16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

A Multicenter Single-arm Extension Study to Characterize the Long-term Safety of Cinacalcet Hydrochloride in the Treatment of Secondary Hyperparathyroidism in Pediatric Subjects With Chronic Kidney Disease on Dialysis

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Table of Abbreviations

Refer to Study Glossary in the protocol. Additional abbreviations are below:

Abbreviation/Acronym	Definition
25(OH)D	25-hydroxyvitamin D
CDM	Clinical Data Management
CSR	Clinical Study Report
EOI	Events of Interest
IV	Intravenous
QTcB	Corrected QT using Bazett's formula
SAP	Statistical Analysis Plan
IPW	**Inverse Probability Weighting**

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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 amendment **3** for cinacalcet Study 20140159 dated **16 March 2016**. The scope of this plan includes the **planned interim and** final **analyses** that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To characterize the long-term safety and tolerability of cinacalcet in pediatric subjects with chronic kidney disease (CKD) receiving dialysis.

2.2 Secondary

To characterize the long-term effect of cinacalcet in pediatric subjects receiving dialysis on laboratory parameters associated with chronic kidney disease – mineral and bone disease (CKD-MBD)

2.3 Exploratory

To characterize the long-term effect of cinacalcet in pediatric subjects on linear and pubertal growth.

3. Study Overview

3.1 Study Design

This is a phase 3, 32-week, multicenter, single-arm, extension study designed to characterize the long-term safety and tolerability of cinacalcet in pediatric subjects. **Subjects will remain on cinacalcet treatment for 28 weeks after enrollment from parent studies 20110100 or 20130356, or until the time of renal transplant or parathyroidectomy, whichever occurs first. The treatment period is followed by a 4-week safety follow-up period.**

The overall study design is described by a study schema at the end of the protocol synopsis section.

3.1.1 Subjects From Study 20130356

The screening period for Study 20140159 begins when the informed consent, and assent if applicable, is signed and concludes when the subject is either enrolled into the trial or screen failed. The informed consent can be signed up to 7 days (± 3 days) prior to Study 20140159 day 1. Eligible subjects who reach Study 20130356 termination or complete the 20-week treatment period in

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study 20130356, will either continue, restart, or start cinacalcet treatment in this study, depending on their cinacalcet treatment status at the time of enrollment. Eligible subjects will begin procedures in Study 20140159 at the Study 20130356 end of investigational product (EOIP) study visit, and will therefore not complete the safety follow-up period in Study 20130356; ie, the EOIP visit in Study 20130356 and Study Day 1 in Study 20140159 will be the same visit unless there is an administrative delay. Eligible subjects will complete **Study** Day 1 **of Study 20140159** assessments and confirm eligibility in IVR system prior to dispensing IP on **study** day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm in Study 20130356 will begin cinacalcet treatment on **Study** Day 1 in Study 20140159 if their iPTH is ≥ 300 pg/mL and cCa is ≥ 8.8 mg/dL **during screening in Study 20140159.** Eligible subjects from the cinacalcet arm in 20130356 will continue cinacalcet treatment on **Study** Day 1 if their iPTH is ≥ 150 pg/mL and cCa is ≥ 8.4 mg/dL **during screening in Study 20140159. If IP has been withheld or missed for more than 14 days on Study Day 1, the subject will resume dosing at the starting dose level once all restart criteria are met.**

All subjects from 20130356 will be eligible to titrate the cinacalcet dose at monthly titration visits **(beginning at week 4)** to a maximum dose of 2.5 mg/kg/day based on the subject's dry weight at **Study** Day 1**,** not to exceed a dose of 180 mg/day.

3.1.2 Subjects From Study 20110100

Eligible subjects will complete the End of Study visit or early termination visit for Study 20110100 and continue or restart cinacalcet treatment in this study on Study Day 1 depending on their cinacalcet treatment status at the time of enrollment, dry weight at the time of enrollment in 20140159 study and age at the time of enrollment in the 20110100 study. Subjects completing the 26-week treatment period in Study 20110100 will be screened during the safety follow-up period in Study 20110100; if eligible, these subjects will begin procedures in Study 20140159 at the Study 20110100 week 26 End of Study visit (Study Day 1 in 20140159 will be the same as EOS in Study 20110100). Subjects who reach Study 20110100 termination before week 26 will not complete the safety follow-up period in Study 20110100, beginning the 20140159 extension study at early termination visit. The early termination/EOS visit in study 20110100 and

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Study Day 1 in Study 20140159 will be the same visit unless there is an administrative delay.

Eligible subjects will complete Study Day 1 assessments and confirm eligibility in IVR system before being dispensed IP on Study Day 1.

Eligible subjects will continue cinacalcet treatment on Study Day 1 based on their dry weight at the time of enrollment in 20140159 study if their iPTH is ≥ 150 pg/mL and cCa is ≥ 8.8 mg/dL (age < 2 years of age) or cCa is ≥ 8.4 mg/dL (age is ≥ 2 years of age) during screening in Study 20140159. If IP has been withheld or missed for > 14 days at the time of Study Day 1 of Study 20140159, the subject will resume dosing at the starting dose level based on dry weight at the time of enrollment once all restart criteria are met.

All subjects from 20110100 will be eligible to titrate the cinacalcet dose at monthly titration visits (beginning at week 4) to a maximum dose of 2.5 mg/kg/day based on the subject's dry weight at Study Day 1 in Study 20140159, not to exceed a dose of 60 mg/day.

Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in protocol Section 6.2.3.

3.2 Sample Size

This is an extension study **for subjects from S**tudy 20130356 **and Study 20110100**. The sample size of approximately 48 for the parent study **20130356 and 30 for the parent Study 20110100** will result in a **planned** sample size of **78** subjects **in Study 20140159**.

4. Study Endpoints

Primary Endpoint:

Incidence of treatment emergent adverse events of interest

Secondary Endpoints:

20140159studyonly(forinterimandfinalanalyses)

Achievement of ≥30% reduction from baseline to mean iPTH during weeks 11 and 15 (SOC arm of Study 20130356 only)

Achievement of ≥30% reduction from baseline to mean iPTH during weeks 23 and 28 (SOC arm of Study 20130356 only)

Percent change from baseline to mean iPTH during weeks 23 and 28 (SOC arm of Study 20130356 only)

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Change in corrected total serum calcium from baseline to mean value during week 23 and 28

Change in serum phosphorus from baseline to mean value during week 23 and 28

Achievement of a mean iPTH value ≤300 pg/mL during week 23 and 28

Serum cCa values at **baseline**, week 11, and week 28

Serum phosphorus values at **baseline**, week 11, and week 28

Combined20130356.20110100and20140159studies(forfinalanalysisonly)

Achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15

Achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 23 and 28

Percent change in iPTH over time from day 1 of cinacalcet treatment

Change in serum cCa over time from day 1 of cinacalcet treatment

Change in serum phosphorus over time from day 1 of cinacalcet treatment

Exploratory Endpoint

20140159studyonly(forfinalanalysisonly)

Growth velocity from **baseline** to EOS

Change in Tanner stage from **baseline** to EOS

Combined20130356.20110100and20140159Studies(forfinalanalysisonly)

Growth velocity from day 1 of cinacalcet treatment to EOS

Change in Tanner stage from day 1 of cinacalcet treatment to EOS

Safety Endpoints:

Nature, frequency, and severity of all adverse events

Blood pressure, heart rate, and changes in laboratory parameters, including clinical chemistry and hematology

5. Hypotheses and/or Estimations

There is no formal statistical testing for this study. The proportions of subjects with treatment emergent adverse events of interest will be estimated.

6. Definitions

6.1 Study Periods

Screening

The screening period begins when the informed consent, and assent if applicable, is signed and concludes when the subject is either enrolled into the trial or screen failed.

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The informed consent can be signed up to **7 days (± 3 days) prior to Study Day 1 of Study 20140159.**

For subjects who do not meet the eligibility criteria in Section 4 of the protocol, re-screening will not be considered in this study.

EndofDosetitrationphase

The end of dose titration phase is Week 24 of Study 20140159.

Timeonstudy

If the subject has ended study, time on study (in days) is defined as: time on study = end of study date – study Day 1 +1.

Otherwise, time on study (in days) = data cutoff day – study Day1 +1, which is applicable for interim analysis only.

Timeoffollow-up(indays;useforfollow-upadjustedAEforthefinalanalysis)

End of study date – Day 1 of cinacalcet treatment +1

6.2 Study Time points

Unless otherwise specified, these study time point definitions are for Study 20140159 only.

Enrollment date

The date the subject has met all eligibility criteria and eligibility has been completed in the IVR/IWR system.

Study Day 1

The date that the initial dose of IP is administered **in Study 20140159. For subjects who didn't take any IP throughout the study, leave as missing.**

Day1ofcinacalcettreatment(combinedstudies20130356,20110100and 20140159)

The date that the initial dose of cinacalcet treatment is administered in studies 20130356, 20110100 or 20140159.

Studyday

For a given study visit, the study day is defined as: study day= (visit date - date of Study Day 1) +1.

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Cinacalcetday(combinedstudies20130356,20110100and20140159)

For a given study visit, the cinacalcet day is defined as: cinacalcet day = (visit date – date of Day 1 of cinacalcet treatment) +1.

End of treatment

For subject who completed treatment as of cutoff date, the end of treatment is defined as the date of the last dose of IP. If subject is ongoing as of cutoff date, leave as missing.

EndofstudyDate(forinterimanalysisonly)

For subjects who completed the study or early terminated from the study as of the data cut-off date, the end of study date is the date on the end of study form. For subjects who are ongoing as of cutoff date, leave the end of study date as missing.

EndofstudyDate(forfinalanalysisonly)

Use the end of study date from the End of Study Form.

StudyVisit

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study visit as follows.

Analysis window for ionized calcium and cinacalcet dose:

Analysis Visit	Target Day	Study Day	Interval (days)
Baseline (for ionized calcium)	1	<= 1	N/A
Day 1 (for cinacalcet dose)	1	1	1
Week 1	8	2 – 11	9
Week 2	15	12 – 18	7
Week 3	22	19 – 25	7
Week 4	29	26 – 32	7
Week 5	36	33 – 39	7
Week 6	43	40 – 46	7
Week 7	50	47 – 53	7
Week 8	57	54 – 60	7
Week 9	64	61 – 67	7
Week 10	71	68 – 74	7
Week 11	78	75 – 81	7
Week 12	85	82 – 88	7
Week 13	92	89 – 95	7

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Analysis window for ionized calcium and cinacalcet dose:

