STATISTICAL ANALYSIS PLAN

An Open-label, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Etelcalcetide (AMG 416) in Paediatric Subjects Aged 2 to Less Than 18 Years With Secondary Hyperparathyroidism (sHPT) Receiving Maintenance Haemodialysis

Protocol Number: **20140336**

Version: **1.0**

Date: **09 June 2016**

Authors: **Biostatistics:**
PPD

Clinical Pharmacology, Modeling and Simulation:
PPD

NCT Number: 2833857
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Table of Contents

List of Appendices

Table of Abbreviations

Abbreviation/Acronym	Definition
ADPC	Analysis Dataset for Pharmacokinetic Concentrations
AE	Adverse Event
AUC	Area under the plasma etelcalcetide concentration-time curve
BMI	Body Mass Index
cCa	Albumin corrected Calcium
cCalcium	Albumin corrected Calcium
C_{max}	Maximum plasma etelcalcetide concentration
CPMS	Clinical Pharmacology and Medical Sciences
CRF	Case Report Form
CRSM	Amgen Clinical Research Study Manager
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
ECG	Electrocardiogram
EOI	Events of Interest
EOS	End of Study
GSO	Amgen Global Safety Officer
GSO-DM	Amgen Global Study Operations-Data Management
ICH	The International Council on Harmonisation
IP	Investigational Product
IPD	Important Protocol Deviations
iPTH	Intact parathyroid hormone
IV	Intravenous
MedDRA	The Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PTH	Parathyroid hormone
QTcB	Corrected (Bazett) QT Interval
QTcF	Corrected (Fridericia) QT Interval
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error

Abbreviation/Acronym	Definition
sHPT	Secondary hyperparathyroidism
$t_{1/2}$	Half-life of plasma etelcalcetide concentration
TEAE	Treatment Emergent Adverse Events
t_{max}	Time of Maximum plasma etelcalcetide concentration
WHO	World Health Organisation

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 20140336, dated 14 March 2016. The scope of this plan includes the primary analysis that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

Primary Objective:

To evaluate the safety and tolerability of etelcalcetide after single dose administration to paediatric subjects aged 2 to less than 18 years with secondary hyperparathyroidism (sHPT) receiving maintenance haemodialysis.

Secondary Objective:

To evaluate the pharmacokinetic profile of plasma etelcalcetide, serum PTH and serum calcium (total calcium, ionized calcium and albumin corrected calcium) levels following single intravenous (IV) administration of etelcalcetide.

3. Study Overview

3.1 Study Design

This is a single arm, open-label, single-dose safety, pharmacokinetic (PK) and pharmacodynamic (PD) study in paediatric subjects with sHPT receiving maintenance haemodialysis. The study considers haemodiafitration and haemodialysis procedures interchangeable. Subjects will receive a single IV administration of 0.035 mg/kg etelcalcetide at the end of haemodialysis. Intensive PK and PD samples will be collected on Day 1 at 10 min and 4 hours after etelcalcetide administration and for 10 days post dose with a safety follow-up period up to 30 days post dose.

Plasma etelcalcetide concentrations will be measured using a validated HPLC assay. Serum intact PTH (iPTH) and serum calcium levels will be measured in a clinical lab. Tolerability will be assessed and the descriptive statistics of PK/PD parameters will be summarized.

3.2 Sample Size

At least 10 children and adolescents (male and female) with ages ranging from 2 to less than 18 years with sHPT receiving maintenance haemodialysis will be enrolled. The sample size is based on practical consideration. No formal sample size calculations have been performed.

At least 5 subjects should be age 2 to less than 12 years old and at least 5 subjects should be age 12 to less than 18 years old. These cohorts are consistent with the age categories defined by ICH guidelines for studying paediatric patients.

Subjects will be enrolled in cohorts according to their age at screening:

- Cohort 1 → At least 5 subjects age 12 to <18 years
- Cohort 2 → At least 5 subjects age 2 to < 12 years

After 2 subjects in Cohort 1 complete the end of study visit, cumulative data will be reviewed prior to enrollment in Cohort 2.

