Statistical Analysis Plan

Protocol Title:	A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects with Chronic Kidney Disease on Hemodialysis
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Authors:	[redacted]
Sponsor:	Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320-1799 Tel: 805-447-1000
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Table of Contents

List of Abbreviations

Abbreviation	Definition/Explanation
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable sample
BMI	Body Mass Index
Ca	Calcium
cCa	Total serum albumin corrected calcium concentration
cCa x P	Corrected calcium-phosphorus product
CI	Confidence Interval
C_{max}	Maximum observed concentration
CRF	Case report form (electronic or paper)
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiogram
EOS	End of Study
GM	Geometric mean
IP	investigational product
iPTH	Intact parathyroid hormone
IV	Intravenous
IVR/IWR	Interactive Voice/Web Response System
MedDRA	Medical dictionary for regulatory activities
P	Phosphorous
PK	Pharmacokinetic(s)
PTH	Parathyroid hormone
SAE	severe adverse event
SHPT	Secondary hyperparathyroidism
TEAE	Treatment Emergent Adverse Events
$T_{1/2}$	Terminal elimination phase half life
TIW	Thrice weekly

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 20140197, Etelcalcetide (AMG 416) dated **25 May 2018**. The scope of this plan includes the primary analysis that is 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 characterize the pharmacokinetics of AMG 416 (etelcalcetide) following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis	• Pharmacokinetic (PK) parameters of etelcalcetide in plasma including maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{last}) over the interdialytic interval following the first and last dose
Secondary	
• To characterize the safety and tolerability of etelcalcetide following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis	• Incidence of adverse events
	• Vital signs, laboratory safety tests including cCa, and ECGs
	• Incidence of anti-etelcalcetide antibodies
Exploratory	
[redacted]	

2.2 Hypotheses and/or Estimations

This study will adequately characterize the pharmacokinetics profile of etelcalcetide in Chinese subjects with chronic kidney disease receiving hemodialysis.

Etelcalcetide will be safe and well tolerated after multiple dose administration in Chinese subjects with chronic kidney disease on hemodialysis.

3. Study Overview

3.1 Study Design

This is a multiple dose, double-blind, randomized, placebo-controlled clinical study. Chinese subjects residing in Mainland China with chronic kidney disease receiving hemodialysis will be randomized in a 3:1 ratio to receive 5 mg IV of etelcalcetide or placebo thrice weekly (TIW) for approximately 4 weeks, with a subsequent follow up period of approximately 4 weeks.

3.2 Sample Size

Approximately 32 subjects will be randomized in a 3:1 ratio to receive 5 mg IV of etelcalcetide or placebo three times a week (TIW) at the end of each regularly scheduled hemodialysis session for 4 weeks (12 doses).

For PK parameter estimation, 2-sided 90% confidence intervals (CI) for geometric means (GM) of PK measurements can be expressed as (GM/θ, GM·θ) where θ is a measure of precision. Based on etelcalcetide study 20120330 (Cohort 3, 5 mg dose), between-subject CV for etelcalcetide AUC_{last} (hr· μg/L) and C_{max} (μg/L) (on original scale) are approximately 50.5% and 52.7%, respectively, following the Day 27 dose. Assuming the same variability for 24 subjects receiving etelcalcetide in this study, it is estimated that the precision (θ) of 2-sided 90% CI of geometric mean will be 1.18 and 1.19 for AUC_{last} and C_{max}, respectively.

For safety considerations, with 24 subjects receiving etelcalcetide, there will be a 21% chance of detecting an adverse event with a true incidence rate of 1% and 98% chance of detecting a more common adverse event with a true incidence rate of 15%.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

No covariate adjusted analyses are planned.

4.2 Subgroups

No subgroup analyses are planned.

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 22 days 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).

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).

Primary Completion

The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis.

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 following any additional parts in the study (ie, safety follow-up) as applicable.

5.2 PK/PD Parameters

AUC_{last}

AUC_{last} is specifically defined in this study as the area under the concentration time curve **measured from the time of** drug administration to the beginning of the **next dialysis session**, following the first and last dose.

C_{max}

C_{max} is defined as the maximum observed **plasma** drug concentration **measured between the time of drug administration to the beginning of the next dialysis session**.

5.3 Demographics and Baseline Related Definitions

Age

Age will be collected as the subject's age in years at enrollment as recorded on the eCRF.

Body Mass Index (BMI)

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

Baseline

Unless otherwise specified, for parameters/assessments scheduled to be performed on the same day as the first administration of the investigational product, the baseline value is the last value measured before the first administration of the investigational product on that day.

For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of the investigational product, the baseline value is the value from the screening period measured closest to the day of first administration of the investigational product.

In the event that multiple pre-dose assessments are done on the same day as the first administration of the investigational product and there is no time associated with the assessments, the value associated with the last clinically planned event (CPE) will be used as the baseline value.

