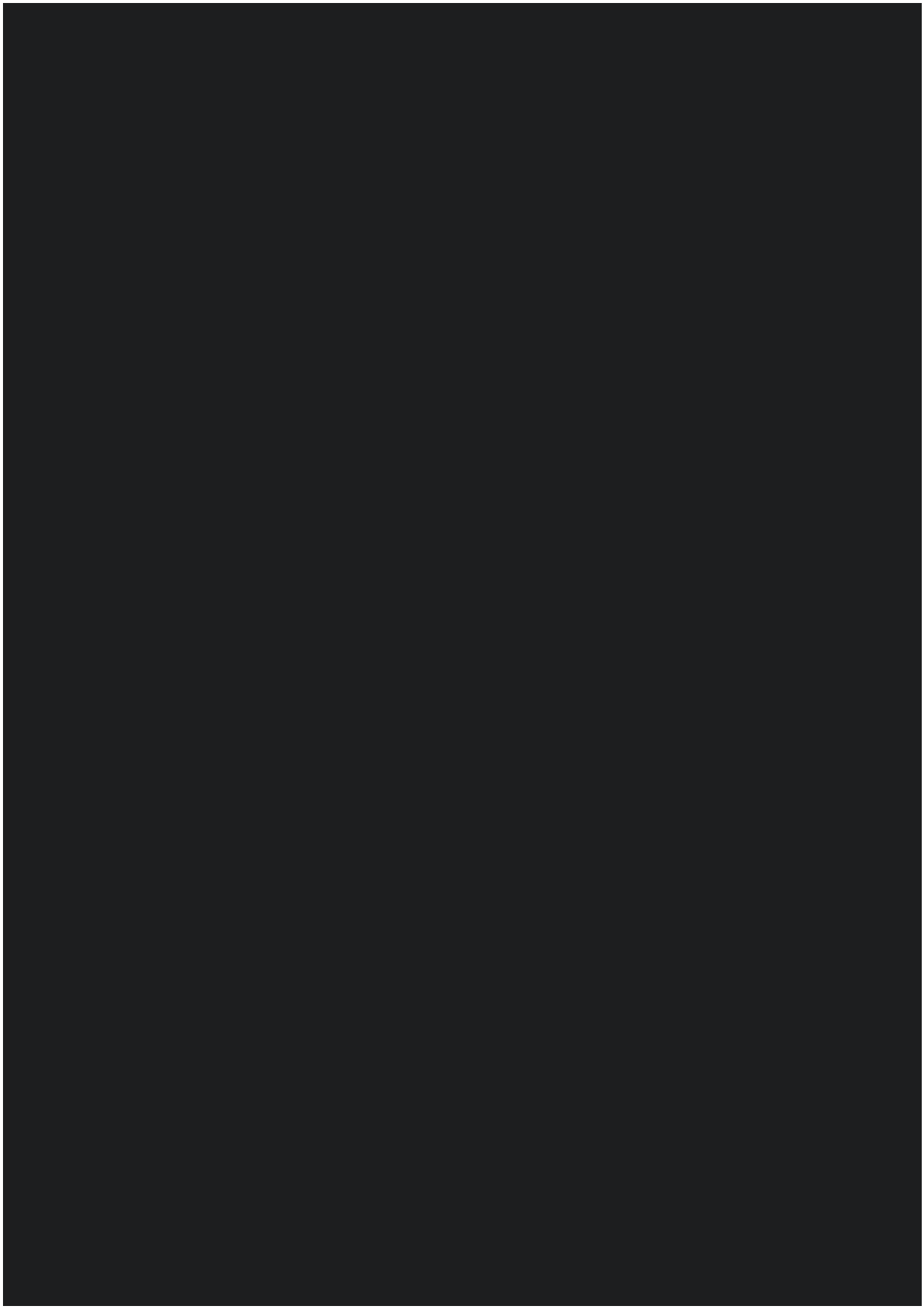
Agresti, A and Hartzel, J. (2000), Stratigies for comparing treatments on a binary response with multi-centre data. Statistics in Medicine, 19:1115-1139.