Analysis Visit	Target Day	Study Day	Interval (days)
Week 14	99	96 – 102	7
Week 15	106	103 – 109	7
Week 16	113	110 - 116	7
Week 17	120	117 – 123	7
Week 18	127	124 – 130	7
Week 19	134	131 – 138	7
Week 20	141	139 – 144	7
Week 21	148	145 – 152	7
Week 22	155	153 – 158	7
Week 23	162	159 – 166	7
Week 24	169	167 – 173	7
Week 25	176	174 – 180	7
Week 26	183	181 – 187	7
Week 27	190	188 – 194	7
Week 28	197	≥195	N/A

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Analysis window for iPTH

Study Visit	Target Day	Study Day	Interval (days)
Baseline	1	<= 1	N/A
Week 3	22	2-36	35
Week 7	50	37-64	28
Week 11	78	65-92	28
Week 15	106	93-120	28
Week 19	134	121-148	28
Week 23	162	149-176	28
Week 28	197	177-211	35
Week 32	225	≥212	N/A

Analysis window for calcium, corrected total serum calcium, serum phosphorus, serum albumin, CaxP

Study Visit	Target Day	Study Day	Interval (days)
Baseline	1	<= 1	N/A
Week 1	8	2-14	13
Week 3	22	15-36	21
Week 7	50	37-64	28
Week 11	78	65-92	28
Week 15	106	93-120	28

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Analysis window for calcium, corrected total serum calcium, serum phosphorus, serum albumin, CaxP

Study Visit	Target Day	Study Day	Interval (days)
Week 19	134	121-148	28
Week 23	162	149-176	28
Week 28	197	177-211	35
Week 32	225	≥212	N/A

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Analysis window for vital signs and all other labs.

Study Visit	Target Day	Study Day	Interval (days)
Baseline	1	<= 1	N/A
Week 3	22	2-36	35
Week 7	50	37-64	28
Week 11	78	65-92	28
Week 15	106	93-120	28
Week 19	134	121-148	28
Week 23	162	149-176	28
Week 27	190	177 – 194	18
Week 28	197	195 – 211	17
Week 32	225	≥212	N/A

If there is more than one observation in a visit window, use the value collected closest to the target day. If multiple observations are equally close to the target day, use the later value.

6.3 Demographics and Baseline Characteristics

Demographics

Sex, ethnicity, race, age at enrollment of parent studies will be transferred from the parent stud**ies** 20130356 **and 20110100**. **Study baseline age at Study Day 1 of Study 20140159 is defined as the subject's age (in years) on the day of enrollment in study 20140159.**

StudyBaseline Values

StudyBaselineatStudyDay1ofStudy20140159

Study Baseline iPTH, corrected total serum calcium, and serum phosphorus values are defined as the mean values of samples collected during the screening period and Study Day 1 pre-dose.

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Ca x P will be calculated at central lab COVANCE using corrected total serum calcium and serum phosphorus. **Study** Baseline value will be the mean of the values during the screening period and **Study** Day 1 pre-dose.

Study Baseline dry weight is defined as the value collected at **Study 20140159** Day 1 visit.

For all other variables, the **study** baseline value is defined as the last non-missing value collected prior to the first dose of IP, either during the screening phase or on Study Day 1.

All **study** baseline values will be calculated to the same number of decimal places as the raw data.

StudyBaseline vitamin D use

Vitamin D use at **study** baseline is defined as any use of nutritional vitamin D or vitamin D sterol within 7 days prior to Study Day 1.

StudyBaseline growth hormone use

Growth hormone use at **study** baseline is defined as any use of growth hormone during the screening period prior to Study Day 1.

StudyBaseline phosphate binder use

Phosphate binder use at **study** baseline is defined as any use of any phosphate binder the day prior to Study Day 1.

StudyBaseline calcium supplement use

Calcium supplement use at **study** baseline is defined as any use of any calcium supplement the day prior to Study Day 1.

Baselineatfirstcinacalcetdose (combinedstudies20130356,20110100and 20140159)

For subjects who received SOC only in Study 20130356, baseline values at first cinacalcet dose are same as study baseline at Study Day 1 of Study 20140159.

For other subjects, all baseline values at first cinacalcet dose will be transferred from the parent studies 20130356 and 20110100.

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6.4 Study Endpoints

Treatment emergent adverse events

20140159studyonly

Treatment-emergent adverse events are defined as adverse events that occurred on or after Study Day 1 **in Study 20140159.**

Combined20130356.20110100&20140159Studies

Treatment-emergent adverse events are defined as adverse events that occurred on or after day 1 of cinacalcet treatment in the parent study (Studies 20140356 and 20110100) or Study 20140159.

Events of interest **(EOI)**

The EOI names and search scopes (provided by Amgen Global Safety) are listed below:

EOI Name	Scope
Acute pancreatitis (SMQ)	Narrow
Cardiac failure (SMQ)	Narrow
Convulsions (SMQ)	Broad
Drug related hepatic disorders - comprehensive search (SMQ)	Narrow
Fractures (Amgen MedDRA Search Strategy)	Narrow
Hypersensitivity (SMQ)	Narrow
Hypocalcemia (Amgen MedDRA Search Strategy)	Narrow
Hypotension (Amgen MedDRA Search Strategy)	Narrow
Ischaemic heart disease (SMQ)	Narrow
Malignant or unspecified tumors (SMQ)	Narrow
Medication errors (SMQ)	Broad
Product use issues (MedDRA HLGT)	Broad
Nervous system disorders excluding seizures (Amgen MedDRA Search Strategy)	Broad
Torsade de pointes/QT prolongation (SMQ)	Narrow
Ventricular tachyarrhythmias (SMQ)	Narrow

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Change from **studybaseline**

For each subject, change from **study** baseline for a given variable at a given time point or pe**rio**ds is defined as:

(Value at the given time point or period – **study** baseline value)

and will be calculated **a**t the same number of decimal places as the raw data provided by laboratory where applicable.

Percent change from **studybaseline**

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

100 x ((value at the given time point or period – **study** baseline value) / **study** baseline value)

and will be calculated to one decimal place.

Changefromday1ofcinacalcettreatment

For each subject, change from baseline at first cinacalcet dose for a given variable at a given time point or period is defined as:

(Value at the given time point or period – baseline at first cinacalcet dose)

and will be calculated at the same number of decimal places as the raw data provided by laboratory where applicable.

Percentchangefromday1ofcinacalcettreatment

For each subject, percent change from baseline at first cinacalcet dose in a given variable at a given time point or period is defined as:

100 x ((value at the given time point or period – baseline at first cinacalcet dose) / baseline at first cinacalcet dose)

and will be calculated to one decimal place.

Growth velocity

Linear growth velocity (cm/year) = 52 x change in height (cm) / number of weeks between the two assessments.

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6.5 Derived Variables

Corrected total serum calcium

Corrected total serum calcium (mg/dL) = measured total serum calcium (mg/dL) + 0.8 (4.0 – Serum albumin (g/dL)), or

Corrected total calcium (mmol/L) = measured total serum calcium (mmol/L) + 0.02 (40 – Serum albumin (g/L)).

Total serum calcium will only be corrected using above formulae if the serum albumin is < 4 g/dL or 40 g/L. The correction will be done at the Covance central lab.

IP compliance

Daily subject compliance with administration of cinacalcet is documented on the IP administration eCRF. IP compliance (%) = 100 x (number of days of planned dosing – number of days dose is changed due to noncompliance) / number of days of planned dosing.

Actualtreatment

Actual treatment of a subject in Study 20140159 is cinacalcet if the subject received at least one dose of IP, and is missing if the subject did not receive any IP throughout the study.

7. Analysis Subsets

7.1 Full Analysis Set

The Full Analysis Set (FAS) includes all Study 20140159 enrolled subjects. All subjects will be analyzed according to the actual treatment **received** in the parent **studies and overall**.

7.2 Safety Analysis Set

The Safety Analysis Set will be used for primary and safety endpoints. **It** includes all subjects who were enrolled **in Study 20140159** and received at least one dose of investigational product. **Subjects will be analyzed according to the treatment received in the parent studies and overall.**

7.3 Efficacy Analysis Set

The efficacy analysis set will be used for secondary endpoints. The efficacy analysis set includes all enrolled subjects in Study 20140159 who received at least one dose of cinacalcet during Study 20140159 and have at least one assessment

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after Study Day 1. Subjects will be analyzed according to the treatment received in the parent studies and overall.

7.4 Study 20130356 SOC Set

The Study 20130356 SOC set will be used for secondary endpoints that analyze subjects from Study 20130356 SOC arm only. The Study 20130356 SOC set includes all Study 20140159 enrolled subjects from Study 20130356 who did not receive cinacalcet prior to Study Day 1 of 20140159 and received at least one dose of cinacalcet in Study 20140159 and have at least one assessment after Study Day 1 of 20140159.

7.5 Per Protocol Set for Study 20140159 Only (for interim and final analyses)

The Per Protocol Set for Study 20140159 only is defined as all **enrolled** subjects who **do not have significant deviations from the protocol (as assess by IPD),** or **missing > 2 doses within any dosing week or ≥2 documented overdoses within a dosing week**.

For each secondary endpoint that requires sensitivity analysis using per protocol set, a subset of the Per Protocol Set for Study 20140159 only who has at least one desired lab measurement during the corresponding evaluation period will be used.

7.6 Per Protocol Set for Combined 20130356, 20110100 and 20140159 Studies (for final analysis only)

The Per Protocol Set for combined 20130356, 20110100 and 20140159 studies is defined as all Study 20140159 enrolled subjects who do not have significant deviations from the protocols of parent studies and Study 20140159 (as assessed by IPD) or non-compliance as defined for each study specifically.

For each secondary endpoint that requires sensitivity analysis using per protocol set, a subset of the Per Protocol Set for Combined 20130356, 20110100 and 20140159 Studies who has at least one corresponding lab measurement during the corresponding evaluation period will be used.

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7.7 Subgroup Analyses

The following characteristics **may** be used in the subgroup analyses planned for the primary, secondary **and safety** endpoints:

baseline age group **in parent studies** (6 to < 12 years old and 12 to **<** 18 years old **for Study 20130356; 28 days to < 2 years old and 2 to < 6 years for Study 20110100)**

gender (male and female)

race (black, white and other). If **any category has ≤ 4 subjects**, the **category** will be pooled together with **other category** for summary purposes.

Tanner stage (1 and >1)

8. Interim Analysis and Early Stopping Guidelines

An interim analysis will be performed to support the sNDA for the pediatric indication. The scope of this interim analysis will be specified in section 10 of this SAP. Additional interim analyses may be performed if necessary to support regulatory inquiries and the SAP may be amended to reflect the additional analyses. There are no plans to change the conduct of the study based on the interim analysis results.

There is no formal statistical testing. The analysis for all endpoints will be descriptive in nature.

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

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. This study will use the RAVE database and non-CTDB database.

9.3 Handling of Missing and Incomplete Data

9.3.1 Examination of the Missing Data

Missing data frequency and pattern for any of the following key variables will be reviewed. The potential impact of these missing values on the planned analysis will be evaluated.

1. Subject Identification Data

   subject identification number

   date of birth

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race

ethnicity

sex

center/site number

country

2. Dates and Times

informed consent date

enrollment date

end of study date

3. Safety Data

dates for onset of adverse events

dates for resolution of adverse events (if not continuing at the end of the study)

CTCAE v4 severity grading, relationship to treatment, seriousness, and action taken for adverse events

4. Efficacy Data

iPTH, corrected total serum calcium values, ionized calcium values, phosphorus values and dates of assessment

5. Investigational Product Administration

Daily planned IP (dose level, date, reason for dose change)

Daily IP administration (dose level, date, reason for dose change/withheld)

box ID numbers

9.3.2 Handling of Missing Data

9.3.2.1 Missing Adverse Event date

For any listings, missing or incomplete dates will be listed as is.

All missing dates (missing entirely or partially) of adverse events occurring after first dose of IP will be queried. **For adverse events with the question "Did event start before first dose of investigational product?" on the eCRF was answered as "Yes", the missing adverse event start dates won't be imputed**. All **other** missing adverse event start dates will be handled as described below:

When the adverse event start year is available and the start day and month are missing, **if the start year is the same as the year of Study Day 1, the start date will be set to date of Study Day 1, otherwise** set to the 1st of January of the onset year.

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When the start year and month are available and the start day is missing**, if the start year and month are the same as the year and month of Study Day 1, the start date will be set to date of Study Day 1, otherwise** the 1st of the month of the onset year.

If the entire start date is missing, it will be set to the date of Study Day 1

9.3.2.2 Other Missing Dates

Partial/missing start dates for vitamin D, phosphate binders, calcium supplements, and growth hormone will be imputed using the **following** algorithm.

If the start year is available and the start day and month are missing, the start date will be set to the 1st of January of the onset year.

If the start year and month are available and the start day is missing, the start date will be set to the 1st of the month of the onset year.

If the entire start date is missing, it will not be imputed.

Partial/missing stop dates for the concomitant medications (not continuing at the end of the study) will be imputed using the following logic:

If the stop year is available and stop month and day are missing, the **stop date** will be reset to **3**1st of **December** of the stop year.

If the stop year and month are available and the stop day is missing, the stop **date** 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 **End of Study** date.

If the entire stop date is missing, it will not be imputed.

9.4 Detection of Bias

This study is an open label, single arm study. Some factors that may bias the results of the study include:

important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints

IP dosing compliance

the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors **as well as potential biases from the parent studies discussed in the parent studies SAPs** will be assessed. Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR). If necessary, the incidence of the other factors will be reported as well.

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9.5 Outliers

This is a descriptive study, all outliers that are not known errors will be included in the relevant analysis. Outliers that are confirmed to be errors that are discovered before the database lock will be corrected in the database by CDM. Any erroneous values discovered after the database lock will be noted in the CSR.

9.6 Distributional Characteristics

There is no distributional assumption being made due to the descriptive nature of the analysis. Both mean and median will be presented for continuous outcomes.

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 and Qualified R.

10. Statistical Methods of Analysis

10.1 General Principles

There is no formal statistical testing for this study. The analysis of all endpoints will be descriptive in nature.

Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD), standard error (SE), median, 25^{th} (Q1) and 75^{th} (Q3) percentiles, minimum and maximum values, and corresponding 2-sided 95% CI, where applicable.) For categorical variables, the number and percentage of subjects in each category**,**will be reported. Graphical presentation may be provided for selected variables.

The laboratory data collected more than 7 days after the last dose of IP will be excluded for the efficacy analyses.

For the interim analysis supporting pediatric sNDA, only data from the 20140159 study before interim data cutoff date will be analyzed according to the actual treatment received from the parent study and overall.

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For the final analysis, final efficacy and safety data from Study 20140159 will be analyzed. In addition, cumulative data combining the parent studies (20130356 and 20110100) and Study 20140159 will also be summarized.

10.2 Subject Accountability

The number (and percent) of subjects who are enrolled, receive investigational product, and complete each study period will be summarized. The number (and percentage) of subjects who withdraw from treatment and from study will be summarized. The time of withdrawal and reason for withdrawal from IP or study will be listed. In addition, the number of subjects in each analysis set will be summarized.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's 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. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs.

Eligibility deviations are defined in the protocol. Important inclusion/exclusion criteria deviations will be listed by subject.

10.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized based on FAS **at Study 20140159 baseline and at baseline at first cinacalcet dose separately** using descriptive statistics:

Sex, age, dry weight, height, race group (white, black, other), ethnicity, dialysis status, Tanner stage, baseline iPTH, corrected total serum calcium, ionized calcium, serum phosphorous, Ca x P, and selected concomitant medication.

10.5 Analysis of Primary Endpoint

The primary endpoint is incidence of treatment emergent adverse events of interest as defined in Section 6.4. The analysis will be based on Safety Analysis Set. Subject incidence of EOIs will be summarized by EOI category and **preferred term for data in Study 20140159 only for both the interim and final analyses**. **The 95% confidence intervals (CI) of the overall subject incidence rates will be reported.**

The secondary analysis of the primary endpoint is follow-up time adjusted incidence of EOIs for combined data from parent studies and data from the 20140159 study for the final analysis.

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10.6 Efficacy Analyses

10.6.1 Analyses of Secondary Endpoints

Analyses of secondary endpoints will be based on **Efficacy Analysis Set or 20130356 SOC Set per endpoint definitions unless otherwise specified**.

Study20140159only

Proportion of subjects achieving the secondary endpoints of ≥30% reduction in iPTH from study baseline to mean value during weeks 11 and 15 will be reported with 95% CI based on 20130356 SOC Set. Subjects who have no iPTH values during weeks 11 or 15 will be considered non-responders.

Proportion of subjects achieving the secondary endpoints of ≥30% reduction in iPTH from study baseline to mean value during weeks 23 and 28 will be reported with 95% CI based on 20130356 SOC Set. For subjects who do not have a iPTH value during weeks 23 and 28, the mean of the last two available post-baseline values in the dose-titration phase will be used. If only one post-baseline value is available, this single value will be used. If no post-baseline value is available, the subject is considered a non-responder.

Summary statistics will be provided for percent change from study baseline to mean iPTH during weeks 23 and 28 based on 20130356 SOC Set, and change in corrected total calcium and change in serum phosphorus from study baseline to mean value during weeks 23 and 28 based on efficacy analysis set by treatment group in the parent studies. For subjects who are missing the efficacy measurement during weeks 23 to 28, the mean of the last two available post-baseline values in the dose titration phase will be used. If only one post-baseline value is available, this single value will be used. If no post-baseline value is available, the subject will be excluded from the analysis.

Proportion of subjects who achieve a mean iPTH value ≤ 300 pg/mL during weeks 23 and 28 will be provided based on efficacy analysis set by the treatment group in parent study with 95% CI. For subjects who do not have an iPTH value during weeks 23 and 28, the mean of the last two available post-baseline values in the dose-titration phase will be used. If only one post-baseline value is available, this single value will be used. If no post-baseline value is available, the subject is considered a non-responder.

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Summary statistics will be provided for serum cCa and phosphorus values at study baseline, week 11, and week 28 for all efficacy analysis set subjects.

Combined20130356,20110100&20140159studies

Proportion of subjects achieving the secondary endpoints of ≥30% reduction in iPTH from day 1 of cinacalcet treatment to mean value during weeks 11 and 15 will be reported with 95% CI for all efficacy analysis set subjects. Subjects who have no weeks 11 or 15 iPTH values will be considered non-responders.

Proportion of subjects achieving the secondary endpoints of ≥30% reduction in iPTH from day 1 of cinacalcet treatment to mean value during weeks 23 and 28 will be reported with 95% CI for all efficacy analysis set subjects. For subjects who do not have an iPTH value during weeks 23 and 28, the mean of the last two available post-baseline values collected at protocol-specified visits in the dose titration phase will be used. If only one post-baseline value is available, this single value will be used. If no post-baseline value is available, the subject is considered a non-responder.

Summary statistics will be provided for percent change in iPTH, change in serum cCa and change in serum phosphorus over time from day 1 of cinacalcet treatment for all efficacy analysis set subjects.

10.6.2 Sensitivity Analysis of Secondary Endpoints

Sensitivity Analysis of the effect of dose interruption (final analysis only)

To study the effect of dose interruption, sensitivity analyses will be performed separately for subjects in the efficacy analysis set who have and do not have dose interruption of >14 days between EOIP of the parent study and Study Day 1 in study 20140159. Secondary endpoints of achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15, and percent change in iPTH over time from day 1 of cinacalcet treatment will be analyzed using combined 20130356, 20110100 and 20140159 studies data.

Sensitivity analyses to assess the effect of missing data or non-compliance

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SecondaryendpointsforStudy20140159only

Secondary endpoint	Sensitivity Analyses	Planned for Interim or Final analysis
Achievement of ≥30% reduction from baseline to mean iPTH during weeks 11 and 15 (SOC arm of Study 20130356 only)	Inverse Probability Weighting (IPW) The missingness model will include study baseline iPTH, cCa, phosphorus, age group, sex, race, and AEs of nausea, vomiting and symptomatic hypocalcemia. Dialysis vintage, AE or IPD related to ending IP may be also included in the model depending on the EOIP reason observed in the study. The final weighted pooled logistic regression model will include study baseline iPTH, cCa, phosphorus and age group. This analysis will be performed using the Study 20130356 SOC set.	Final analysis only
	Completer analysis: Only subjects completing 15 weeks of study in the Study 20130356 SOC set will be included in the analysis. Subjects with no iPTH values during weeks 11 and 15 will be considered as nonresponders.	Final analysis only
	Per protocol analysis: Subjects in per protocol set who did not receive cinacalcet in the parent study and have at least one iPTH value during weeks 11 and 15 will be used.	Interim and Final analyses
	Nearest 2 imputation If no values are observed during weeks 11 and 15, the nearest two values at or after week 7 will be used, including unscheduled visit values, values prior to or after weeks 11 and 15. Subjects with no observed values at or after week 7 will be considered nonresponders.	Final analysis only

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SecondaryendpointsforStudy20140159only

Secondary endpoint	Sensitivity Analyses	Planned for Interim or Final analysis
Achievement of ≥30% reduction from baseline to mean iPTH during weeks 23 and 28 (SOC arm of Study 20130356 only) Achievement of a mean iPTH value ≤300 pg/mL during week 23 and 28 (efficacy analysis set)	IPW: The IPW method is same as specified for the sensitivity of binary endpoint "Achievement of ≥30% reduction from study baseline to mean iPTH during weeks 11 and 15".	Final analysis only
	Completer analysis: Only subjects with at least one iPTH value during week 23-28 will be included in the analysis.	Final analysis only
	Per protocol analysis: Subjects from in per protocol set for Study 20140159 only who did not receive cinacalcet in the parent study and have at least one iPTH value during weeks 23 and 28 will be used for the endpoint defined for SOC arm of Study 20130356 only. Subjects from the per protocol set for Study 20140159 only and with at least one iPTH value during weeks 23 and 28 will be used for the other endpoint.	Interim and Final analyses

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SecondaryendpointsforStudy20140159only

Secondary endpoint	Sensitivity Analyses	Planned for Interim or Final analysis
Percent change from baseline to mean iPTH during weeks 23 and 28 (SOC arm of Study 20130356 only) Change in corrected total serum calcium from baseline to mean value during week 23 and 28 (efficacy analysis set) Change in serum phosphorus from baseline to mean value during week 23 and 28 (efficacy analysis set)	Repeated measures mixed effect model: The repeated measures model will include treatment group, study baseline age group, scheduled visits, and interaction of treatment group and scheduled visits. An unstructured covariance will be used for the model.	Final analysis only
	Completer analysis: Only subjects with at least one required lab value for the endpoint during week 23-28 will be included in the analysis.	Final analysis only
	Per protocol analysis: Subjects in both the Study 20130356 SOC set and per protocol set for Study 20140159 only and with at least one iPTH value during weeks 23 and 28 will be used for the endpoint defined for SOC arm of Study 20130356 only. Subjects from the per protocol set for Study 20140159 only and with at least one corresponding lab value during weeks 23 and 28 will be used for other endpoints.	Interim and Final analyses

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Secondaryendpointsforcombined20130356,20110100and20140159studies

Secondary endpoint	Sensitivity Analyses	Planned for Interim or Final analysis
Achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15	**IPW:** The missingness model will include baseline iPTH, cCa, phosphorus, age group at first cinacalcet dose, sex, race, and AEs of nausea, vomiting and symptomatic hypocalcemia. Dialysis vintage, AE or IPD related to ending IP may be also included in the model depending on the EOIP reason observed in the study. The final weighted pooled logistic regression model will include baseline iPTH, cCa, phosphorus and age group at first cinacalcet dose.This analysis will be performed.	Final analysis only
	Completer analysis: Only enrolled subjects who completed 15 weeks from Day 1 of cinacalcet treatment will be included in the analysis. Subjects with no iPTH values during weeks 11 and 15 since Day 1 of cinacalcet treatment will be considered as nonresponders.	Final analysis only
	Per protocol analysis: Subjects from the per protocol set for combined 20130356, 20110100 and 20140159 studies and with at least one iPTH value during weeks 11 and 15 will be used.	Final analysis only
	Nearest 2 imputation If no values are observed during weeks 11 and 15 from Day 1 of cinacalcet treatment, the nearest two values at or after week 7 from Day 1 of cinacalcet treatment will be used, including unscheduled visit values, values prior to or after weeks 11 and 15. Subjects with no observed values at or after week 7 will be considered nonresponders.	Final analysis only

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Secondaryendpointsforcombined20130356.20110100and20140159studies

Secondary endpoint	Sensitivity Analyses	Planned for Interim or Final analysis
Achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 23 and 28	IPW: The IPW method is same as specified for the sensitivity of binary endpoint "Achievement of ≥ 30% reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15	Final analysis only
	Completer analysis: Only subjects with at least one iPTH value during week 23-28 since Day 1 of cinacalcet treatment will be included in the analysis.	Final analysis only
	Per protocol analysis: Subjects from the per protocol set for combined 20130356, 20110100 and 20140159 studies and with at least one iPTH value during weeks 23 and 28 will be used.	Final analysis only

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10.6.3 Analyses of Exploratory Endpoints

20140159studyonly

Analyses of exploratory endpoints will be based on Efficacy Analysis Set. Growth velocity and change in Tanner stage from **Study D**ay 1 **in study 20140159 to end of study** will be summarized using descriptive statistics. **The analysis will only include subjects who have growth velocity values available or tanner stage assessments available at both Study Day 1 in study 20140159 and end of study; no imputation will be done for missing values.**

Actual values, change and percent change of iPTH, serum cCa, serum phosphorus and CaxP values at scheduled visits from study baseline for all Efficacy Analysis Set subjects through last dose of IP+7 days will be summarized and presented graphically.

20130356.20140159and20110100studiescombined

Summary statistics of the exploratory endpoints will also be presented from day 1 of cinacalcet treatment through end of study of 20140159.

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The analysis will only include subjects who have growth velocity values available and Tanner stage assessments available at both day 1 of cinacalcet treatment and end of study; no imputation will be done for missing values.

Actual values, change and percent change of iPTH, serum cCa, serum phosphorus and CaxP values at scheduled visits from baseline at first cinacalcet dose for all Efficacy Analysis Set subjects through last dose of IP+7 days will be summarized and presented graphically.

10.7 Safety Analyses

The Safety Analysis Set is used for all analyses specified in this section unless otherwise specified.

10.7.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 or later will be used to code all adverse events (AE) to a system organ class and a preferred term. All adverse event tables will be summarized.

20140159studyonly

An overall summary of treatment-emergent adverse events**, defined for study 20140159 only in section 6.4,** by toxicity grade and type will be provided.

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

Subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, and EOIs by preferred term in descending order of frequency.

Subgroup analyses **of age groups** will be presented by system organ class **in alphabetical order** and preferred term in descending order of frequency if there are more than 4 subjects in each subgroup.

Treatment-emergent AEs will be listed for subjects who experienced QTcB ≥ 500 msec on study.

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Focused adverse events questionnaires were administered for events of hypocalcemia, seizure, and infection, of which subject incidence will also be summarized.

Combined20130356.20140159and20110100studies

Subject follow-up time adjusted incidence of all treatment-emergent AEs and EOIs, defined for studies 20130356, 20140159 and 20110100 combined in section 6.4, will also be tabulated by preferred term in descending order of follow-up time adjusted incidence rates for all subjects.

10.7.2 Laboratory Test Results

All laboratory test results in 20140159 study only and combined with parent studies will be summarized by treatment received in parent studies and overall.

20140159studyonly

Descriptive statistics for actual values, changes, and percent changes from **study** baseline of selected laboratory parameters below will be presented at **scheduled visits** during the study. In addition, shift tables will summarize toxicity grades using CTCAE (version 3) by worst increase and decrease between **study** baseline and any visit up to the end of the study for selected laboratory parameters below.

	Summary over time	Shifts in grade from study baseline
Serum Chemistry		
Albumin	X	one way shift (decreased)
Bicarbonate	x	
Blood Urea Nitrogen	x	
Chloride	x	
Creatinine	x	
Potassium		two-way shift
Sodium		two-way shift
Total Protein		
Liver function test		
ALT		one way shift (increase)
AST		one way shift (increase)
Total Bilirubin		one way shift (increase)
Alk Phos		one way shift (increase)

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	Summary over time	Shifts in grade from study baseline
Hematology		
Platelets		one way shift (decrease)
Hemoglobin	x	one way shift (decrease)
White blood cell count		one way shift (decrease)
Red blood cell count		
Other		
iPTH	x	
Corrected Ca	x	**two-way shift**
Ionized Ca	x	**two-way shift**
Phosphorus	x	
Ca x P	x	
BALP, NTx, CTx, P1NP **(For 20140159 subjects from parent Study 20130356 only)**	x	
FGF 23 **(For 20140159 subjects from parent Study 20130356 only)**	x	
25(OH)D **(For 20140159 subjects from parent Study 20130356 only)**	x	
Total and bioavailable testosterone (male)	x	

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Subject incidence of corrected total serum calcium value < 8.4 mg/dL, <8.0 mg/dL, <7.5 mg/dL or ionized calcium value < 1.05 mmol/L, <1.00 mmol/L and <0.94 mmol/L respectively **during study 20140159** will also be summarized.

20130356,20110100and20140159studiescombined

Actual values, change and percent change of serum cCa, serum phosphorus and CaxP values at scheduled visits from baseline at first cinacalcet dose for all Safety Analysis Set subjects will be summarized.

10.7.3 Vital Signs

Change from baseline **in study 20140159** in systolic and diastolic blood pressure (post-dialysis blood pressure for hemodialysis), will be summarized at each protocol specified time point.

Sitting heart rate will be summarized at each protocol-specified time point.

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10.7.4 Electrocardiogram (ECG)

The 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 QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; only summaries statistics will be provided for QTcB, and these data would not be expected to be useful for meta-analysis with data from other trials. ECG data of subjects who **had abnormal ECG results or** experienced QTcB ≥ 500 msec on study will be listed.

10.7.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product **in study 20140159 and in study 20140159 combined with parent studies**. The number of days on investigational product, the minimum and maximum daily dose, the cumulative total dose of cinacalcet, and the number and percentage of subjects receiving each dose level of investigational product will be summarized using descriptive statistics. In addition, starting and maximum weight-adjusted dose will also be summarized. Compliance to the investigational product regimen will be calculated for each subject and summarized using descriptive statistics.

10.7.6 Exposure to Concomitant Medication

The number and proportion of subjects receiving vitamin D sterol, nutritional vitamin D supplement, phosphate binder, calcium containing phosphate binder or Ca supplement **in study 20140159** will be summarized over time. Intravenous Paricalcitol-equivalent dose at scheduled visits will also be summarized in a table and graphically. IV Paricalcitol-equivalent dose is calculated using the following: 2µg Paricalcitol (IV) = 1 µg Doxercalciferol (IV) = 1 µg Alfacalcidol (IV) = 0.5 µg Calcitriol (IV) = 1 µg Paricalcitol (PO) = 0.8 µg Doxercalciferol (PO) = 0.5 µg Alfacalcidol (PO) = 0.25 µg Calcitriol (PO).

The number and proportion of subjects receiving bisphosphonates and growth hormone **in study 20140159** will be summarized.

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11. Literature Citations / References

Fleiss J.L., Tytun A., Ury S.H.K. "A simple approximation for calculating sample sizes for comparing independent proportions" Biometrics 36(1980) pp. 343-346

Liu M, Wei L and Zhang J (2006). Review of guidelines and literature for handling missing data in longitudinal clinical trials with a case study. Pharmaceutical Statistics 2006; 5: 7-18

SAS/STAT 9.2 User's Guide, Fourth Edition. Cary, NC: SAS Institute Inc.; 2009.

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12. Appendices

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Appendix A. Reference Values/Toxicity Grades

For CTCAE grading system V3, please refer to:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

For CTCAE grading system V4, please refer to:

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

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