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoints:

- Common treatment-emergent adverse events [including changes in physical examinations]
- Changes in key laboratory safety tests [albumin corrected calcium (cCalcium), phosphorus, potassium, parathyroid hormone (PTH)], ECGs and vital signs

Secondary Endpoints:

- Pharmacokinetic parameters (AUC, Cmax, tmax, t1/2) of etelcalcetide in plasma
- Pharmacodynamics: concentration of parathyroid hormone (PTH), serum calcium [total calcium, ionized calcium and albumin corrected calcium] over time
- Anti-etelcalcetide antibodies
- Incidence of treatment-emergent adverse events

4.2 Planned Covariates

Not applicable.

5. Hypotheses and/or Estimations

No hypothesis will be tested for this study. All analyses are descriptive.

6. Definitions

Albumin Corrected Calcium

The albumin corrected calcium will be calculated as

cCa (mg/dL) = total Calcium (mg/dL) + (4 – albumin (g/dL))*0.8

Adverse Event (AE)

Treatment-Emergent AE (TEAE):

A treatment-emergent adverse event is any adverse event that begins or worsens after the initial dose of investigational product (IP) and up to 30 days after the last IP administration. The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA version 18.1 or higher.

Adverse Events of Interest (EOI):

Adverse Events of Interest are: convulsions, hypersensitivity, hypocalcemia, hypophosphatemia, infusion reaction, Torsade de pointes-QT prolongation and ventricular tachyarrhythmias . Unless otherwise specified, the narrow search scope will be used for all EOIs.

Common Treatment-Emergent AE:

Common treatment-emergent adverse events include those with occurrence in 2 or more subjects.

Serious Adverse Event:

Refer to Section 9.1.2 of the protocol for the definition of serious adverse event.

Treatment-Related AE:

A treatment-related AE is any treatment-emergent AE that per investigator's review has a reasonable possibility of being caused by the investigational product.

Baseline

For any variable, unless otherwise defined, baseline is the last assessment taken prior to the first investigational product administration.

Baseline iPTH, cCa, total calcium, ionized calcium are defined as the average of screening and Day -2 assessments. If not all the values are available, the average will be calculated based on available value(s).

Baseline pre-dialysis ECG parameters including PR, QRS, QT, QTcB and QTcF are defined as the average of last non-missing pre-dialysis screening assessment and Study Day -2 pre-dialysis assessment.

The use of 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 the baseline value:

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Percent change from Baseline

Percent Change from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Body Mass Index (BMI)

BMI will be calculated as weight (kg)/ [height (m)]^2 in the clinical database.

Corrected (Bazett) QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec) ($QTcB=QT/(RR/1000)^{0.50}$).

Corrected (Fridericia) QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec) ($QTcF=QT/(RR/1000)^{0.33}$).

End-of-Study

The EOS is the last planned clinical visit for each subject enrolled in this study. The last planned visit day for subjects in cohort 1 and 2 is on Study Day 30.

Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last participated in the study. The date will be recorded on the End of Study CRF page.

Enrollment

A subject will be considered enrolled when the Investigator decides that the subject has met all eligibility criteria. Enrollment Date is defined as the date collected on the CRF.

Investigational Product

The term investigational product is used in reference to etelcalcetide.

Screening Date

Screening date is defined as the date of screening assessment.

Study Day 1

Day 1 is defined as the day that investigational product is administered to the subject.

Study Day

Post day of dose: study day= (study date - date of study Day 1) +1

Pre day of dose: study day= (study date – date of study Day 1)

The day prior to the first investigational product dosing is Day -1 while the day of the first investigational product dose is Day 1.

Concomitant Medications of Interest

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

7. Analysis Subsets

7.1 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least 1 dose of investigational product.

7.2 Pharmacokinetic (PK) Concentration Analysis Set

The pharmacokinetic (PK) concentration analysis set will contain all subjects who received investigational product and have at least one PK sample collected.

7.3 Subgroup Analyses

No subgroup analysis is planned.

8. Interim Analysis and Early Stopping Guidelines

No formal interim analysis is planned.

After 2 subjects in Cohort 1 complete the end of study visit, cumulative data will be reviewed prior to enrollment in Cohort 2 by a team composed of the Investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designee and additional members as needed (eg, Amgen Clinical Research Study Manager (CRSM), Biostatistician, PK Scientist, etc.). The voting members include the Principal Investigator or designee, Amgen Medical Monitor, and Amgen Global Safety Officer or designee. All available study data, including demographics, IP administration, medical history,

concomitant medications, adverse events, ECGs, vital signs, laboratory and PK results will be reviewed. Data review will not require that all queries be resolved or source verified. Cohort 2 will open for enrollment when the dose has been found to be reasonably tolerated based on available study data for at least 2 subjects enrolled in Cohort 1 and upon unanimous decision by the review committee. Based on emerging safety and PK data, the review committee may make other decisions (eg,. lower the dose level, enroll additional subjects in Cohort 1, etc.).

9. Data Screening and Acceptance

9.1 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.

9.2 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 data base are provided in the corresponding study data transfer plans. See details in the Data Management Plan (DMP).

An Analysis Dataset for PK Concentrations (ADPC) will be provided to Clinical Pharmacology, Modeling and Simulation (CPMS) from Biostatistics.

9.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required:

- Incomplete or missing adverse event and concomitant medication dates will be imputed as described in Appendix B. If imputed dates are used, then they will be identified as such in the final study report.
- PK concentrations below the lower limit of quantification will be omitted from PK parameter estimates.

9.4 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.

9.5 Outliers

All confirmed outlier data will be included in the analyses presented in this statistical analysis plan.

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 CPMS practice. All excluded observations will be detailed by CPMS along with reasons for exclusion, in accordance with standard CPMS practices.

9.6 Distributional Characteristics

Not applicable.

9.7 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 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

Descriptive statistics will be provided for selected demographics, safety, PK, and PD data. Descriptive statistics on continuous measurements will include means, medians, standard deviations (SD), standard errors (SE), first and third quartiles and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be summarized using the safety analysis set, unless otherwise specified, by cohorts.

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all post-baseline assessments, including unscheduled assessments will be used.

10.2 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 by cohort and overall. A table and a subject listing noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting reason for discontinuation of treatment and reason for discontinuing the study will be provided.

10.3 Important Protocol Deviations

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

The final IPD list will be used to produce the Summary of IPDs table and the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, sex, race and ethnicity), medical history, and baseline characteristics (ie, height, weight and BMI) will be summarized by cohorts and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

A listing of the demographic and baseline characteristics will be provided. Listings of medical history will be provided.

10.5 Primary Endpoints

10.5.1 Common Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. Determination of the severity of all adverse events (AE) will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless specified otherwise.

Subject incidence of all common treatment-emergent adverse events will be tabulated by system organ class and preferred term by cohort and overall.

10.5.2 Laboratory Test Results

Hematology and chemistry data will be listed and reviewed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings. In addition, subject incidence of low corrected calcium (<7.0 mg/dL, <7.5 mg/dL, <8.0 mg/dL and <8.3 mg/dL) post-baseline will be provided. Summaries of key laboratory values [albumin corrected calcium (cCalcium), phosphorus, potassium, parathyroid hormone (PTH)] over time and changes from baseline over time will also be provided at each time point when samples are collected.

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:

1) ALT or AST > 3 x ULN

2) Total bilirubin (TBL) > 2 x ULN

3) ALT or AST > 3 x ULN and TBL > 2 x ULN

4) ALT or AST > 3 x ULN and TBL > 2 x ULN and ALP < 2 x ULN

For post-baseline, if more than one value exist for a lab measure, the highest value will be used for these evaluations.

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.

10.5.3 Vital Signs

Vital signs will be listed and reviewed for each subject. Summaries of heart rate, termperature and blood pressure data over time and change from baseline will be provided.

10.5.4 Electrocardiogram (ECG)

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters including PR, QRS, QT, QTcF and QTcB.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcF and QTcB. Unscheduled assessments will be included in the determination of the maximum change.

- <=30 msec
- >30 – 60 msec
- >60 msec

The number and percentage of subjects in each group will be summarized.

Subjects will also be categorized into the following groups per their maximum post-baseline QTcF and QTcB. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- <=450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

The number of subjects in each group will be summarized for each cohort. All on-study ECG data will be listed.

10.6 Secondary Endpoints

10.6.1 Antibody Formation

Binding antibody formation will be assessed at pre-dose and at EOS. Antibody data will be summarized and listed for each subject.

10.6.2 Pharmacokinetic Parameters

The PK concentration analysis set will be used for the analysis of the PK endpoints. Biostatistics will provide the ADPC dataset to CPMS for PK analyses. All PK analyses specified in this section will be performed by CPMS.

Individual plasma concentration-time plots for etelcalcetide will be presented graphically for each subject as well as mean (SE) concentration-time plots for each cohort. PK parameters will be estimated using non-compartmental analysis (NCA) using Phonenix WinNonlin Software (Certara, Princeton, NJ). Actual dosing and sampling times will be used for calculation of PK parameters. Descriptive statistics will be generated for each PK parameter if data allows.

10.6.3 Pharmacodynamic Parameters

For concentrations of serum iPTH and serum calcium (total calcium, albumin corrected calcium, and ionized calcium) over time, the absolute value and percent change from baseline at each post-baseline time point will be summarized by cohort and overall. Individual and mean (SE) of the absolute value, change from baseline and percent change from baseline at each post-baseline time point will be plotted. A combined plot with plasma concentration for etelcalcetide and iPTH concentration over time may be provided.

10.6.4 Subject Incidence of TEAE

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs related to investigational product, and fatal AE.

The number and percentage of subjects will be tabulated by system organ class (SOC) and preferred term (PT). The TEAEs will also be presented by worst CTCAE grade. This also includes summary of subject incidence of TEAEs with grade ≥3 or ≥4 overall and by SOC and PT. Subject incidence of EOIs will be summarized according to the EOI

search strategy categories defined by the EOI steering committee unless otherwise specified (see below).

- Torsade de pointes-QT prolongation [Standard MedDRA Query (SMQ)]
- Ventricular tachyarrhythmias [SMQ])
- Convulsions (SMQ)
- Hypersensitivity (SMQ)
- Hypocalcemia (EOI)
- Hypophosphatemia (EOI)
- Infusion reaction (EOI) : only include events with onset day coincide with IP infusion and resolved on the same day or the day after onset.

All adverse event tables will be summarized by cohort and overall. Details of each adverse event will be listed.

10.7 Other Safety Endpoints

10.7.1 Exposure to Investigational Product

Subject listing of manufacturing lot numbers and a separate listing of unique manufacturing lot numbers used in this study will be provided. Details for each etelcalcetide administration will be listed for every subject.

10.7.2 Exposure to Concomitant Medication

All medications will be coded using the World Health Organisation Drug (WHO DRUG) dictionary. A subject listing of concomitant medications during the study will be presented.

The count and percentage 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 cohort and overall at baseline and during the study.

The number and proportion of subjects with each dialysate calcium concentration at baseline will be summarized. Summary of changes in dialysate calcium concentration during the study will be provided if data allows.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

12. Literature Citations / References

Not applicable.

13. Appendices

Appendix A. Reference Values / Toxicity Grades

For CTCAE grading system V4.0, please refer to:

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

Appendix B. Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, impute it with EOS date. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Dates

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		**<1st Dose**	**≥1st Dose**	**<1st Dose yyyymm**	**≥1st Dose yyyymm**	**<1st Dose yyyy**	**≥1st Dose yyyy**	**Missing**
Partial: yyyymm	**=1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**=1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.
Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.