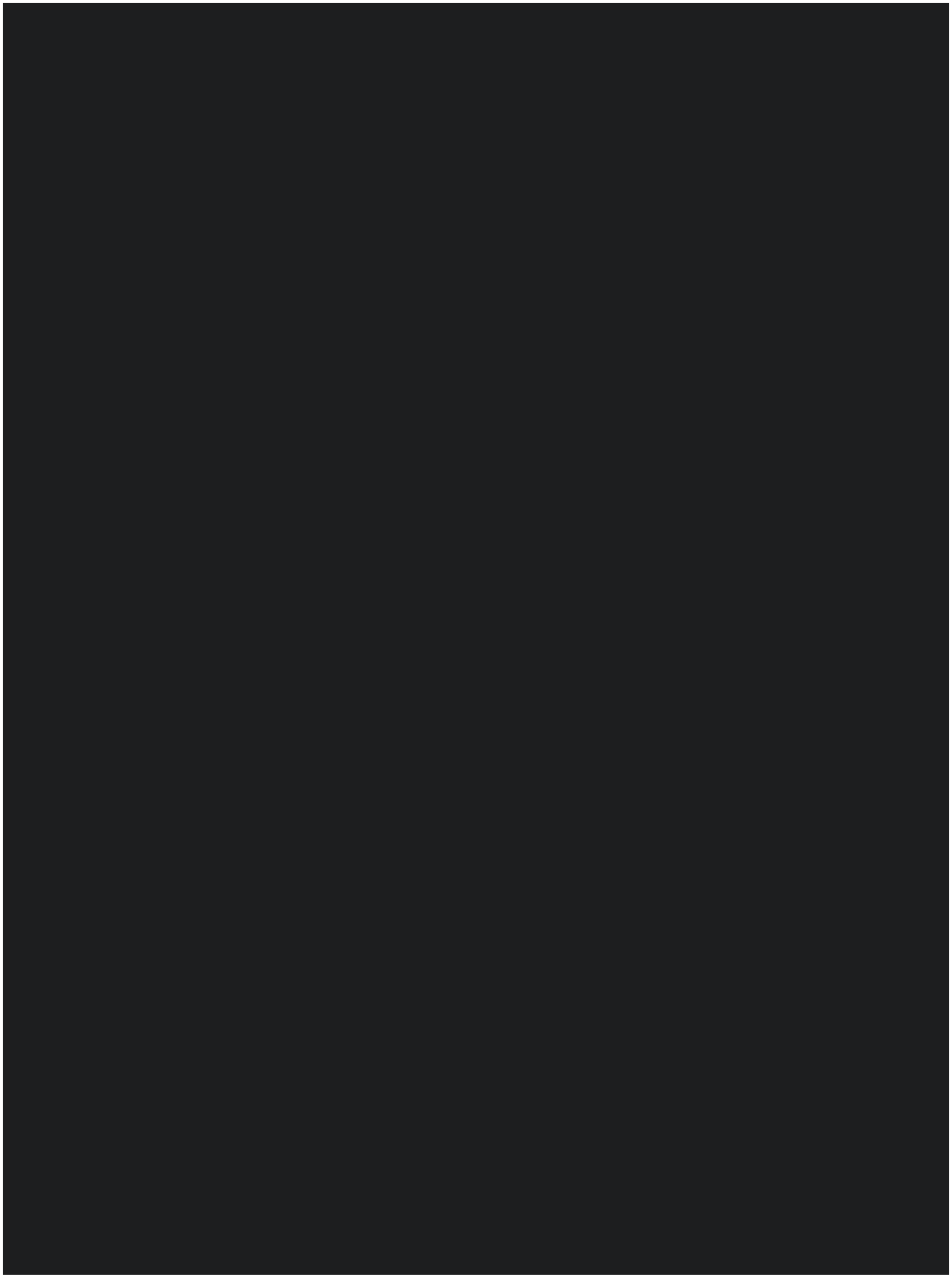
Koch, G.G., Comments on ‘current issues in non-inferiority trials’ by Thomas R. Fleming, Statistics in Medicine, 2008; 27, 333-342.