Baseline iPTH, serum albumin and cCa is the average of predialysis assessments on day -2 and Day 1. **If screening lab tests occur within 7 days prior to start of IP, then day -2 lab tests can be waived. Then baseline iPTH, serum albumin and cCa is the average of predialysis assessments at screening and day 1.**

Change from Baseline

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

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

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

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

5.4 Other Study Related Definitions

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 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.

Treatment Emergent Adverse Events (TEAE)

Adverse events (AEs) starting on or after the first dose of IP 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 or EOS date, whichever is **earlier**.

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 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who received at least one dose of investigational product.

6.2 PK Concentration Analysis Set

The PK Concentration Analysis Set will contain all subjects who received at least one dose of etelcalcetide and have at least one PK sample collected.

6.3 PK Parameter Analysis Set

The PK Parameter Analysis Set will contain all subjects who received at least one dose of etelcalcetide and for whom at least one PK parameter can be adequately estimated.

6.4 Intent-to-treat Analysis Set

The Intent-to-treat Analysis Set (ITT) includes all subjects randomized. Subjects will be analyzed by randomized treatment. ITT Analysis Set will be used for study disposition summary.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim analysis is planned.

7.2 Primary Analysis

The primary analysis for this study will occur when all subjects have completed all planned study procedures up to and including the EOS visit, as outlined in the Schedule of Assessments, and any follow up of a clinically significant clinical or laboratory abnormality and following database lock.

7.3 Final Analysis

Not applicable.

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.

Details of PK, antibody and external lab data transfers to the database are provided in the corresponding study data transfer plans.

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 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 of interest will be imputed using the algorithm above with the reference date being Study Day 1. Partial/missing stop dates for these 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
- 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

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

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

8.6 Distributional Characteristics

There are no distributional requirements for the planned analyses. Therefore no assessment will be made.

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, figures, 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 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Demographics, baseline characteristics, and safety data will be summarized by treatment groups. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety Analysis Set. Descriptive statistics on continuous measurements will include mean, median, standard deviation, and range, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. Descriptive

summaries will be provided to characterize all primary and secondary endpoints in this study.

9.2 Subject Accountability

The number and percent of subjects who received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, or discontinued the study (including reasons for discontinuing) will be summarized. The number of subjects included in and excluded from each analysis set will be summarized. Key study dates for the first subject enrolled, last subject enrolled and last subject's EOS 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.

9.4 Demographic and Baseline Characteristics

Demographics data including sex, age, race, ethnicity and BMI will be summarized for each treatment using descriptive statistics. The same analysis will be performed for baseline characteristics and medical history.

9.5 Pharmacokinetic Endpoints

Plasma concentrations of etelcalcetide will be determined using a validated assay from PK Concentration Analysis Set. Individual and mean plasma concentration-time plots for etelcalcetide will be presented.

The PK parameters (ie, C_{max}, AUC_{last}) will be estimated using noncompartmental methods. Nominal dose and actual sampling time data will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter. Due to the effect of hemodialysis on the plasma concentration of etelcalcetide, AUC_{last} is specifically defined in this study, as the area under the concentration-time curve during the time interval between dose administration and the beginning of the subsequent hemodialysis treatment.

The PK Parameter analysis set will be used in the analyses for the primary endpoint.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 or later.

Subject incidence of all treatment-emergent adverse events, will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product and treatment-emergent hypocalcemia (depending on number of subject incidences) and event of interest (EOI) will be provided. Besides, subject incidence of AEs will also be summarized for all treatment-related AEs, treatment-related serious AEs, treatment-related fatal AEs and treatment-related AEs leading to withdrawal of IP**.**

9.6.2 Clinical Laboratory Test Results

Serum albumin, iPTH, cCa and phosphorus measurements will be summarized by treatment group for all scheduled visits. Change and percent change from baseline may also be summarized for all post-baseline scheduled visits by treatment group, as applicable.

9.6.3 Vital Signs

Vital signs will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital sign data by treatment group at each protocol-specified time point may be provided.

9.6.4 Physical Measurements

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

9.6.5 Electrocardiogram

The ECG measurements from this clinical study are to be performed per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned.

Subject level listing will be provided for all on-study ECG measurements.

9.6.6 Anti-drug Antibodies

The incidence and percentage of subjects who develop anti-etelcalcetide antibodies (binding) at any time will be tabulated.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be calculated to describe the exposure to investigational product by treatment group. A listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

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 the treatment period, and the number and percentage of subjects receiving each dose level (0mg, 5 mg or missing for etelcalcetide) of IP at each visit during the study.

9.6.8 Exposure to Other Protocol-specified Treatment

N/A

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.

9.7 Exploratory Endpoints

[redacted]

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Not applicable.

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

14. Appendices

Appendix A. Reference Values/Toxicity Grades

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 4.0, published: May 28, 2009 (v4.03: June 14, 2010) for AE and lab shift grading and information. The CTCAE is available at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html