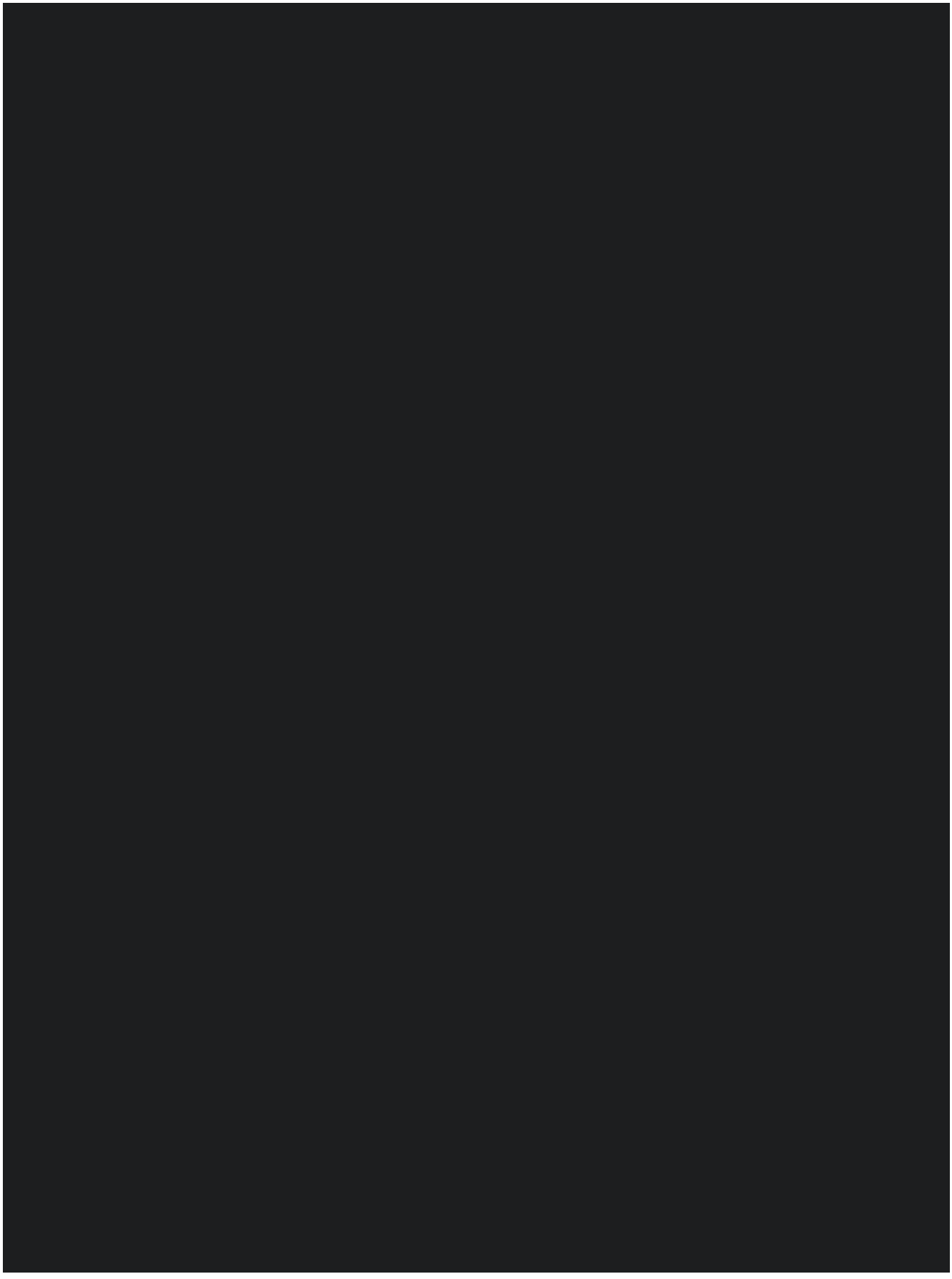
Little, R.J.A., and Rubin, D.B. (2002). Statistical Analysis with Missing Data, 2nd edition. New York: Wiley.

Shapiro, S. S. and Wilk, M. B. (1965), “An Analysis of Variance Test for Normality (Complete Samples),” Biometrika, 52, 591–611.

## 12. Appendices







## Appendix C. Reference Values/Toxicity Grades

For CTCAE grading system V4, please refer to:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf