

16.1.1 Protocol and Amendments

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Protocol Number: 20140159
Date: 01 June 2016

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Title: 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

Amgen Protocol Number (cinacalcet HCl) 20140159

EudraCT number 2014-003563-38

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Date: 05 August 2014
Amendment 1: 18 December 2014
Amendment 2: 22 July 2015
Amendment 3: 16 March 2016
Superseding 3: 01 June 2016

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Investigator's Agreement

I have read the attached protocol entitled "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," dated **01 June 2016**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

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Signature

Name of Investigator

Date (DD Month YYYY)

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Protocol Synopsis

Title: 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

Study Phase: 3

Indication: Management of secondary hyperparathyroidism in pediatric subjects with chronic kidney disease (CKD) receiving dialysis

Primary Objective: To characterize the long-term safety and tolerability of cinacalcet in pediatric subjects with CKD receiving dialysis

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

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

Hypotheses: A formal hypothesis does not apply for the study. The long-term safety of cinacalcet in pediatric subjects will be characterized in this study.

Primary Endpoint:

- Incidence of treatment-emergent adverse events of interest

Secondary Endpoints:

Study 20140159 only

- Achievement of $\geq 30\%$ reduction from baseline to mean intact parathyroid hormone (iPTH) during weeks 11 and 15 (standard of care [SOC] arm of Study 20130356 only)
- Achievement of $\geq 30\%$ 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)
- Change in corrected total serum calcium from baseline to mean value during weeks 23 and 28
- Change in serum phosphorus from baseline to mean value during weeks 23 and 28
- Achievement of a mean iPTH ≤ 300 pg/mL during weeks 23 and 28
- Serum corrected calcium (cCa) at baseline, week 11, and week 28
- Serum phosphorus at baseline, week 11, and week 28

Combined Studies 20130356, 20110100, and 20140159

- Achievement of $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15
- Achievement of $\geq 30\%$ 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 Endpoints:

Study 20140159 only

- Growth velocity from baseline to end of study (EOS)
- Change in Tanner stage from baseline to EOS

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Combined Studies 20130356, 20110100, and 20140159

- 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

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 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.

Sample Size: Up to 78 subjects may be enrolled

Summary of Subject Eligibility Criteria: Subjects who complete the 20-week treatment period or reach study termination in Study 20130356 or the week 26 End of Study visit or reach study termination in Study 20110100 will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, followed by a 4-week safety follow-up. Subjects must also meet the inclusion and exclusion criteria for this extension study in order to be eligible. Subjects must provide written informed consent (parents or guardian) and assent, where appropriate, according to local regulations specific to the procedures in this study.

- Subjects enrolled in the SOC arm of Study 20130356 will be eligible for the extension study if the iPTH is ≥ 300 pg/mL and the cCa is ≥ 8.8 mg/mL within 7 days of day 1 in Study 20140159.
- Eligible subjects from the cinacalcet arm of Study 20130356 will restart or continue cinacalcet treatment following the dosing rules described in [Section 6.2.3.1.1](#).
- Eligible subjects from Study 20110100 will restart or continue cinacalcet following the dosing rules as described in [Section 6.2.3.1.2](#).

Subjects will be excluded from this study if they have adverse events continuing from Study 20130356 or 20110100 that are considered related to investigational product (IP) and are \geq CTCAE grade 3 and/or considered clinically significant by the investigator. For a full list of eligibility criteria, please refer to [Section 4.1.1](#) through [Section 4.1.2](#).

Investigational Product

Amgen Investigational Product Dosage and Administration: Cinacalcet is a calcimimetic agent which is synthesized as a hydrochloride salt. Cinacalcet will be provided as 5 mg capsules for sprinkling or as film coated tablets for swallowing in a strength of 30 mg.

The capsules provided must not be swallowed whole and must be opened and either sprinkled on soft food or suspended into a sucrose syrup to create a liquid suspension for administration.

The protocol-specified doses (PSD) for use in this study are: 1, 2.5, 5, 7.5, 10, 15, 30, 60, 90, 120, and 180 mg.

Subjects will receive cinacalcet daily and all doses should be administered with food or shortly after a meal at the same time each day. On study visit days where a blood sample is to be drawn, cinacalcet should not be administered until after the blood sample has been obtained.

Non-investigational Product

Non-Amgen Non-investigational Product Dosage and Administration: All subjects will receive standard of care treatment including vitamin D sterols, calcium supplementation, and phosphate binders at the discretion of the investigator.

Procedures: Informed consent, and assent where applicable, for this study should be presented during the Studies 20130356 or 20110100. The informed consent, including assent as

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appropriate, will be obtained prior to execution of any study procedures for this extension study. Where the Screening and day 1 assessments for Study 20140159 overlap with visits in the 20130356 or 20110100 studies, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments, eg, 20130356 end of investigational product (EOIP) and 20140159 Screening. The subject visits and assessments for this study will occur from baseline through to the end of study. Assessments during this study will include:

- collection of blood samples for the evaluation of blood chemistry, hematology, calcium, iPTH, and bone biomarkers
- physical assessments including vital signs (ie, blood pressure, heart rate)
- 12-lead electrocardiogram (ECG) at baseline and week 32 (if the subject ends the study prior to week 32, the 12-lead ECG will be performed at the last study visit)
- assessments for symptoms of hypocalcemia
- recording of adverse events, concomitant medications, and IP compliance

Subjects from Study 20130356: Subjects who complete the 20-week treatment period in study 20130356 or are still on study at the time of Study 20130356 termination, will be eligible to receive cinacalcet treatment in the current study.

- **Subjects from the SOC group in 20130356:** After confirming eligibility, subjects in the 20130356 SOC group will receive the initial dose of cinacalcet based on the subject's dry weight at day 1 in Study 20140159, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects from the 20130356 SOC group will follow the same cinacalcet titration schedule as subjects who received cinacalcet in Study 20130356.
- **Subjects from the cinacalcet group in 20130356:** After confirming eligibility, subjects from the cinacalcet group will continue to receive cinacalcet at the same dose as EOIP visit if there are ≤ 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159. If the cinacalcet dose has been withheld or missed for > 14 days at the time of day 1 of Study 20140159, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg (based on 20140159 day 1 dry weight), not exceeding 180 mg, has not been reached and they meet the titration criteria defined in [Section 6](#).

Subjects from Study 20110100: Subjects who complete the week 26 End of Study visit or are still on study at the time of Study 20110100 termination, will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects will continue to receive cinacalcet at the same dose as EOIP visit if there are ≤ 14 days between the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159. If the cinacalcet dose has been withheld or missed for > 14 days at the time of day 1 of Study 20140159, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159 and age at time of enrollment to 20110100, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects will follow the dose adjustments outlined in [Section 6.2.3.1.2](#). Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg (based on 20140159 day 1 dry weight), not exceeding 60 mg, has not been reached and they meet the titration criteria defined in [Section 6](#).

During the 20140159 study:

Weekly monitoring of ionized calcium will be required for all subjects through the end of the treatment period, week 28.

Cinacalcet doses will be calculated by the site staff and confirmed by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in [Section 6](#). The titration tables are based on cCa and iPTH values from the central laboratory collected one week before dose titration. Final dose assignment will be based on the ionized calcium obtained

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on the day of titration. An assessment of symptomatic hypocalcemia will also be performed on the day of titration. Additional weekly dose adjustments for safety are permitted as described in [Section 6.2.3.1](#). The maximum dose assigned for all subjects will be 2.5 mg/kg/day (based on dry weight at day 1 in Study 20140159) not to exceed a dose of 180 mg/day for subjects from 20130356 and 60 mg/day for subjects from 20110100.

For all subjects, it is recommended that the vitamin D sterols, calcium supplementation, and phosphate binders be administered as appropriate per individual clinical practice. The use of medications that may prolong the corrected QT (QTc) interval (eg, ondansetron, albuterol), CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine), and commercial cinacalcet during the course of the trial are prohibited while the subject is receiving investigational product.

Serious adverse events will be collected from the date of the first dose through 30 days following the last dose of investigational product. Adverse events will be collected from the date of the first dose through 30 days following the last dose of investigational product.

For a full list of study procedures, including the timing of each procedure, please refer to [Section 7](#) and the Schedule of Assessments ([Table 4](#)).

Statistical Considerations: There is no formal statistical testing for this study. The analysis of the primary and secondary endpoints will be descriptive in nature.

For categorical variables, the number and percentage of subjects in each category will be reported. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, where applicable). All summary tables will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet) and Study 20110100 and overall, unless otherwise specified.

Graphical presentations may be provided for selected variables.

All adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary and the subject incidence will be tabulated.

For a full description of statistical analysis methods, please refer to [Section 10](#).

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Data Element Standards	Version (s) 4.0
Version(s)/Date(s):	31 October 2013

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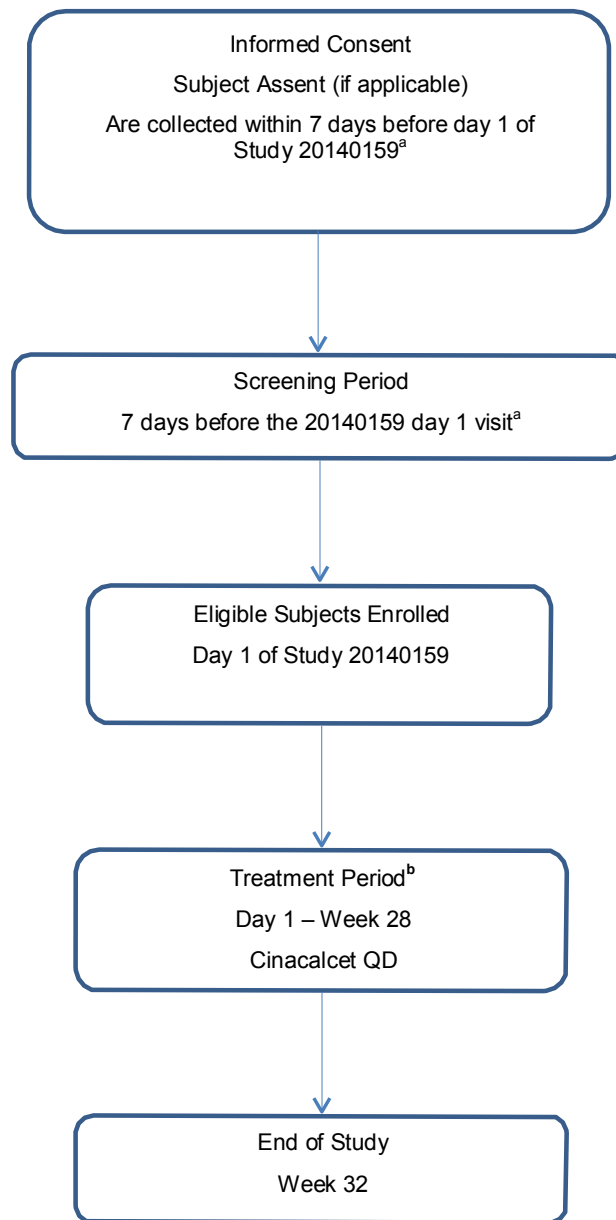
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Study Design and Treatment Schema



^a When it is not possible to perform a study visit at the specified time point, the visit may be performed within ± 3 days.

^b The initial dose of cinacalcet assigned will be based on the dosing in the originating parent study. Refer to [Section 6](#) of the protocol for additional details.

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Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BALP	Bone specific alkaline phosphatase
Bazett's formula	QT/\sqrt{RR}
Ca	serum calcium
CaSR	calcium sensing receptor
CBC	complete blood count
cCa	corrected calcium
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral bone disease
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Type 1 collagen cross-linked telopeptide
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic patient diary
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial
End of Study	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data
End of Study for Individual Subject (EOS)	defined as the last day that protocol-specified procedures are conducted for an individual subject
EOIP	end of investigational product
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
FAS	full analysis set
FDA	Food and Drug Administration
FGF 23	fibroblast growth factor 23
HD	hemodialysis
IB	investigator brochure
IEC	independent ethics committee
INR	international normalized ratio
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.

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Abbreviation or Term	Definition/Explanation
Interactive Web Response (IWR)	web based technology that is linked to a central computer in real time as an interface to collect and process information.
IP	investigational product
IPIM	Investigational Product Instruction Manual
iPTH	Intact parathyroid hormone
IRB	institutional review board
LFT	liver function test
NAPRTCS	North American Pediatric Renal Trials and Collaborative Services
NASH	nonalcoholic fatty liver disease including steatohepatitis
NTx	Cross-linked N-telopeptides of type 1 collagen
Primary Completion	the time when the last subject is assessed during the study (ie, week 32)
P1NP	Amino terminal propeptide of type 1 collagen
PD	peritoneal dialysis
POC	point of care
PSD	protocol specified dose
PTH	parathyroid hormone
QTc	corrected QT
SD	standard deviation
SE	standard error
SHPT	secondary hyperparathyroidism
sNDA	Supplemental New Drug Application
SOC	standard of care
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
Study Day 1	defined as the date that the initial dose of investigational product is administered
TBL	total bilirubin
ULN	upper limit of normal
US	United States

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1. OBJECTIVES

1.1 Primary

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

1.2 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).

1.3 Exploratory

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

2. BACKGROUND AND RATIONALE

2.1 Secondary Hyperparathyroidism in Pediatric Subjects

Secondary hyperparathyroidism (SHPT) develops relatively early in the course of CKD, worsens with declining renal function, and is commonly associated with serious complications both in adults and in children on dialysis. CKD in children, as in adults, is a devastating illness. In children with CKD, growth retardation is a prominent finding and SHPT is an important contributor to this disorder ([Kuizon et al, 1999](#)).

In both the United States (US) and Europe, there are few children with CKD on dialysis compared with the adult population. The rate of Stage 5 CKD in children was estimated at 15.2 per million population in the US over the 2007-2011 time period. This correlates with 6800 incident children with Stage 5 CKD reported during this same time period ([USRDS, 2013](#)). Data from the published [2011 European Renal Association-European Dialysis and Transplant Association \(ERA-EDTA\)](#) registry, show 2115 prevalent pediatric patients with Stage 5 CKD receiving maintenance dialysis. Of these, 207 patients were 0 to 4, 323 patients were 5 to 9, 566 patients were 10 to 14, and 1019 patients were 15 to 19 years of age.

Children on dialysis experience similar laboratory disturbances with regards to parathyroid hormone (PTH), serum calcium (Ca) and phosphorous as adults ([Bacchetta et al, 2012](#)). Traditional therapies for SHPT (eg, vitamin D sterols) are widely used in the pediatric dialysis population, but are sometimes insufficient to manage SHPT due to their potential to increase serum calcium and phosphorus.

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A survey conducted among 18 sites belonging to North American Pediatric Renal Trials and Collaborative Services (NAPRTCS) ([NAPRTCS, unpublished data](#)), included data from 320 pediatric hemodialysis (HD) and peritoneal dialysis (PD) patients, between the ages of 2 to less than 18. The results show that overall, 49% of the pediatric dialysis population has intact parathyroid hormone (iPTH) levels above 300 pg/mL (31.8 pmol/L), the upper limit recommended by the NKF-K/DOQI™ guidelines for all pediatric age groups (NKF-KDOQI™, 2005).

Published pediatric CKD-MBD guidelines markedly differ with respect to the recommended PTH target ranges. For children with stage 5 CKD, the guidelines recommend targets in the range between 120 and 540 pg/mL ([Klaus et al, 2006](#); [NKF KDOQI, 2005](#); [KDIGO CKD-MBD Working Group, 2009](#)). None of these recommendations has been validated in a large pediatric stage 5 CKD cohort.

2.2 Cinacalcet Background

Cinacalcet is a first-in-class calcimimetic agent that acts as an allosteric modulator of the calcium sensing receptor (CaSR) located on the surface of the parathyroid chief cell, increasing the sensitivity of the CaSR to extracellular calcium. Cinacalcet has been shown to be safe and efficacious in simultaneously controlling PTH, calcium, and phosphorus in the adult dialysis population. Cinacalcet was initially approved in 2004 by the US Food and Drug Administration (FDA) for the treatment of SHPT in adult patients with CKD receiving dialysis. As of 28 February 2014, cinacalcet is approved for this indication in 67 countries. Cinacalcet is not approved for use in pediatric patients in any country.

Refer to the [Cinacalcet HCl Investigator's Brochure \(IB\)](#) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Standard of Care Therapy

Standard of care (SOC) in the treatment of children with CKD-MBD and SHPT consists of vitamin D sterols (eg, calcitriol, paricalcitol), calcium supplementation, and phosphate binders (calcium based and non-calcium based).

2.4 Pediatric Risk Assessment

In the 4 interventional studies conducted by Amgen in the pediatric population to date, 48 subjects between 1 to 17 years of age have been exposed to cinacalcet. The overall adverse event profile in children was similar to that seen in the adult population treated with cinacalcet. The most commonly observed adverse events were nausea, vomiting,

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and hypocalcemia. One fatal adverse event was reported in a pediatric subject receiving cinacalcet in the double-blind interventional study in the presence of severe hypocalcemia. While the cause of death was multi-factoral, severe hypocalcemia was observed and a role of cinacalcet could not be excluded.

Additional risk mitigation measures implemented in this trial include:

- collection of real-time ionized calcium measurements,
- weekly monitoring of calcium,
- incorporation of local laboratory total calcium values into the dosing schema,
- subject investigational product (IP) compliance measures,
- dispensing limited quantities of IP to minimize the potential for overdosing
- addition of exclusionary electrocardiogram (ECG) criteria

A dosing strategy, using a weight-based starting dose of ≤ 0.2 mg/kg in pediatric subjects, which is approximately 50% below the adult starting dose, will be employed in this study. The dose of cinacalcet will be titrated based on iPTH, corrected calcium (cCa) levels, ionized calcium, and subject safety information. The maximum dose in this study will be 2.5 mg/kg/day based on day 1 dry weight, not to exceed a dose of

- 180 mg/day for subjects from 20130356
- 60 mg/day for subjects from 20110100

Serum calcium will be monitored throughout the study. In the event a subject experiences protocol-defined hypocalcemia, an adverse event deemed related to IP or other adverse event that warrants IP dose withhold, the dose of cinacalcet will be reduced or discontinued as appropriate. Vitamin D sterols, calcium supplementation and/or calcium-based phosphate binders can be used to raise serum calcium levels and should be administered as appropriate per individual clinic practice. Training and informational tools will be provided to investigators for dissemination to care givers and subjects regarding the symptoms and risks of hypocalcemia.

Volumes of blood withdrawn for analysis will be minimized as appropriate for this pediatric population based on dry weight.

2.5 Studies Eligible to Roll-over to 20140159

2.5.1 Amgen Study 20130356

Amgen Study 20130356 is a phase 3 randomized, multicenter, open-label, controlled study. In Study 20130356, cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 6 and < 18 years, with SHPT and CKD receiving either

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hemodialysis or peritoneal dialysis. Approximately 48 subjects are planned to be randomized into the study to one of two treatment arms in a 1:1 allocation ratio; daily oral administration of cinacalcet in addition to SOC or SOC only. Once randomized, the expected treatment period in 20130356 is 20 weeks with a 4-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the 20-week treatment period in 20130356 or following Study 20130356 termination and within 7 days of day 1 of 20140159, unless there is an administrative delay. The end of study (EOS) procedures for an individual subject will occur at the same time as the end of investigational product (EOIP) visit for subjects enrolling in Study 20140159. The 4-week safety follow-up period in 20130356 will not apply for these subjects.

2.5.2 Amgen Study 20110100

Amgen Study 20110100 is a phase 2, multicenter, open-label, single-arm study. In Study 20110100 cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 28 days and < 6 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. The expected treatment period in 20110100 is 24 weeks of daily oral administration of cinacalcet in addition to SOC with a 2-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the week 26 End of Study visit or at Study 20110100 termination and within 7 days of day 1 of 20140159 unless there is an administrative delay. For subjects enrolled in the 20140159 extension study at the time of 20110100 study termination, the 2-week safety follow-up period in 20110100 will not apply for these subjects and the EOS procedures for an individual subject will occur at the time as the EOIP visit for subjects enrolling in Study 20140159.

2.6 Rationale

Cinacalcet has been shown to be safe and efficacious in treating adult CKD patients with SHPT by controlling iPTH, calcium, and phosphorus. The current study is an extension of Amgen studies 20130356 and 20110100 designed to assess the long-term safety and tolerability of cinacalcet in pediatric CKD subjects.

2.7 Clinical Hypotheses

A formal hypothesis does not apply for the study. The long-term safety and tolerability of cinacalcet in pediatric subjects will be characterized in this study.

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3. EXPERIMENTAL PLAN

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 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 Design and Treatment Schema](#) at the end of the protocol synopsis section.

The study endpoints are defined in [Section 10.1.1](#).

3.1.1 Subjects From Study 20130356

Eligible subjects will complete the 20-week treatment period in Study 20130356, or reach Study 20130356 termination and either continue, restart, or start cinacalcet treatment in this study. Eligible subjects will not complete the safety follow-up period in Study 20130356, beginning the extension study at the 20130356 EOIP study visit. The EOIP visit in Study 20130356 and day 1 in Study 20140159 will be the same visit unless there is an administrative delay. Eligible subjects will complete day 1 of 20140159 assessments ([Section 7.1](#)) and confirm eligibility in the interactive voice response (IVR) system before dispensing IP on day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm in Study 20130356 will begin cinacalcet treatment on 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 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 > 14 days at the time of day 1 of Study 20140159, the subject will resume dosing at the starting dose level once all restart criteria are met.

Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in [Section 6.2.3](#).

Subjects will complete day 1 assessments ([Section 7.1](#)) and confirm eligibility in IVR system prior to dispensing IP on day 1.

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 day 1 in Study 20140159, not to exceed a dose of 180 mg/day.

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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 day 1 based on dosing instructions outlined in [Section 6.2.3](#). Eligible subjects completing the full treatment period in Study 20110100 will be screened during the safety follow-up period in Study 20110100 and will be required to have their 20140159 day 1 visit and their 20110100 week 26 End of Study visit at the same visit. Eligible 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 the 20110100 early termination visit. The early termination/EOS visit in Study 20110100 and day 1 in Study 20140159 will be the same visit unless there is an administrative delay.

Subjects will complete day 1 assessments ([Section 7.1](#)) and confirm eligibility in IVR system before being dispensed IP on day 1.

Eligible subjects will continue cinacalcet treatment on 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 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. Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in [Section 6.2.3.1.2](#).

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 day 1 in Study 20140159, not to exceed a dose of 60 mg/day.

3.2 Number of Sites

This study will be conducted at approximately 60 sites in North America, Europe, Russia, Latin America, and Australia.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects".

This study is open to subjects who complete the 20-week treatment period or reach study termination in Study 20130356 or the week 26 End of Study visit or reach study termination in Study 20110100. There may be up to 78 subjects enrolled in this study.

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3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The total duration for this study is 32 weeks; a 28-week treatment period and 4-week safety follow-up period.

3.5.2 End of Study

The end of study is the primary completion date. This is defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data.

4. SUBJECT ELIGIBILITY

Before any study-specific activities/procedure, written informed consent must be obtained (see [Section 11.1](#)). In addition to written informed consent from a legally acceptable representative, the assent of the child also must be obtained, as appropriate and if requested by the institutional review board/independent ethics committee (IRB/IEC).

Subjects from the cinacalcet arm of Study 20130356 or subjects in Study 20110100 who had their dose withheld at the EOIP visit, may enroll in this study if they meet eligibility criteria but will not restart dosing until the criteria for restarting dosing, defined in [Section 6.2.3](#), are met.

Subjects who were ≤ 18 years old at week 20 in the 20130356 study or at the time of study termination, are eligible to enter this Study 20140159 even if they have already turned 18 years of age or are due to turn 18 years of age during their planned participation in the 20140159 study.

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

All Subjects

- 101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any Study 20140159 activities/procedures being initiated.
- 102 Dialysate calcium concentration ≥ 2.5 mEq/L at day 1

All subjects with > 14 days between the last study visit in Study 20130356 or Study 20110100 and screening for Study 20140159

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103 Subjects on anti-convulsant medication must be on a stable dose

All subjects from 20130356

104 Completed treatment through week 20 in the 20130356 study or on study at the time of Study 20130356 termination

105 Dry weight \geq 12.5 kg at day 1 of Study 20140159

Subjects Randomized to the 20130356 Standard of Care Arm Only

106 iPTH value \geq 300 pg/mL (within 7 days of day 1 in Study 20140159)

107 Corrected calcium value \geq 8.8 mg/dL within 7 days of day 1 in Study 20140159

All Subjects from 20110100

108 Completed week 26 End of Study visit in the, 20110100 study or on study at the time of Study 20110100 termination

109 Dry weight \geq 7 kg at day 1 of Study 20140159

4.1.2 Exclusion Criteria

General

Studies 20130356 or 20110100

- 201 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s), other than Amgen Studies 20130356 or 20110100.
- 202 Other investigational procedures while participating in this study are excluded.
- 203 Malignancy except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years.
- 204 Subject has known sensitivity to any of the products to be administered during dosing.
- 205 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, electronic patient diary [ediary]) to the best of the subject and investigator's knowledge
- 206 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
- 207 Subject previously has entered this study.
- 208 If sexually active, subject is not willing to use acceptable contraception during treatment and for at least 9 days after the end of treatment.
- 209 Subject is pregnant or breast feeding, or planning to become pregnant during the study or within 9 days after the end of treatment
- 210 History of congenital long QT syndrome, second or third degree heart block, ventricular tachyarrhythmias, or other conditions associated with prolonged QT interval

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211 A new onset of seizures or worsening of pre-existing seizure disorder

All Subjects with > 14 days between the last study visit in Study 20130356 or Study 20110100 and the screening visit in Study 20140159 will have the following exclusion criteria applied during screening and day 1:

- 212 Unstable chronic heart failure defined as worsening pulmonary edema or other signs and symptoms as per investigator assessment during screening
- 213 Received therapy with commercial cinacalcet after the last study visit in Study 20130356 or Study 20110100 before day 1 of Study 20140159
- 214 Scheduled date for kidney transplantation from a known living donor that makes completion of the study unlikely
- 215 Either new or recurrent cardiac ventricular arrhythmias requiring a change in treatment within 10 days prior to screening visit or day 1 of Study 20140159 screening
- 216 Hepatic impairment indicated by elevated levels of hepatic transaminase or bilirubin (aspartate aminotransferase [AST] $\geq 1.5 \times$ upper limit of normal [ULN] OR alanine aminotransferase [ALT] $\geq 1.5 \times$ ULN OR total bilirubin $\geq 1 \times$ ULN per institutional laboratory range) during screening

All Subjects - Day 1 Study Visit

- 217 Subject has an ongoing adverse event from Studies 20130356 or 20110100 that is considered related to IP and:
- Is \geq CTCAE (v 4.0) grade 3, and/or
 - Considered clinically significant in the opinion of the investigator
- 218 Central laboratory values were not obtained/are not available at day 1 in Study 20140159
- 219 Corrected QT Interval (QTc) > 500 ms, using Bazett's formula
- 220 QTc ≥ 450 to ≤ 500 ms, using Bazett's formula, unless written permission to enroll is provided by the investigator after consultation with a pediatric cardiologist
- 221 Use of grapefruit juice, herbal medications, CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), or CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine)
- 222 Use of concomitant medications that may prolong the QTc interval (eg, ondansetron, albuterol)

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 11.2](#)). Before commencement of study-specific activities/procedures the subject's legally acceptable representative(s) must personally sign and date the

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informed consent form, and the subject must personally sign and date the assent form as appropriate and if required by the IRB/IEC.

Subjects will retain the unique subject identification number received in studies 20130356 or 20110100. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

5.1 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. The informed consent can be signed up to 7 days (\pm 3 days) prior to 20140159 day 1.

For subjects who do not meet the eligibility criteria in [Section 4](#), re-screening will not be considered in this study.

5.2 Enrollment

Following confirmation that subjects met eligibility criteria in [Section 4](#), the subject will be registered in the interactive voice response/interactive web response (IVR/IWR) system. The subject will be considered enrolled in the extension study:

- 20130356 subjects will be assigned a cinacalcet dose based on the treatment arm and/or last dose received in Study 20130356 following the dosing instructions in [Section 6.2.3](#).
- 20110100 subjects will be assigned a cinacalcet dose based on the last dose received at the EOIP visit in Study 20110100 following the dosing instructions in [Section 6.2.3](#).

6. TREATMENT PROCEDURES

6.1 Standard of Care

Standard of care therapy will include the use of vitamin D sterols, calcium supplementation, and phosphate binders.

Standard of care therapy that is commercially available will not usually be provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for obtaining supplies of these therapies unless they are provided by Amgen.

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6.2 Cinacalcet

6.2.1 Classification of Product

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of cinacalcet.

6.2.2 Investigational Product

Cinacalcet will be manufactured and packaged by Amgen Inc., or designee, and distributed using Amgen clinical study drug distribution procedures. Cinacalcet will be provided as capsules or as film coated tablets and will be orally administered daily. For subjects unable to swallow, the dose of cinacalcet may be administered via their feeding tube using the liquid suspension.

Capsules

Each capsule will contain 5 mg of cinacalcet in addition to the following inactive excipients: microcrystalline cellulose, pregelatinized starch, povidone, crospovidone, and colloidal silicon dioxide. Cinacalcet capsules will be provided in bottles containing 10 capsules each. The capsules provided must not be swallowed whole. Capsules must be opened and either sprinkled onto soft food (eg, applesauce) or suspended into a sucrose syrup to create a liquid suspension for administration. Once opened, the empty capsule shells should be discarded.

Tablets

Tablets will be provided in bottles containing 10 tablets of cinacalcet in a strength of 30 mg. Tablets of cinacalcet are to be swallowed whole and contain the following inactive excipients in addition to cinacalcet: microcrystalline cellulose, pregelatinized starch, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. Each tablet is color-coated with Opadry II (green) and Opadry clear coatings then covered with carnauba wax.

6.2.3 Dosage, Administration, and Schedule

Cinacalcet will be administered daily. All doses are to be taken orally and administered with food or shortly after a meal at the same time each day. For subjects unable to swallow, cinacalcet may be administered via their feeding tube using the liquid suspension. It is expected that for children under the age of 12 the daily administration of cinacalcet will be under the supervision of their parent(s) or legal guardian(s). On

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study visit days where a blood sample is to be drawn, cinacalcet should not be administered until after the blood sample has been obtained.

The protocol-specified doses (PSD) for use in this study are:

- Subjects ≥ 6 years of age: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg. Subjects from Study 20130356 will either continue to receive cinacalcet at the same dose as at the EOIP visit if ≤ 14 days have passed between last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159. If > 14 days have passed, subjects will start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at Study 20140159 day 1 time point and age at time of enrollment in Study 20130356, rounded down to the lowest PSD.
 - Subjects from 20130356 may receive capsules for any dose which is an exact multiple of 5 mg. Subjects who are assigned doses of 60 to 180 mg/day will require administration of two to six 30 mg tablets per dose. For those subjects unable to swallow tablets, capsules may be dispensed.
 - The maximum dose of cinacalcet that will be administered at any time during the study will be 2.5 mg/kg/day based on the subject's day 1 dry weight in Study 20140159 or 180 mg daily, whichever is lower.
- Subjects < 6 years of age: 1, 2.5, 5, 7.5, 10, 15, 30, and 60 mg. Subjects from Study 20110100 will either continue to receive cinacalcet at the same dose as at the EOIP visit if ≤ 14 days have passed between last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159. If > 14 days have passed, subjects will start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at the 20140159 day 1 time point and age at time of enrollment in 20110100 study, rounded down to the lowest PSD.
 - Subjects assigned a dose between 10 to 60 mg/day will require more than 1 capsule per dose be sprinkled on soft food or used to create the liquid suspension for administration.
 - Subjects enrolling into 20140159 from 20110100 would have a maximum dose of 2.5 mg/kg/day based on the subject's 20140159 day 1 dry weight or 60 mg daily, whichever is lower.

Subjects will be required to return all unused medication, including empty bottles, at each study visit. Site staff will confirm that the previously assigned medication bottle(s) have been returned prior to dispensing a new bottle(s) of IP. In the event unused medications or empty bottles have been permanently misplaced, contact Amgen prior to dispensing new bottle(s) of IP.

If no ionized calcium values are available at the time of a study visit, a new bottle of IP will not be dispensed to the subject. Once the ionized calcium value has been obtained and in accessible range, IP may be dispensed as appropriate.

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6.2.3.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Dosage adjustments, titrations, and withholding/restarting rules will be the same as the parent studies.

6.2.3.1.1 Subjects From Study 20130356

On day 1 of Study 20140159, subjects from the SOC arm in 20130356 will receive the initial dose of cinacalcet as defined in [Section 6.2.3.1.1.1](#)

Subjects from the cinacalcet arm with ≤ 14 days between last dose of cinacalcet treatment in Study 20130356 and Study 20140159 day 1 will continue at the same dose as the last dose at EOIP and will follow the dose adjustments outlined in [Table 1](#) in [Section 6.2.3.1.1.1](#). Dose titration cannot occur until week 4 per [Table 1](#). If subjects from the cinacalcet arm in 20130356 are on a dose that was withheld or missed for > 14 days and ≤ 1 month at day 1 of Study 20140159, the iPTH and cCa restart values (iPTH > 150 pg/mL and cCa > 8.4 mg/dL) must be reached prior to resuming cinacalcet will receive the initial dose of cinacalcet in the current extension study outlined in [Table 1](#) in [Section 6.2.3.1.1.1](#).

Subjects from the cinacalcet arm with > 1 month between the last dose of cinacalcet treatment in Study 20130356 and Study 20140159 day 1, will receive the initial dose of cinacalcet as defined in [Section 6.2.3.1.1.1](#). To commence dosing, all subjects must have:

- ionized calcium ≥ 1.05 mmol/L prior to initiation of treatment on day 1 in this study
- iPTH value ≥ 300 pg/mL within 7 days of day 1
- corrected calcium value ≥ 8.8 mg/dL within 7 days of day 1

6.2.3.1.1.1 Dosage Adjustments

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1 of Study 20140159, rounded down to the lowest PSD.

Subjects from the cinacalcet arm with ≤ 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159 will start cinacalcet dosing at the same dose they received at the completion of the EOIP visit and follow weekly dose adjustment based on the [Table 1](#). For subjects from the cinacalcet arm with > 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of

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Study 20140159, the initial dose of cinacalcet will be 0.20 mg/kg/day, based on the subject's dry weight at day 1 of 20140159, rounded down to the lowest PSD, will be assigned.

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the dose adjustment criteria in [Table 1](#).

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- central laboratory corrected calcium value is >8.4 mg/dL
- iPTH is > 150 pg/mL
- ionized calcium is >1.05 mmol/L
- subject has no symptoms of hypocalcemia
- subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of >1.05 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (2.5 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 2.5 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

If IP has been withheld or missed for > 14 days, the subject will resume dosing at the starting dose level once (initial dose in parent Studies 20130356 or 20110100) all restart criteria are met based on dry weight at day 1 of Study 20140159.

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If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table 1. Dose Adjustment Rules: Monthly, Weekly, and Withholding in Children 6-18 Years of age

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16, 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27)				Dose Withholding for Safety at Any Time (Monthly, Weekly or Unscheduled)
	↑ one PSD (if <u>all</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	
Corrected Calcium (central laboratory)	≥ 8.4 mg/dL	≥ 8.4 mg/dL	≥ 8.0 - < 8.4 mg/dL	< 8.0 mg/dL	≥ 8.4 mg/dL	≥ 8.0 - < 8.4 mg/dL	< 8.0 mg/dL	< 8.0 mg/dL	
	(≥ 2.1 mmol/L)	(≥ 2.1 mmol/L)	(≥ 2.0- < 2.1 mmol/L)	(< 2.0 mmol/L)	(≥ 2.1 mmol/L)	(≥ 2.0- < 2.1 mmol/L)	(< 2.0 mmol/L)	(< 2.0 mmol/L)	
Ionized Calcium	≥ 1.05 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	< 1.00 mmol/L	
Total Calcium (local laboratory)	N/A	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	
iPTH	≥ 300 pg/mL	≥ 150 - < 300 pg/mL	≥ 100 - < 150 pg/mL	< 100 pg/mL	≥ 150 pg/mL	≥ 100 - < 150 pg/mL	< 100 pg/mL	< 100 pg/mL	
	(≥ 31.8 pmol/L)	(≥ 15.9 - < 31.8 pmol/L)	(≥ 10.6 - < 15.9 pmol/L)	(< 10.6 pmol/L)	(≥ 15.9 pmol/L)	(≥ 10.6 - < 15.9 pmol/L)	(< 10.6 pmol/L)	(< 10.6 pmol/L)	
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes	
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes	

* restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > 150 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

** if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased per dose adjustment procedures of that visit.

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6.2.3.1.2 Subjects From Study 20110100

For subjects where the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159 occurs within 14 days, in order to commence dosing, subjects from Study 20110100 will follow the weekly dose adjustment criteria as outlined in [Table 2](#) for age < 2 years and [Table 3](#) for age ≥ 2 years. Dose titration cannot occur until week 4.

For subjects with > 14 days and < 1 month between last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, in order to commence dosing at the initial dose, all subjects from Study 20110100 must meet restart criteria per weekly dose adjustment criteria as outlined in [Table 2](#) for age < 2 years and [Table 3](#) for age ≥ 2 years. Dose titration cannot occur until week 4.

- Additionally the phosphorus value within 7 days of day 1 should be:
 - ≥ 5.0 mg/dL (1.25 mmol/L) if age is < 1 year
 - ≥ 4.5 mg/dL (1.13 mmol/L) if age is ≥ 1 year

For subjects with > 1 month between last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, in order to commence dosing, subjects from Study 20110100 must have:

- ionized calcium prior to initiation of treatment on day 1 in this study
 - ≥ 1.13 mmol/L if age is < 2 years
 - ≥ 1.05 mmol/L if age is ≥ 2 years
- iPTH value ≥ 300 pg/mL within 7 days of day 1
- corrected calcium value within 7 days of day 1
 - ≥ 9.4 mg/dL if age is < 2 years
 - ≥ 8.8 mg/dL if age is ≥ 2 years
- phosphorus value within 7 days of day 1
 - ≥ 5.0 mg/dL (1.25 mmol/L) if age is < 1 year
 - ≥ 4.5 mg/dL (1.13 mmol/L) if age is ≥ 1 year

6.2.3.1.2.1 Subjects < 2 Years of Age

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system.

For subjects with > 14 days since the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, in the 20140159 study rounded down to the lowest PSD.

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For subjects with ≤ 14 days between the last dose of cinacalcet in Study 20110100 and Study 20140159 day 1, subjects will continue the same dose of cinacalcet they received at the completion EOIP visit or early termination visit at Study 20110100 termination and follow the weekly dose adjustments outlined in [Table 2](#). Dose titration cannot occur until week 4. If subjects from the Study 20110100 are on a dose withhold at day 1 of Study 20140159, the iPTH and cCa restart values (iPTH > 150 pg/mL and cCa > 9.0 mg/dL) must be reached prior to resuming cinacalcet in the Study 20140159.

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the criteria in [Table 2](#).

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- central laboratory corrected calcium value is >9.0 mg/dL
- iPTH is >150 pg/mL
- ionized calcium is >1.13 mmol/L
- subject has no symptoms of hypocalcemia
- subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of >1.13 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (1 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 1 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

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If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level (initial dose in parent Studies 20130356 or 20110100) once all restart criteria are met.

If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table 2. Dose Adjustment Rules: Monthly, Weekly, and Withholding in Subjects < 2 Years old

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16, 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19)				Dose Withholding for Safety at Any Time (Monthly, Weekly or Unscheduled)
	↑ one PSD (if <u>all</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	
Corrected Calcium (central laboratory)	≥ 9.0 mg/dL	≥ 9.0 mg/dL	≥ 8.6 - < 9.0 mg/dL	< 8.6 mg/dL	≥ 9.0 mg/dL	≥ 8.6 - < 9.0 mg/dL	< 8.6 mg/dL	< 8.6 mg/dL	
	(≥ 2.25 mmol/L)	(≥ 2.25 mmol/L)	(≥ 2.15 - < 2.25 mmol/L)	(< 2.15 mmol/L)	(≥ 2.25 mmol/L)	(≥ 2.15 - < 2.25 mmol/L)	(< 2.15 mmol/L)	(< 2.15 mmol/L)	
Ionized Calcium	≥ 1.13 mmol/L	≥ 1.13 mmol/L	≥ 1.08 - < 1.13 mmol/L	< 1.08 mmol/L	≥ 1.13 mmol/L	≥ 1.08 - < 1.13 mmol/L	< 1.08 mmol/L	< 1.08 mmol/L	
Total Calcium (local laboratory)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)	
iPTH	≥ 300 pg/mL 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (≥ < 10.6 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes	
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes	

* restart one PSD below last dose when cCa is > 9.0 mg/dL, iPTH is > 150 pg/mL, ionized calcium is > 1.13 mmol/L symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

** if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased.

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6.2.3.1.2.2 Subjects \geq 2 Years of Age

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system.

For subjects with > 14 days since the last dose of cinacalcet in Study 20110100 and day 1 of Study 20140159, subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1 in Study 20140159, rounded down to the lowest PSD.

For subjects with ≤ 14 days since the last dose of cinacalcet in Study 20110100 and day 1 of Study 20140159, subjects will continue cinacalcet based on the dose at the EOIP visit or early termination/EOS at study termination and follow the weekly dose adjustments outlined in [Table 3](#). Dose titration cannot occur until week 4. If subjects from the Study 20110100 are on a dose that was withheld at day 1 of Study 20140159, the iPTH and cCa restart values (iPTH > 150 pg/mL and cCa > 8.4 mg/dL) must be reached before resuming cinacalcet in Study 20140159.

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the criteria in [Table 3](#).

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- central laboratory corrected calcium value is >8.4 mg/dL
- iPTH is >150 pg/mL
- ionized calcium is >1.05 mmol/L
- subject has no symptoms of hypocalcemia
- subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of >1.05 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

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Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (1 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 1 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

If IP has been withheld or missed for more than 14 days (initial dose in parent Studies 20130356 or 20110100), the subject will resume dosing at the starting dose level once all restart criteria are met.

If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table 3. Dose Adjustment Rules: Monthly, Weekly, and Withholding in Subjects ≥ 2 Years old in Study 20110100

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16, 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27)				Dose Withholding for Safety at Any Time (Monthly, Weekly or Unscheduled)
	↑ one PSD (if <u>all</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	
Corrected Calcium (central laboratory)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0- < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0- < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	
Ionized Calcium	≥ 1.05 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	< 1.00 mmol/L	
Total Calcium (local laboratory)	N/A	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	
iPTH	≥ 300 pg/mL (≥ 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	≥ 150 pg/mL (≥ 15.9 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes	
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes	

* restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > 150 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

** if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased per dose adjustment procedures of that visit.

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6.2.3.1.3 Missed Doses

If a subject misses > 14 consecutive doses of cinacalcet for any reason, including temporary dose withholding due to the administration of concomitant medications as noted above, they will be restarted at their initial dose of cinacalcet (0.20 mg/kg/day based on dry weight at day 1 in Study 20140159) when administration of IP resumes per the dose titration guidelines outlined in [Table 1](#), [Table 2](#), and [Table 3](#).

6.2.3.2 Measures of Compliance With Cinacalcet Administration

Poor compliance and/or intermittent dosing or ingestion of cinacalcet may lead to changes (ie, increases or decreases) in iPTH and calcium concentrations that do not conform to those seen in clinical trials where subjects have consistently received daily doses of cinacalcet. Increases in iPTH can be interpreted to be a result of subtherapeutic dosing leading to increases in cinacalcet doses which may result in potentially severe hypocalcemia, particularly in the setting of intermittent ingestion of IP.

Electronic patient diaries (eDiary) and IP accountability information will be reconciled and utilized in this study to document subject compliance with daily administration of cinacalcet therapy. The data entered into the eDiary will be available to the investigator and/or study coordinator on a daily basis to enable ongoing reviews of subject compliance. The eDiary and IP accountability data collected will be reviewed with the subject and/or their parent(s) or legal guardian(s) by the investigator and/or study coordinator during the weekly study visits.

For this study non-compliance is defined as:

- missing > 2 doses within any dosing week, or
- ≥ 2 documented overdoses within a dosing week
- other indicators of non-compliance per physician judgment

If a subject is considered to be non-compliant, the dose of cinacalcet should not be increased and additional counseling should be provided about the importance of taking the study medication as prescribed. It will also be documented on the eCRF. The additional counseling should be documented in the subject's source documents. If the subject remains non-compliant, removal from IP dosing should be considered.

6.2.3.3 Overdose

An overdose of cinacalcet will be defined as receiving any dose greater than the assigned daily dose. This can cause hypocalcemia. Hypocalcemia may cause anxiety, muscular cramping or stiffness, twitching, tingling, paresthesias around the mouth or

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extremities, tetany, abdominal cramping, arrhythmias, hypotension, worsening of pre-existing chronic heart failure, convulsions, or death.

If an overdose is suspected, the Amgen Study Manager, Amgen Medical Monitor, and/or Amgen Clinical Safety representative should be contacted within 24 hours of discovery. For subjects in whom an overdose is suspected, close monitoring for signs and symptoms of hypocalcemia and appropriate measures (eg, including intravenous calcium gluconate and more frequent monitoring of calcium levels) should be considered by the investigator in those with acute symptomatic hypocalcemia.

Once hypocalcemia and any symptoms associated with the overdose have resolved, subjects resume cinacalcet administration dose. To resume dosing, the subject must meet the dosing restart criteria for his/her respective age group as specified in [Sections 6.2.3.1.1, 6.2.3.1.2.1, and 6.2.3.1.2.2](#).

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the [Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009](#).

Cinacalcet is metabolized by the liver. Subjects with moderate to severe hepatic impairment have the potential for 2- to 4-fold higher area under the curve (AUC) of cinacalcet concentration and may require additional follow-up.

6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Cinacalcet should be discontinued permanently and the subject should be followed according to the recommendations in [Appendix A](#) (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2 × upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant day 1 value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3 × ULN

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- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
 - Hepatobiliary tract disease
 - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
 - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
 - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
 - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
 - Alpha-one antitrypsin deficiency
 - Alcoholic hepatitis
 - Autoimmune hepatitis
 - Wilson's disease and hemochromatosis
 - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
 - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen IP and other protocol-required therapies should be withheld (see [section 6.3.2](#)) or permanently discontinued, as deemed appropriate for the safety of the subject.

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6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen IP outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen IP and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	$> 8 \times \text{ULN}$ at any time
Any	$> 5 \times \text{ULN}$ but $< 8 \times \text{ULN}$ for ≥ 2 weeks
Any	$> 5 \times \text{ULN}$ but $< 8 \times \text{ULN}$ and unable to adhere to enhanced monitoring schedule
Any	$> 3 \times \text{ULN}$ with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL $> 3 \times \text{ULN}$ at any time
- OR: ALP $> 8 \times \text{ULN}$ at any time

Cinacalcet should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in [Appendix A](#) for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline ([Section 6.3.3](#)).

6.3.3 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject's legally acceptable representative(s), investigator, and Amgen.

If signs or symptoms recur with rechallenge, then cinacalcet should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Section 6.3.1](#)) should never be rechallenged.

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6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.6](#).

Vitamin D sterols, calcium supplementation, and/or phosphate binders should be administered as appropriate per individual clinic practice.

Dialysate calcium concentrations should not be adjusted during the course of the trial, remaining at ≥ 2.5 mEq/L.

All concomitant medications taken by a subject while on study are to be recorded on the eCRF. Refer to [Section 7.3.7](#) for additional information regarding what is to be recorded.

6.5 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.6 Excluded Treatments and/or Procedures During Study Period

Subjects are prohibited from participating in other interventional studies (eg, studies which require medical device use or drug therapy or with protocol-required procedures) while participating in this study.

Cinacalcet is not approved for use in children and the use of commercial cinacalcet while participating in this study is prohibited. Refer to [Section 7.3.7](#) for additional information regarding the reporting of commercial cinacalcet use.

Subjects should not receive any medications known to prolong the QT interval (eg, ondansetron, albuterol) while participating in this study. In addition, the use of grapefruit juice, herbal medications, CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), or CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine) are excluded during the study. If subjects require these medications for temporary use, the administration of cinacalcet is to be withheld until the concomitant medication has been discontinued, at which time

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cinacalcet administration can be resumed. Additional information may be found in the IPIM.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Screening assessments and study procedures required for each visit are outlined in this section and the Schedule of Assessments ([Table 4](#)). The informed consent, and assent if applicable, must be obtained prior to performing any screening or study procedures.

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Table 4. Schedule of Assessments

	Screening	Day 1	Treatment Period (Week)																											FU Period	
	Week -1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	EOIP W28	ET/EOS W32
GENERAL & SAFETY ASSESSMENTS																															
Informed consent, Assent (if applicable)	X																														
Medical/Surgical History		X																													
12-lead ECG		X																												X	X
Physical Exam		X ¹																													X
Height, Tanner Stage		X ¹																													X
Dry Weight		X ¹																													X
Dialysate Ca Concentration		X																													
Blood Pressure, Heart Rate		X ¹			X				X				X				X				X				X				X	X	X
Concomitant Medications ²	X ²		Record Continuously																											X	X
Patient Diary Review		X ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ²			Record Continuously																											X	X
Serious Adverse events ²			Record Continuously																											X	X
LABORATORY ASSESSMENTS																															
Ionized Ca		X ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver Function Tests	X ²	X											X												X						X
Chemistry, hematology, 25(OH)Vit D ³	X ²	X ¹																												X	X
Ca, Albumin, cCa, P	X ¹	X ¹	X		X				X				X				X				X				X					X	X
iPTH	X ¹	X ¹			X				X				X				X				X				X					X	X
Total & Bioavail Testosterone (male)		X ¹																												X	
Serum Pregnancy Test (females of child bearing potential)	X																														X
BIOMARKER ASSESSMENTS																															
BALP, NTx, CTx, P1NP, FGF 23 ³		X ¹																												X	
DOSING																															
Dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cinacalcet Dose Titration		X				X				X				X				X					X				X				

Footnotes defined on next page

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Note: When it is not possible to perform a study visit at the specified time point, the visit may be performed within ± 3 days.

1 - Where the Screening and day 1 assessments for Study 20140159 overlap with visits in the Studies 20130356 or 20110100, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments.

2 - These procedures are required for Study 20140159 screening visit if > 14 days since last study visit in Studies 20130356 or 20110100 for subjects impacted by study termination.

3 - Biomarker Assessments and 25 (OH) Vit D are not required for subjects previously enrolled in 20110100. If baseline FGF23 is not collected at day 1, it must not be collected at week 28.

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Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.2 General Study Procedures

All on-study visits and dosing should be scheduled from day 1. Week 1 begins one week after the day 1 visit. It is important to perform study assessments and obtain samples at the time points outlined in the Schedule of Assessments in [Section 7.1](#).

The duplicate study assessments will be collected once for both studies as described in [Section 7.2.2](#).

When it is not possible to perform a study visit at the specified time point, the visit may be performed within ± 3 days. If a study visit is missed, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

With the exception of screening assessments, all study procedures for a visit must be completed on the same day.

It is the responsibility of the investigator to ensure that all procedures are performed according to the protocol.

Any blood or serum collected according to the Schedule of Assessments may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

Details regarding each type of procedure are provided in [Section 7.3](#)

7.2.1 Screening and Enrollment

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments ([Section 7.1](#), [Table 4](#)):

- Confirmation that the Informed Consent Form and Assent Form (if applicable) have been signed
- Registration of the subject in the IVR/IWR system
- Serum pregnancy test
- Serum calcium, serum albumin, and calculation of cCa, phosphorus
- iPTH

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7.2.2 Day 1

The following day 1 procedures are also required for the EOIP study visit for Amgen Study 20130356 and End of Study visit for Study 20110100 except where indicated. These procedures should not be duplicated and may be collected once where study visits overlap and entered onto the appropriate eCRF once eligibility for this study has been confirmed:

- 12-lead ECG
- physical exam
- dry weight
- height/Tanner stage
- dialysate calcium, type of dialysis
- blood pressure, heart rate
- ionized calcium
- central laboratory assessments including the following
 - serum calcium, serum albumin, and calculation of cCa, phosphorus
 - iPTH
 - liver Function Tests (LFT)
 - chemistry panel
 - hematology panel
 - 25 (OH) Vitamin D (not required for subjects from 20110100)
 - total & bioavailable testosterone (male)
 - bone specific alkaline phosphatase (BALP), cross-linked N-telopeptides of type 1 collagen (NTx), type 1 collagen cross-linked telopeptide (CTX), amino terminal propeptide of type 1 collagen (P1NP), FGF23 (not required for subjects from 20110100).

The following day 1 procedures will be recorded on the day 1 eCRF:

- medical history (including ongoing AEs/SAEs from studies, 20130356 and 20110100)
- concomitant medications
- adverse event reporting
- serious adverse event (SAE) reporting
- diary provision and training (all subjects)

Following completion of the day 1 visit assessments, eligibility, dry weight, and enrollment will be entered in the IVR/IWR system, as applicable. Following enrollment in the IVR/IWR system, IP will be dispensed and recorded on the day 1 eCRF.

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7.2.3 Treatment

The following procedures will be completed during the 28-week treatment period at the times designated in the Schedule of Assessments ([Table 4](#)). Study visits will occur weekly \pm 3 days. All blood samples for laboratory assessments for hemodialysis subjects are to be collected prior to initiating the dialysis session during the visit. Cinacalcet will be dispensed to subjects to take home for daily administration at the conclusion of the study visit weekly.

The following procedures and assessments will be completed at the times designated in the Schedule of Assessment ([Table 4, Section 7.1](#)) and recorded on the eCRF:

- concomitant medications
- documentation of subject compliance with daily administration of cinacalcet
 - patient diary review
 - counts of returned bottles of tablets/capsules/suspension
- adverse events, including signs and symptoms of hypocalcemia, seizures, and infections
- serious adverse events
- ionized calcium
- central laboratory assessments including the following:
 - serum calcium, serum albumin, and calculation of cCa, phosphorous
 - iPTH
 - LFT (weeks 11 & 23)

7.2.4 End of Investigational Product

The end of investigational product (EOIP) visit will occur at week 28. The procedures to be performed at this visit include the following:

- 12-lead ECG
- blood pressure, heart rate
- concomitant medications
- documentation of subject compliance with daily administration of cinacalcet
 - patient diary review
 - counts of returned bottles of tablets/capsules/suspension
- adverse events, including signs and symptoms of hypocalcemia, seizures, and infections
- serious adverse events

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- ionized calcium
- central laboratory assessments including the following:
 - serum calcium, serum albumin, and calculation of cCa, phosphorus
 - chemistry panel
 - hematology
 - 25 (OH) Vitamin D (not required for subjects from 20110100)
 - iPTH
 - total and bioavailable testosterone (male)
 - BALP, NTx, CTx, P1NP, FGF23 (not required for subjects from 20110100)

7.2.5 Early Termination

Subjects who discontinue participation in the study prior to week 28 will be asked to complete an early termination visit and should have all EOIP and EOS evaluations performed as outlined in the Schedule of Assessments and in [Sections 7.2.4](#) and [7.2.6](#).

7.2.6 End of Study Visit

Subjects will complete an EOS visit at week 32 within +/- 3 days of the scheduled visit date or at early termination. The following evaluations apply to the EOS visit:

- physical exam
- dry weight
- height/Tanner stage
- 12-lead ECG
- blood pressure, heart rate
- concomitant medications
- adverse events, including signs and symptoms of hypocalcemia, seizures, and infections
- serious adverse events
- central laboratory assessments including the following:
 - serum calcium, serum albumin, and calculation of cCa, phosphorous
 - chemistry panel
 - CBC, LFTs
 - 25 (OH) Vitamin D (not required for subjects from 20110100)
 - iPTH
 - serum pregnancy test (female of child bearing potential)

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7.3 Description of General Study Procedures

7.3.1 Informed Consent/Assent

All subjects must have a parent or legal representative sign and personally date the IRB/IEC approved informed consent form before any study specific procedures are performed. In addition, subjects must sign and personally date the assent form when applicable prior to the performance of any study specific procedures. See [Section 11.1](#) for further details.

7.3.2 Demographic Data

Demographic data including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. These data will be transferred from the studies 20130356 and 20110100.

7.3.3 Medical and Surgical History

The subject's complete medical and surgical history will be reviewed on day 1. The investigator or designee will collect a complete medical and surgical history for conditions that started within 5 years of the date of enrollment, including information on the subject's concurrent conditions. Ongoing adverse events and serious adverse events in studies 20130356 and 20110100 will be entered as concurrent conditions on the medical history form. This information will be recorded on the medical history eCRF for subjects enrolled into the study.

7.3.4 Physical Exam, Height, Tanner Stage, Dry Weight

A physical exam will be performed on day 1. Breast, genital, and rectal examinations are not required for any study visit unless specific evaluation is warranted.

The physical examination at the EOS visit will consist of a follow-up examination to monitor for any changes from the day 1 physical examination. Any clinically significant changes in the physical examination per the investigator's opinion should be recorded on the adverse event eCRF.

Information regarding the subject's residual urine output will be collected on day 1.

Height will be collected on day 1 and at the EOS visit and should be measured with the subject's shoes removed.

Tanner stage will be determined on day 1 and at the EOS visit and recorded in the eCRF.

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The subject's dry weight should be collected at day 1 and at the EOS visit post-dialysis for hemodialysis subjects and at the study visit, while the peritoneal cavity is empty, for peritoneal dialysis subjects. For all subjects the weight is to be measured with the subject wearing light clothing and with his/her shoes removed.

7.3.5 Blood Pressure and Heart Rate

The blood pressure should be taken with the subject's arm supported at heart level using the appropriate sized cuff with the subject comfortably seated in a chair with his/her back supported and both feet on the ground. Subjects should be resting quietly for at least 5 minutes before the blood pressure and heart rate are measured. For subjects receiving hemodialysis, blood pressure and heart rate are to be measured at the conclusion of the dialysis session. For subjects receiving peritoneal dialysis, blood pressure and heart rate are to be measured during the study visit. All measurements will be recorded in the eCRF.

7.3.6 ECG

The subject must be in a supine position in a calm and resting state for at least 5 minutes before the ECG assessment is conducted. If the subject is unable to be in a supine position, he/she should be in the most recumbent position possible.

The ECG must include the following measurements: heart rate, QRS, QTc, and RR, QT intervals. For the purposes of this study, the QTc should be provided or calculated using Bazett's formula (QT/\sqrt{RR}). For subjects receiving hemodialysis, the ECG is to be obtained prior to the initiation of the dialysis session. For subjects receiving peritoneal dialysis, the ECG is to be obtained during the study visit. All measurements will be recorded in the eCRF.

The investigator will review, sign, and date all ECGs. Once signed the original ECG tracing will remain in the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.3.7 Concomitant Medications

Concomitant medications will be collected beginning on day 1 through the end of study, and recorded in the eCRF for this study as described below.

The administration of vitamin D sterols, calcium supplementation, bisphosphonates, and phosphate binders, including the name of the medication, dose, unit, route, frequency, and start and stop dates of administration, will be collected.

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Commercial cinacalcet is an excluded medication during this study ([Section 6.6](#)). For subjects who receive commercial cinacalcet, this will be documented as a protocol deviation and the name of the medication, dose, unit, route, frequency, and start and stop dates of administration will be collected.

Changes in dialysate calcium concentration during the course of the trial will be documented as a protocol deviation. For subjects in whom the dialysate calcium concentration changes during the course of the trial, the change in concentration and start date will be collected.

For all other concomitant medications, including over the counter and herbal medicines, the name of the medication, start and stop dates of administration will be collected.

7.3.8 Electronic Patient Diary

Subject compliance with daily administration of cinacalcet will be collected using a handheld eDiary. The eDiary will collect date, time and amount of cinacalcet taken each day. Subjects will use the eDiary daily beginning on day 1 and completing at their week 28 study visit. It is expected that children under the age of 12 will have their parent(s) or legal guardian(s) complete the eDiary daily. Children ≥ 12 years of age may either have their parent(s) or legal guardian(s) complete the eDiary daily or do this themselves under the supervision of their parent(s) or legal guardian(s). The subjects will be instructed to bring their eDiary with them to every study visit. The data entered into the eDiary will be available to the investigator and/or study coordinator on a daily basis to enable ongoing reviews of subject compliance. The data collected will be reviewed with the subject by the investigator and/or study coordinator during the weekly study visits. The investigator and/or study coordinator will also reconcile any discrepancies between the eDiary and the IP accountability data during the weekly study visits. Reasons for discrepancies will be documented and subjects and/or parents/legal guardians counseled on the importance of compliance with the administration of cinacalcet during the trial. The data collected will be captured in the study database.

Refer to [Section 6.2.3.2](#) for additional information regarding the measures of compliance for this study and the eDiary manual for additional details.

7.3.9 Ionized Calcium

All ionized calcium values will be collected as specified in the Schedule of Assessments for identification of potential hypocalcemia. Ionized calcium values will be obtained either per routine practice at the clinical site or using a point of care device provided by

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Amgen. The clinical site will document the method that is being used to obtain the ionized calcium for each subject enrolled at the site and ensure that this remains consistent for the duration of the trial. All measurements should occur on the day of the study visit prior to the administration of cinacalcet. For sites that use the point of care device provided by Amgen, refer to the device manual provided for further information.

The measurements obtained will be entered into the IVR/IWR system at each study visit and entered into the eCRF.

In addition, cCa values from the central laboratory will be collected as specified in the Schedule of Assessments. These cCa values will be utilized for monthly dose titration visits.

7.3.10 Adverse Events

Adverse events will be collected in the eCRF for each subject at all study visits. Targeted questions regarding hypocalcemia, seizures and infections will be asked and data will be entered into the eCRF at each study visit.

All clinically significant (according to the investigator's judgment), laboratory abnormalities will be reported as adverse events. In assessing clinical significance of a low serum calcium value, the investigator should consider factors such as presence of clinical symptoms associated with hypocalcaemia, dose adjustment of cinacalcet or concomitant medications (eg, vitamin D, phosphate binders). In addition, the investigator should indicate on the eCRF whether hypocalcemia was symptomatic, and if so provide the accompanying symptoms.

Serious adverse events that occur in a subject from the date of the first dose through 30 days after the last dose of IP will be recorded in the adverse event eCRF. All adverse events that occur from the date of the first dose through 30 days after the last dose of IP will be recorded in the adverse event eCRF. Refer to [Section 9](#) for additional information.

7.3.11 Laboratory Assessments

All study laboratory samples, with the exception of the ionized calcium samples, will be processed and sent to the central laboratory for assessment. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all blood samples. All blood samples will be obtained via venipuncture prior to the administration of IP. The date and time of the sample collection will be recorded in the source documents at the site.

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Table 5 below outlines the specific analytes that will be assessed at the central laboratory:

Table 5. Analytes

Serum Chemistry	Hematology
Bicarbonate	Hemoglobin
Blood Urea Nitrogen	Hematocrit
Chloride	Platelets
Creatinine	White blood cell count
Potassium	Red blood cell count
Sodium	Liver Function Tests
Total Protein	ALT
Total Bilirubin	AST
Phosphorus	Alk Phos
Other	
iPTH, Albumin, Calcium	
Serum Pregnancy (females of child bearing potential)	
Corrected Calcium ^a	
Total and bioavailable testosterone (male)	
BALP, NTx, CTx, P1NP, 25(OH) Vitamin D, FGF23 (not required for subjects from 20110100)	

^a Corrected calcium will be determined by the central laboratory using the following formula, where 4.0 represents the average albumin level. No correction will be made if the serum albumin level is ≥ 4.0 g/dL.

Corrected calcium (mg/dL) = Measured total serum calcium (mg/dL) + 0.8 (4.0-serum albumin [g/dL])

7.3.12 Home Healthcare

Subjects receiving peritoneal dialysis may not have to be seen routinely by the investigator at the clinical site on a weekly basis. These subjects will be required to be seen in the clinic every 2 weeks, including the week prior to the monthly dosing titration visit and those visits where central laboratory samples are collected, at a minimum during the trial. The investigator may utilize their site staff or a qualified home healthcare service provider to conduct the procedures required for remaining weekly study visits, subject to the investigator's direction and oversight.

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

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Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to cinacalcet.

Blood Samples

Blood samples are to be collected for biomarker development at the following time points: day 1 and EOIP visit (week 28).

7.5 Sample Storage and Destruction

Any blood or biomarker sample collected according to the Schedule of Assessments (Table 4) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If permitted by local regulations and informed consent is provided by the subject's legally acceptable representative(s), Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the CKD and SHPT, the dose response and/or prediction of response to cinacalcet, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed.

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However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See [Section 11.3](#) for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments ([Table 4](#)) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments ([Table 4](#)) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.1 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from IP, protocol procedures, or the study as a whole at any time prior to study completion.

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Subjects may be eligible for continued treatment with Amgen IP(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with [Section 12.1](#).

8.2 Reasons for Removal From Study

8.2.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required IP(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- protocol-specified criteria (eg, renal transplant, parathyroidectomy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

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If the toxicity grade of an adverse event worsens from the date of onset to the date of resolution, record as a single event with the worst CTCAE grade on the Adverse Event Summary eCRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to [Section 6.3.1](#) for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see [Appendix A](#) for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

Ongoing adverse events and serious adverse events in studies 20130356 or 20110100, will be entered as a concurrent condition on the Medical History eCRF.

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the date of the first dose and up to

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30 days after the last dose of IP, are reported using the applicable eCRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- toxicity,
- assessment of relatedness to IP, and
- action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). The grading scale used in this study is described in [Appendix A](#). The investigator must assess whether the adverse event is possibly related to the IP. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the IP?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur from the date of the first dose through 30 days after the last day of the dosing interval of IP or end of study visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the serious adverse event form.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the

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investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

See [Appendix A](#) for a sample of the Serious Adverse Event Worksheet.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapy, report the pregnancy to Amgen as specified below.

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In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of cinacalcet through 90 days.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet ([Appendix C](#)). Amgen Global Patient Safety will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking cinacalcet report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of cinacalcet through 90 days.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet ([Appendix C](#)).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

- Incidence of treatment emergent adverse events of interest

Secondary Endpoints:

20140159 study only

- Achievement of $\geq 30\%$ reduction from baseline to mean iPTH during weeks 11 and 15 (SOC arm of Study 20130356 only)
- Achievement of $\geq 30\%$ 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)
- Change in corrected total serum calcium from baseline to mean value during weeks 23 and 28
- Change in serum phosphorus from baseline to mean value during weeks 23 and 28
- Achievement of a mean iPTH ≤ 300 pg/mL during weeks 23 and 28
- Serum cCa at baseline, week 11, and week 28
- Serum phosphorus at baseline, week 11, and week 28

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Combined 20130356, 20110100, and 20140159 Studies

- Achievement of $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15
- Achievement of $\geq 30\%$ 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 Endpoints:

Study 20140159 only

- Growth velocity from baseline to EOS
- Change in Tanner stage from baseline to EOS

Combined Studies 20130356, 20110100, and 20140159

- 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

10.1.2 Analysis Sets

Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects in Study 20140159.

Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who receive at least one dose of cinacalcet.

Efficacy Analysis Set

The Efficacy Analysis Set includes all enrolled subjects **who received at least one dose of cinacalcet and have at least one assessment after day 1.**

10.1.3 Covariates and Subgroups

The primary, secondary, and safety endpoints may be summarized by baseline age group (6 to < 12 years and 12 to < 18 years for Study 20130356; 28 days to < 2 years and 2 to < 6 years for Study 20110100) as supportive analyses upon availability of data in each subgroup.

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10.2 Sample Size Considerations

This is an extension study of Studies 20130356 and 20110100. The sample size may be up to 78 subjects.

10.3 Planned Analyses

10.3.1 Interim Analysis

Several interim analyses may be conducted. The first interim analysis will be performed to support the Supplemental New Drug Application (sNDA) for pediatric indication. Its scope of analysis will be limited to the planned analysis using 20140159 study data only. The rest of interim analyses may be performed to support further request from regulatory. The scope of these analyses will be specified in a separate statistical analysis plan of interim analysis. There is no plan to conduct formal statistical testing. There are no plans to change the conduct of the study based on interim analysis results.

10.3.2 Primary Analysis

The general approach is to provide estimates for the primary and secondary endpoints for the study population.

The primary analysis of all endpoints will be conducted after all subjects have completed the week 32 EOS visit or terminated early from Study 20140159.

The primary analysis of all endpoints will be conducted after all subjects have completed the week 32 EOS visit or terminated early from Study 20140159.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

There is no formal statistical testing for this study. The analysis for all endpoints will be descriptive in nature. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, and minimum and maximum values, where applicable).

For categorical variables, the number and percentage of subjects in each category will be reported. Graphical presentations may be provided for selected variables.

All summary tables will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet) and Study 20110100 and overall, unless otherwise specified.

10.4.2 Primary Endpoint

The analysis of the primary endpoint will be based on the Safety Analysis Set. The primary analysis of the primary endpoint is subject incidence of events of interest (EOI;

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eg, hypocalcemia, convulsions, hypotension, worsening of heart failure, hypersensitivity, ischemic heart disease, QT prolongation/ventricular tachyarrhythmias, fracture, acute pancreatitis, drug-related hepatic disorders, nervous system disorders [excluding seizures], neoplastic events, and infection) for data in the 20140159 study only. The secondary analysis of the primary endpoint is the incidence of events of interest adjusted by the amount of safety follow-up time for combined data from parent studies and data from the 20140159 study. The 95% confidence intervals (CI) of the overall incidence rates will be reported.

10.4.3 Secondary Endpoints

The **analysis of secondary endpoints will be based on Efficacy Analysis Set. The approach for handling the missing data will be described for each endpoint in the statistical analysis plan.**

20140159 study only

The proportion of subjects who achieve a $\geq 30\%$ reduction from baseline of Study 20140159 to mean iPTH at weeks 11 and 15 and to mean iPTH at weeks 23 and 28 will be assessed for the SOC arm in Study 20130356 with a 95% CI.

Summary statistics will be provided for the percent change in mean iPTH from baseline in Study 20140159 during weeks 23 and 28 for the SOC group in Study 20130356.

Summary statistics will be provided for the change in corrected total serum calcium and change in serum phosphorus from baseline of Study 20140159 to mean value at weeks 23 and 28 by treatment group in the parent study.

The proportion of subjects who achieve a mean iPTH value of ≤ 300 pg/mL during weeks 23 and 28 will be provided by treatment group in the parent study with a 95% CI.

Summary statistics will be provided for serum cCa and phosphorus values at baseline to week 11 and week 28.

Combined 20130356, 20110100, and 20140159 Studies

The proportion of subjects who achieve a $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH at weeks 11 and 15 and to mean iPTH at weeks 23 and 28 will be provided by previous treatment group in the parent study with a 95% CI.

The percent change in iPTH, change in corrected serum calcium, and change in serum phosphorus from day 1 of cinacalcet treatment at each measurement time point will be summarized overall.

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10.4.4 Safety Endpoints

The safety analysis will be based on the safety analysis set. All safety endpoints in 20140159 study only and combined with their parent studies will be summarized by treatment group in the parent studies and overall.

Adverse Events

All treatment-emergent adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary. The subject incidence of all treatment-emergent adverse events, serious adverse events, treatment-related adverse events, and serious treatment-related adverse events will be tabulated by system organ class and preferred term in descending order of frequency. Tables of treatment-emergent adverse events, fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product or from study will be tabulated by preferred term.

Laboratory Data, Blood Pressure, and Heart Rate

Descriptive statistics for values, changes and percent changes of selected laboratory parameters from first dose of IP date will be presented at each measurement time point during the study. In addition, shift tables will summarize grades using CTCAE (version 3) by worst grades between baseline and any visit up to the end of the study for selected hematology and chemistry parameters.

The incidence of hypocalcemia after the first dose of IP will be summarized using descriptive statistics. Hypocalcemia will be defined in two ways: with the subject incidence of corrected serum calcium of < 7.5 mg/dL, < 8.0 mg/dL, and < 8.4 mg/dL being summarized; **and with** subject incidence of ionized calcium value < 0.94 mmol/L, < 1.05 mmol/L, and < 1.00 mmol/L **being** summarized. Blood pressure (systolic and diastolic) and heart rate will be summarized at each time point.

Medications of Interest

Use of vitamin D sterols and phosphate binders during study.

ECG

The ECG measurements from this clinical study will be 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, summaries

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and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen clinical study manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the

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subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

In this study, obtaining assent from the child and consent from the parents or legally authorized representative, except if the child is very young, as defined by local law will apply. A child is defined as a person who has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place. The local IRB/IEC will determine the process for obtaining and documenting the assent process for pediatric subject, but should follow the guidelines established by the Department of Health and Human Services (DHHS) Office of Human Research Protections guidelines, which state an explanation of the procedures involved in the study should be made in a language appropriate to the child's age, experience, maturity, and condition.

11.2 Institutional Review Board/Independent Ethics Committee A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

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whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements should include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, IB, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical

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research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

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12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments ([Table 4](#)), the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES[®] (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the [International Committee of Medical Journal Editors \(ICMJE\)](#) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

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- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Additional information on the current guidelines for publications can be found at the following location: <http://www.icmje.org/>.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

During the study, the subjects may be reimbursed for reasonable expenses associated with the study (eg, transportation), if permitted under applicable regional laws or regulatory guidelines. The subjects' parents or legal representatives may be compensated for other inconveniences not associated with study-related injuries (eg, lost work time), if permitted under applicable regional laws or regulatory guidelines. These arrangements for compensation are described in the Informed Consent that is available as a separate document.

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14. APPENDICES

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Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in [Section 6.3](#) require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in [Section 9.1.2](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Sections 6.3.1](#) and [6.3.2](#) or who experience AST or ALT elevations > 3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

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Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
 - Obtain complete blood count (CBC) with differential to assess for eosinophilia
 - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
 - Obtain serum acetaminophen (paracetamol) levels
 - Obtain a more detailed history of:
 - Prior and/or concurrent diseases or illness
 - Exposure to environmental and/or industrial chemical agents
 - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
 - Prior and/or concurrent use of alcohol, recreational drugs and special diets
 - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

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[illegible]

01 Fatal	03 Required hospitalization	05 Persistent or significant disability/incapacity	07 Other significant health hazard
02 Immediately life-threatening	04 Prolonged hospitalization	06 Congenital anomaly/birth defect	

4. HOSPITALIZATION

	Date Admitted			Date Discharged		
	Day	Month	Year	Day	Month	Year

5. INVESTIGATIONAL PRODUCT IP

Initial/Start Date	Prior to, or at time of Event	Product	Action Taken with Product
Date of Dose	Illicit Use	Route	Frequency
			01 Still being administered
			02 Potentially discontinued

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Open Label	Day	Month	Year	Day	Month	Year	US Withhold
6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy)							Ally Relevant Medications?
Medication Name(s)							Treatment
Start Date							Stop Date
Cosuspect							Continuing
Dose							Route
freq.							



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AMGEN 20140159	Clinical Trial Serious Adverse Event Report Phase 1-4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input checked="" type="checkbox"/> Follow-up
---------------------------------	---	---

1. <i>Site Number</i>	2. <i>Subject ID Number</i>	3. <i>Venue</i>

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory Values? ☐ No ☒ Yes. If yes, please complete:

Test	Date	Unit	Result	Reference Range	Abnormal	Comments

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* My other Relevant tests? ☐ No ☒ Yes. If yes, please complete:

Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* For each event in section 3, where relationship = Yes, please provide rationale.

Signature of Investigator or Designee	Date

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Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE N/A/FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (_____) _____ Fax (_____) _____

Email _____

Institution _____

Address _____

Subject ID # _____

Subject Gender: ☐ Female ☐ Male

Subject DOB: mm ____ / dd ____ / yyyy ____

3. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____

Did the subject Withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by: _____

Print Name: _____

Title: _____

Signature: _____

Date: _____

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Ati'GETf Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX LINE

1. Case Administrator

Protocol/Study Number: _____

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone _____ Fax _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____

Did the subject Withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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Amendment 1

Protocol Title: A MulticenterSingle-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

Amgen Protocol Number (Cinacalcet HCl) 20140159

Amendment Date: 18 December 2014

Rationale:

The purpose of this amendment is to incorporate language regarding the transition of eligible subjects from the parent study (Amgen Study 20130356) to this open label extension. The amendment also addresses updates made to language regarding study procedures for consistency within the cinacalcet pediatric program.

Minor administrative changes and clarifications have also been incorporated.

Additions are noted in **bold** text.

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Description of Changes:

Section: Global

Replace date of protocol:

5 August 2014

With:

18 December 2014

Section: Cover Page

Replace:

PPD [REDACTED], MS

One Amgen Center Drive
Thousand Oaks, CA 91320

PPD [REDACTED]

With:

PPD [REDACTED]

PRA Health Services

520 Virginia Drive

Fort Washington, PA 19034

PPD [REDACTED]

Cover:

Replace:

<<for all other countries, insert the local toll-free Medical Information number>>

With:

**for all other countries, please call the local toll-free Medical Information number or
the US toll-free number (1-800-772-6346).**

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Section: Protocol Synopsis, Page 3

Replace:

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

With:

- Blood pressure, heart rate, and changes in laboratory parameters

Section: Protocol Synopsis, Page 3

Replace:

Subjects who complete the 20-week treatment period in the parent study 20130356 will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study.

With:

Subjects who complete the 20-week treatment period in the parent study 20130356 will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, **followed by a 4-week safety follow-up.**

Section: Protocol Synopsis, Page 4

Replace:

Weekly monitoring with a point of care (POC) device during this study will be required for these subjects through the end of the treatment period, week 28.

With:

Weekly monitoring of ionized calcium will be required for these subjects through the end of the treatment period, week 28.

Section: Protocol Synopsis, Page 4

Replace:

Subjects from the cinacalcet group who complete the 20-week treatment period in parent study 20130356, will continue in the extension study on the same dose of cinacalcet they received at the completion of the treatment period (week 20) in the parent study.

With:

Subjects from the cinacalcet group who complete the 20-week treatment period in the parent study 20130356, will continue in the extension study on cinacalcet at the

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completion of the treatment period (week 20) in the parent study **following the dose titration rules outlined in Table 1 in Section 6.2.3.1.2.**

Section: Protocol Synopsis, Page 4

Replace:

Cinacalcet doses will be assigned by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6.

With:

Cinacalcet doses will be **calculated by the site staff and confirmed** by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6.

Section: Protocol Synopsis, Page 4

Replace:

Final dose assignment will be based on the ionized calcium. An assessment of symptomatic hypocalcemia will also be assessed on the day of titration.

With:

Final dose assignment will be based on the ionized calcium **obtained on the day of titration**. An assessment of symptomatic hypocalcemia will also be **performed** on the day of titration. **Additional weekly dose adjustments for safety are permitted as described in Section 6.2.3.1.3.**

Section: Protocol Synopsis, Page 5

Replace:

The use of medications that may prolong the corrected QT (QTc) interval (eg, ondansetron, albuterol), CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), and commercial cinacalcet during the course of the trial are prohibited.

Serious adverse events will be collected from study day 1 through 30 days following the last dose of investigational product.

With:

The use of medications that may prolong the corrected QT (QTC) interval (eg, ondansetron, albuterol), CYP3A4 inhibitors (eg, erythromycin, clarithromycin,

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ketoconazole, itraconazole), **CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortryptiline, clomipramine)**, and commercial cinacalcet during the course of the trial are prohibited **while the subject is receiving investigational product**.

Serious adverse events will be collected from **the date of the first dose** through 30 days following the last dose of investigational product.

Section: Glossary, Page 8

Replace:

Study Day 1	defined as the date that the day 1 laboratory assessments are performed
-------------	---

With:

Study Day 1	defined as the date that the initial dose of investigational product is administered
-------------	---

Section: 2.4 Pediatric Risk Assessment, Page 15

Replace:

Additional risk mitigation measures implemented in this trial include:

- use of a point of care (POC) device to provide real-time calcium measurements

With:

Additional risk mitigation measures implemented in this trial include:

- **collection of** real-time **ionized** calcium measurements

Section: 2.5 Amgen Study 20130356, Page 16

Add:

Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the 20-week treatment period in 20130356. The 4-week safety follow-up period in 20130356 will not apply for these subjects.

Section: 3.1 Study Design, Page 17

Replace:

All subjects will be eligible to titrate the cinacalcet dose at monthly titration visits to a maximum dose of 2.5 mg/kg/day, not to exceed a dose of 180 mg/day.

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With:

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

Section: 3.2 Number of Sites, Page 17

Replace:

This study will be conducted at approximately 60 sites in North America, Europe, Russia, Latin America, and Australia.

With:

This study will be conducted at approximately **50** sites in North America, Europe, Russia, Latin America, and Australia.

Section: 4.1.1 Inclusion Criteria, Page 18

Replace:

104 Dialysate calcium ≥ 2.5 mEq/L at day 1

With:

104 Dialysate calcium **concentration** ≥ 2.5 mEq/L at day 1

Section: 4.1.2 Exclusion Criteria, Page 19

Replace:

215 Use of grapefruit juice, herbal medications or CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole)

With:

215 Use of grapefruit juice, herbal medications, CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), **or CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine)**

Section: 5.1 Screening, Page 19

Replace:

The informed consent can be signed up to 1 week prior to day 1 (eg, at week 19 in 20130356).

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With:

The informed consent can be signed up to 1 week (**± 3 days**) prior to day 1 (eg, at week 19 in 20130356).

Section: 6.2.3.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Page 22

Replace:

If subjects from the cinacalcet arm in 20130356 are on a dose withhold at day 1, the iPTH and cCa restart values (iPTH \geq 150 pg/mL and cCa \geq 8.4 mg/dL) must be reached prior to resuming cinacalcet in the current extension study.

With:

If subjects from the cinacalcet arm in 20130356 are on a dose withhold at day 1, the iPTH and cCa restart values (iPTH $>$ **100** pg/mL and cCa $>$ 8.4 mg/dL) must be reached prior to resuming cinacalcet in the current extension study.

Section: 6.2.3.1.1 Dosage Adjustments, Page 22

Replace:

The initial dose of cinacalcet and all subsequent doses will be assigned by the IVR/IWR system.

With:

The initial dose of cinacalcet and all subsequent doses will be **calculated by the site staff and confirmed** by the IVR/IWR system.

Section: 6.2.3.1.2 Monthly Dose Titration, Page 22

Replace:

Cinacalcet doses will be titrated up or down one PSD or maintained monthly by the IVR/IWR system using the corrected serum calcium and iPTH values obtained from the central laboratory the week prior to the dose titration visit, as well as assessments of symptoms of hypocalcemia and ionized calcium values from the POC device obtained on the day of the titration visit, as outlined in Table 1 below.

With:

Cinacalcet doses will be titrated up or down one PSD or maintained monthly **and confirmed** by the IVR/IWR system using the corrected serum calcium and iPTH values

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obtained from the central laboratory the week prior to the dose titration visit, as well as assessments of symptoms of hypocalcemia and ionized calcium values obtained on the day of the titration visit, as outlined in Table 1 below.

Section: 6.2.3.1.2 Monthly Dose Titration, Page 23

Replace:

If the central laboratory corrected calcium value is < 8.0 mg/dL at any time during the trial, the dose of cinacalcet is to be withheld until the central laboratory corrected calcium value is > 8.4 mg/dL, at which time the dose may be restarted at one PSD below the previous dose received, if the iPTH is > 100 pg/mL, the ionized calcium using the POC device is > 1.05 mmol/L, and the subject has no symptoms of hypocalcemia.

With:

If the central laboratory corrected calcium value is < 8.0 mg/dL at any time during the trial, the dose of cinacalcet is to be withheld until the central laboratory corrected calcium value is > 8.4 mg/dL, at which time the dose may be restarted at one PSD below the previous dose received, **provided that** the iPTH is > 100 pg/mL, the ionized is > 1.05 mmol/L, and the subject has no symptoms of hypocalcemia.

Section: 6.2.3.1.3 Dose Adjustments for Safety, Page 23

Replace:

Administration of cinacalcet may be withheld at any time during the study based on the ionized calcium obtained using the POC device, local laboratory total corrected calcium values, and/or if the subject has signs/symptoms of hypocalcemia. The dose may be decreased based on the ionized calcium obtained using the POC device, as described in Table 2 below.

With:

Administration of cinacalcet may be withheld at any time during the study based on the ionized calcium, local laboratory total calcium values, and/or if the subject has signs/symptoms of hypocalcemia. The dose may be decreased based on the ionized calcium, as described in Table 2 below.

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Section: 6.2.3.1.3 Dose Adjustments for Safety, Page 24

Replace:

If at any time the subject has a local total corrected calcium value of < 8.0 mg/dL, the dose of investigational product must be withheld until an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained, at which time the dose may be resumed at one PSD below the previous dose.

With:

If at any time the subject has a local total calcium value of < 8.0 mg/dL, the dose of investigational product must be withheld until an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained, at which time the dose may be resumed at one PSD below the previous dose.

Section: 6.2.3.1.3 Dose Adjustments for Safety, Page 24

Replace:

In addition, if subjects require temporary administration of concomitant medications that are known to prolong the QTc interval or are CYP 3A4 inhibitors, the administration of cinacalcet is to be withheld. The dose may be restarted when an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained, at which time the dose may be resumed either at one PSD below the previous dose or at the initial dose if the criteria in Section 6.2.3.1.4 are met.

With:

In addition, if subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, **or are CYP2D6 substrates**, the administration of cinacalcet is to be withheld. The dose may be restarted when **treatment with the concomitant medication has completed** and an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained at which time the dose may be resumed either at one PSD below the previous dose or at the initial dose if the criteria in Section 6.2.3.1.4 are met.

Section: 6.4 Concomitant Therapy, Page 28

Replace:

Dialysate calcium levels should not be adjusted during the course of the trial, remaining at ≥ 2.5 mEq/L.

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With:

Dialysate calcium **concentrations** should not be adjusted during the course of the trial, remaining at ≥ 2.5 mEq/L.

Section: 6.6 Excluded Treatments and/or Procedures During Study Period, Page 29

Replace:

In addition, the use of grapefruit juice, herbal medications, or CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole) are excluded during the study.

With:

In addition, the use of grapefruit juice, herbal medications, CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole), **or CYP2D6 substrates (eg, flecainide, propafenone, metoprolol, desipramine, nortriptyline, clomipramine)** are excluded during the study.

Section: Schedule of Assessments, Table 3, Page 30

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Replace:

	Screening	Day 1	Treatment Period (Week)																											FU Period	
	Week -1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	EoIP W28	ET/EOS W32
GENERAL & SAFETY ASSESSMENTS																															
Height, Tanner Stage		X ²																													X
Dry Weight		X ²																													X
Dialysate Ca		X																													
LABORATORY ASSESSMENTS																															
Ionized Ca		X ²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Liver Function Tests		X											X																		X

With:

	Screening	Day 1	Treatment Period (Week)																											FU Period		
	Week -1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	EoIP W28	ET/EOS W32	
GENERAL & SAFETY ASSESSMENTS																																
Height, Tanner Stage		X ²																														X
Dry Weight		X ²																														X
Dialysate Ca Concentration		X																														
LABORATORY ASSESSMENTS																																
Ionized Ca		X ²	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Liver Function Tests		X										X													X							X

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Section: 7.2 General Study Procedures, Page 31

Replace:

The duplicate study assessments from the end of investigational product (EOIP) visit in the parent study, 20130356, and from the day 1 visit can be collected once for both studies as described in Section 7.2.2.

With:

The duplicate study assessments from the end of the investigation product (EOIP) visit in the parent study, 20130356, and from the day 1 visit **will** be collected once for both studies as described in Section 7.2.2.

Section: 7.2.1 Screening and Enrollment, Page 31

Add:

- **Registration of the subject in the IVR/IWR system**

Section: 7.2.2 Day 1, Page 32

Replace:

- Laboratory Assessments including the following:
 - Ionized calcium using a POC device
 - Serum calcium, serum albumin, and calculation of corrected calcium, phosphorus

With:

- **Ionized calcium**
- **Central** laboratory assessments including the following
 - Serum calcium, serum albumin, and calculation of corrected calcium, phosphorus

Section: 7.2.2 Day 1, Page 32

Replace:

Following completion of the day 1 visit assessments, eligibility, and enrollment will be entered into the IVR/IWR system, as applicable.

With:

Following completion of the day 1 visit assessments, eligibility, **dry weight**, and enrollment will be entered in the IVR/IWR system, as applicable.

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Section: 7.2.3 Treatment, Page 33

Replace:

Laboratory Assessments including the following

- Laboratory Assessments including the following:
 - Serum calcium, serum albumin, and calculation of corrected calcium, phosphorous
 - iPTH
 - LFT (Weeks 11 & 23)
 - Ionized calcium using the POC device

Ionized calcium will be collected prior to IP dispensing.

With:

- **Ionized calcium**
- **Central** laboratory assessments including the following:
 - Serum calcium, serum albumin, and calculation of corrected calcium, phosphorous
 - iPTH
 - LFT (Weeks 11 & 23)

Section: 7.2.4 End of Investigational Product, Page 33

Remove:

- Dry weight, Tanner stage

Section: 7.2.4 End of Investigational Product, Page 33

Replace:

- Laboratory assessments including the following:

With:

- **Ionized calcium**
- **Central** laboratory assessments including the following:

Section: 7.2.6 End of Study, Page 34

Add:

- **Dry weight**
- **Height/Tanner stage**

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Section: 7.2.6 End of Study, Page 34

Replace:

- Laboratory assessments including the following:

With:

- Central laboratory assessments including the following:

Section: 7.3.4 Physical Exam, Height, Tanner Stage, Dry Weight, Page 35

Replace:

Height will be collected on day 1 and at the EOIP visit...

Tanner stage will be determined on day 1 and at the EOIP visit...

The subject's dry weight should be collected at day 1 and at the end of investigational product visit...

With:

Height will be collected on day 1 and at the **EOS** visit...

Tanner stage will be determined on day 1 and the **EOS** visit...

The subject's dry weight should be collected at day 1 and at the **EOS** visit...

Section: 7.3.9 Ionized Calcium, Page 37

Replace:

All ionized calcium values will be collected as specified in the Schedule of Assessments for identification of potential hypocalcemia. Ionized calcium values will be obtained using a POC device provided by Amgen. All measurements should occur on the day of the study visit prior to the administration of cinacalcet. The blood sample to be used for ionized calcium measurements will be obtained by venipuncture. The utilization of blood obtained by a finger or heel stick for ionized calcium evaluations will not be permitted.

With:

All ionized calcium values will be collected as specified in the Schedule of Assessments for identification of potential hypocalcemia. Ionized calcium values will be obtained **either per routine practice at the clinical site or using a point of care device** provided by Amgen. **The clinical site will document the method that is being used to obtain the ionized calcium for each subject enrolled at the site and ensure that this**

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remains consistent for the duration of the trial. All measurements should occur on the day of the study visit prior to the administration of cinacalcet. **For sites that use the point of care device provided by Amgen, refer to the device manual provided for further information.**

Section: 7.3.10 Adverse Events, Page 38

Replace:

Serious adverse events that occur in a subject from study day 1 through 30 days after the last dose of investigational product will be recorded in the adverse event eCRF. All adverse events that occur after enrollment through 30 days after the last dose of investigational product will be recorded in the adverse event eCRF.

With:

Serious adverse events that occur in a subject from **the date of the first dose** through 30 days after the last dose of investigational product will be recorded in the adverse events eCRF. All adverse events that occur **from the date of the first dose** through 30 days after the last dose of investigational product will be recorded in the adverse event eCRF.

Section: 7.3.12 Home Healthcare, Page 39

Replace:

These subjects will be required to be seen in the clinic every 2 weeks, including the monthly dosing titration visit, at a minimum during the trial.

With:

These subjects will be required to be seen in the clinic every 2 weeks, including the **week prior to the** monthly dosing titration visit, at a minimum during the trial.

Section: 9.2.1 Reporting Procedures for Adverse events that do not meet Serious Criteria, Page 44

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after day 1 and up to 30 days after the last dose of IP, are reported using the applicable CRF (eg, Adverse Event Summary).

With:

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The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from the date of the first dose** and up to 30 days after the last dose of IP, are reported using the applicable **eCRF** (eg, Adverse Event Summary).

Section: 9.2.2 Reporting Procedures for Serious Adverse Events, Page 45

Replace:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after day 1 through 30 days after the last day of the dosing interval of investigational product or end of study visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen.

With:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur **from the date of the first dose** through 30 days after the last day of the dosing interval of investigational product or end of study visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen.

Section: 10.2 Sample Size Considerations, Page 47

Replace:

The sample size of 48 for the parent study will result in a maximum of 48 subjects.

With:

The sample size of **approximately** 48 for the parent study will result in a maximum of 48 subjects.

Section: 10.4.2 Primary Endpoint, Page 48

Replace:

The primary endpoint is subject incidence of events of interest (EOI; eg, symptomatic hypocalcemia, seizure, hypotension, worsening heart failure, hypersensitivity reactions, ventricular arrhythmia, fracture, pancreatitis, drug-related hepatic disorders, nervous system disorders, and infection).

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With:

The primary endpoint is subject incidence of events of interest (EOI; hypocalcemia, **convulsions**, hypotension, worsening **of** heart failure, hypersensitivity, **ischemic heart disease, QT prolongation/ventricular tachyarrhythmias**, fracture, **acute** pancreatitis, drug-related hepatic disorders, nervous system disorders **[excluding seizures]**, **neoplastic events**, and infection).

Section: 10.4.4 Safety Endpoints, Page 49

Replace:

All treatment-emergent adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary and the subject incidence will be tabulated by system organ class and preferred term in descending order of frequency by parent study treatment group.

With:

All treatment-emergent adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary. **The** subject incidence **of all treatment-emergent adverse events, serious adverse events, treatment-related adverse events, and serious treatment-related adverse events** will be tabulated by system organ class and preferred term in descending order of frequency by parent study treatment group.

Section: 10.4.4 Safety Endpoints, Page 49

Replace:

Descriptive statistics for values, changes and percent changes of laboratory parameters from first dose of IP date will be presented by parent study treatment group at each measurement time point during the study.

With:

Descriptive statistics for values, changes and percent changes of **selected** laboratory parameters from first dose of IP date will be presented by parent study treatment group at each measurement time point during the study.

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Date: 22 July 2015

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Amendment 2

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

Cinacalcet HCl
Amgen Protocol Number 20140159

Amendment Date: 22 July 2015

Rationale:

- Added inclusion of eligible subjects from 20110100 into this extension study.
- Added investigational product (IP) holding for other adverse events that warrant IP dose withhold. Original protocol only specified hold for corrected calcium (cCa), ionized calcium (iCa), intact parathyroid hormone (iPTH), and symptomatic hypocalcemia.
- Made restart criteria consistent for all IP holds.
- Revised the Dose Adjustments section for clarity.
- Clarified the iCa value on Day 1 must be ≥ 1.05 mmol/L prior to initiation of treatment for all subjects enrolling from 20120356 study and only subjects who are ≥ 2 years of age in Study 20110100. The iCa value on Day 1 for subjects who are < 2 years of age enrolling from Study 20110100 must be ≥ 1.13 mmol/L.
- Updated Key Contact from PPD to PPD
- Removed reference to serious adverse events being reported via the electronic case report form (eCRF). For this open-label extension study, serious adverse events are reported via a paper form.
- Clarified eligibility for the 20140159 study for those subjects who turn 18 years of age while participating in the 20130356 study.
- Revised the wording to indicate that standard of care therapy that is commercially available will not usually be provided or reimbursed by Amgen (except if required by local regulation) as these will need to be provided to sites in Russia.
- Updated study design and treatment schema to be consistent with the other changes in the protocol.

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Description of Changes:

Section: Global

Replace:

18 December 2014

With:

22 July 2015

Section: Title Page

Add:

Amendment 2: 22 July 2015

Section: Title Page

Key Sponsor Contact

Replace:

PPD

PRA Health Services
520 Virginia Drive
Fort Washington, PA 19034

PPD

With:

PPD

Amgen Limited
1 Sanderson Road (Uxbridge Business Park),
Uxbridge, Middlesex, United Kingdom, UB8 1DH

PPD

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Section: Synopsis, Study Design

Paragraph 1

Replace:

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. Eligible subjects will complete the 20-week treatment period in the parent Study 20130356 prior to enrollment in this trial.

With:

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 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.

Section: Synopsis, Sample Size

Replace:

Up to 48 subjects may be enrolled

With:

Up to **78** subjects may be enrolled

Section: Synopsis, Summary of Subject Eligibility Criteria

Replace:

Subjects who complete the 20-week treatment period in the parent Study 20130356 will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, followed by a 4-week safety follow-up. Subjects must also meet the inclusion and exclusion criteria for this extension study in order to be eligible. Subjects must provide written informed consent (parents or guardian) and assent, where appropriate, according to local regulations specific to the procedures in this study. Subjects enrolled in the standard of care arm of Study 20130356 will be eligible for the extension study if the iPTH ≥ 300 pg/mL and the cCa ≥ 8.8 mg/mL at the week 19 visit. Eligible subjects from

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the cinacalcet arm in Study 20130356 will continue cinacalcet treatment following the dosing rules described in Section 6.2.3. Subjects will be excluded from this study if they have adverse events continuing from Study 20130356 that are considered related to investigational product (IP) and are \geq CTCAE grade 3 and/or considered clinically significant by the investigator. For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

With:

Subjects who complete the 20-week treatment period in Study 20130356 **or Week 26 End of Study visit in Study 20110100** will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, followed by a 4-week safety follow-up. Subjects must also meet the inclusion and exclusion criteria for this extension study in order to be eligible. Subjects must provide written informed consent (parents or guardian) and assent, where appropriate, according to local regulations specific to the procedures in this study.

- Subjects enrolled in the standard of care arm of Study 20130356 will be eligible for the extension study if the iPTH \geq 300 pg/mL and the cCa \geq 8.8 mg/mL at the week 19 visit. Eligible subjects from the cinacalcet arm in Study 20130356 will continue cinacalcet treatment following the dosing rules described in Section 6.2.3.
- **Eligible subjects from 20110100 study will restart cinacalcet treatment as described in Section 6.2.3.1.**

Subjects will be excluded from this study if they have adverse events continuing from Study 20130356 **or 20110100** study that are considered related to investigational product (IP) and are \geq CTCAE grade 3 and/or considered clinically significant by the investigator. For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

Section: Synopsis, Amgen Investigational Product Dosage and Administration

Paragraph 3

Replace:

The protocol-specified doses (PSD) for use in this study are: 2.5, 5, 10, 15, 30, 60, 90, 120 and 180 mg.

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With:

The protocol-specified doses (PSD) for use in this study are: 1, 2.5, 5, 7.5, 10, 15, 30, 60, 90, 120 and 180 mg.

Section: Synopsis, Procedures

Paragraphs 1, 2, 3, and 4

Replace:

Informed consent, and assent where applicable, for this study should be presented during the parent Study 20130356. The informed consent, including assent as appropriate, will be obtained prior to execution of any study procedures for this extension study. The study assessments from the parent study End of Investigational Product (EOIP) visit may be collapsed with the study assessments for the baseline visit in the current study to minimize duplicate study assessments. The subject visits and assessments for this study will occur from baseline through to the end of study. Assessments during this study will include:

- Collection of blood samples for the evaluation of blood chemistry, hematology, calcium, iPTH, and bone biomarkers
- Physical assessments including vital signs (ie, blood pressure, heart rate)
- 12-lead electrocardiogram (ECG) at baseline and week 32 (if the subject ends the study prior to week 32, the 12-lead ECG will be performed at the last study visit)
- Assessments for symptoms of hypocalcemia
- Recording of adverse events, concomitant medications, and IP compliance

Subjects who complete the 20-week treatment period in Study 20130356 will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects in the 20130356 Standard of Care (SOC) group will receive the initial dose of cinacalcet based on the subject's dry weight at baseline, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects from the 20130356 SOC group will follow the same cinacalcet titration schedule as subjects who received cinacalcet in the parent Study 20130356. Weekly monitoring of ionized calcium will be required for these subjects through the end of the treatment period, week 28.

Subjects from the cinacalcet group who complete the 20-week treatment period in parent Study 20130356, will continue in the extension study on cinacalcet at the completion of

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the treatment period (week 20) in the parent study following the dose titration rules outlined in Table 1 in Section 6.2.3.1.2. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg has not been reached and they meet the titration criteria defined in Section 6.

Cinacalcet doses will be calculated by the site staff and confirmed by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6. The titration tables are based on cCa and iPTH values from the central laboratory collected one week before dose titration. Final dose assignment will be based on the ionized calcium obtained on the day of titration. An assessment of symptomatic hypocalcemia will also be performed on the day of titration. Additional weekly dose adjustments for safety are permitted as described in Section 6.2.3.1.3. The maximum dose assigned for all subjects will be 2.5 mg/kg/day (based on dry weight at day 1) not to exceed a dose of 180 mg/day for any subject.

With:

Informed consent, and assent where applicable, for this study should be presented during the Studies 20130356 or 20110100. The informed consent, including assent as appropriate, will be obtained prior to execution of any study procedures for this extension study. **Where the Screening and Day 1 assessments for Study 20140159 overlap with visits in the 20130356 or 20110100 studies, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments, eg, 20130356 week 19 and 20140159 Screening.** The subject visits and assessments for this study will occur from baseline through to the end of study. Assessments during this study will include:

- Collection of blood samples for the evaluation of blood chemistry, hematology, calcium, iPTH, and bone biomarkers
- Physical assessments including vital signs (ie, blood pressure, heart rate)
- 12-lead electrocardiogram (ECG) at baseline and week 32 (if the subject ends the study prior to week 32, the 12-lead ECG will be performed at the last study visit)
- Assessments for symptoms of hypocalcemia
- Recording of adverse events, concomitant medications, and IP compliance

Subjects from 20130356: Subjects who complete the 20-week treatment period in study 20130356 will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects in the 20130356 Standard of Care (SOC) group will

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receive the initial dose of cinacalcet based on the subject's dry weight at baseline, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects from the 20130356 SOC group will follow the same cinacalcet titration schedule as subjects who received cinacalcet in study 20130356. Subjects will continue in the extension study on cinacalcet at the completion of the treatment period (week 20) in **20130356** study following the dose **adjustments** outlined in Section **6.2.3.1.1.1**. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg has not been reached and they meet the titration criteria defined in Section 6.

Subjects from 20110100: Subjects who complete the Week 26 End of Study visit will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159 and age at time of enrollment to 20110100, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects will follow the dose adjustments outlined in Section 6.2.3.1.1.1. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg has not been reached and they meet the titration criteria defined in Section 6.

Weekly monitoring of ionized calcium will be required for all subjects through the end of the treatment period, week 28.

Cinacalcet doses will be calculated by the site staff and confirmed by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6. The titration tables are based on cCa and iPTH values from the central laboratory collected one week before dose titration. Final dose assignment will be based on the ionized calcium obtained on the day of titration. An assessment of symptomatic hypocalcemia will also be performed on the day of titration. Additional weekly dose adjustments for safety are permitted as described in Section **6.2.3.1.1.1**. The maximum dose assigned for all subjects will be 2.5 mg/kg/day (based on dry weight at day 1) not to exceed a dose of 180 mg/day **for subjects from 20130356 and 60 mg/day for subjects from 20110100.**

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Section: Synopsis, Statistical Considerations

Paragraph 2

Replace:

For categorical variables, the number and percentage of subjects in each category will be reported. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, where applicable).

With:

For categorical variables, the number and percentage of subjects in each category will be reported. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, where applicable).

All summaries will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, overall) and Study 20110100.

Section: Study Design and Treatment Schema

Updated study design and treatment schema

Section: 2.4 Pediatric Risk Assessment

Paragraph 2

Replace:

Additional risk mitigation measures implemented in this trial include:

- collection of real-time ionized calcium measurements,
- weekly monitoring of calcium,
- incorporation of local laboratory total calcium values into the dosing schema,
- subject investigational product (IP) compliance measures,
- dispensing limited quantities of IP to minimize the potential for overdosing
- addition of exclusionary electrocardiogram (ECG) criteria

A dosing strategy, using a weight-based starting dose of ≤ 0.2 mg/kg in pediatric subjects, which is approximately 50% below the adult starting dose, will be employed in

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this study. The dose of cinacalcet will be titrated based on iPTH, corrected calcium levels, ionized calcium, and subject safety information. The maximum dose in this study will be 2.5 mg/kg/day based on day 1 dry weight, not to exceed a dose of 180 mg/day for any subject.

With:

Additional risk mitigation measures implemented in this trial include:

- collection of real-time ionized calcium measurements,
- weekly monitoring of calcium,
- incorporation of local laboratory total calcium values into the dosing schema,
- subject investigational product (IP) compliance measures,
- dispensing limited quantities of IP to minimize the potential for overdosing
- addition of exclusionary electrocardiogram (ECG) criteria

A dosing strategy, using a weight-based starting dose of ≤ 0.2 mg/kg in pediatric subjects, which is approximately 50% below the adult starting dose, will be employed in this study. The dose of cinacalcet will be titrated based on iPTH, corrected calcium (cCa) levels, ionized calcium, and subject safety information. The maximum dose in this study will be 2.5 mg/kg/day based on day 1 dry weight, not to exceed a dose of

- 180 mg/day **for subjects from 20130356**
- 60 mg/day **for subjects from 20110100.**

Section: 2.4 Pediatric Risk Assessment

Paragraph 3

Replace:

Serum calcium will be monitored throughout the study. In the event a subject experiences protocol-defined hypocalcemia or an adverse event deemed related to IP, the dose of cinacalcet will be reduced or discontinued as appropriate. Vitamin D sterols, calcium supplementation and/or calcium-based phosphate binders can be used to raise serum calcium levels and should be administered as appropriate per individual clinic practice. Training and informational tools will be provided to investigators for dissemination to care givers and subjects regarding the symptoms and risks of hypocalcemia.

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With:

Serum calcium will be monitored throughout the study. In the event a subject experiences protocol-defined hypocalcemia, an adverse event deemed related to IP **or other adverse events that warrants IP dose withhold**, the dose of cinacalcet will be reduced or discontinued as appropriate. Vitamin D sterols, calcium supplementation and/or calcium-based phosphate binders can be used to raise serum calcium levels and should be administered as appropriate per individual clinic practice. Training and informational tools will be provided to investigators for dissemination to care givers and subjects regarding the symptoms and risks of hypocalcemia.

Section: 2.5 Studies Eligible to Roll-over to 20140159

Heading

Add:

2.5 Studies Eligible to Roll-Over to 20140159

Section: 2.5.1 Amgen Study 20130356

Paragraph 1, sentence 1 and 2

Replace:

Amgen Study 20130356 (parent study) is a phase 3 randomized, multicenter, open-label, controlled study. In Study 20130356, cinacalcet is being evaluated in pediatric subjects between the ages of 6 and < 18 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis.

With:

Amgen Study 20130356 is a phase 3 randomized, multicenter, open-label, controlled study. In Study 20130356, cinacalcet is being evaluated in pediatric subjects **enrolled** between the ages of 6 and < 18 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis.

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Section: 2.5.2 Amgen Study 20110100

Heading

Add:

2.5.2 Amgen Study 20110100

Section: 2.5.2 Amgen Study 20110100

Paragraph 1

Add:

Amgen Study 20110100 is a phase 2, multicenter, open-label, single-arm study. In Study 20110100 cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 28 days and < 6 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. The expected treatment period in 20110100 is 24 weeks of daily oral administration of cinacalcet in addition to SOC with a 2-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the Week 26 End of Study visit.

Section: 2.6 Rationale

Paragraph 1

Replace:

Cinacalcet has been shown to be safe and efficacious in treating adult CKD patients with SHPT by controlling iPTH, calcium, and phosphorus. The current study is an extension of Amgen Study 20130356 designed to assess the long-term safety and tolerability of cinacalcet in pediatric CKD subjects.

With:

Cinacalcet has been shown to be safe and efficacious in treating adult CKD patients with SHPT by controlling iPTH, calcium, and phosphorus. The current study is an extension of Amgen Studies 20130356 **and 20110100** designed to assess the long-term safety and tolerability of cinacalcet in pediatric CKD subjects.

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Section: 3.1 Study Design

Section was reorganized to accommodate addition of heading for Section 3.1.1.

Section: 3.1 Study Design

Replace:

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. Eligible subjects will complete the 20-week treatment period in study 20130356 and either continue or start cinacalcet treatment in this study. Eligible subjects will not complete the safety follow-up period in study 20130356, beginning the extension study at the week 20 end of investigational product (EOIP) study visit in the parent study. Week 20 in study 20130356 and day 1 in this study will be the same visit. Eligible subjects will complete day 1 assessments (Section 7.1) and confirm eligibility in IVRS prior to dispensing IP on day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm will begin cinacalcet treatment on day 1 if their iPTH is ≥ 300 pg/mL and cCa is ≥ 8.8 mg/dL at week 19 of study 20130356. Eligible subjects from the cinacalcet arm in 20130356 will continue cinacalcet treatment on day 1 if their iPTH is ≥ 150 pg/mL and cCa is ≥ 8.4 mg/dL at week 19 of study 20130356. Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in Section 6.2.3.

Subjects will remain on cinacalcet treatment for 28 weeks after enrollment or until the time of renal transplant, whichever occurs first. The treatment period is followed by a 4 week safety follow-up period. All subjects will be eligible to titrate the cinacalcet dose at monthly titration visits to a maximum dose of 2.5 mg/kg/day, not to exceed a dose of 180 mg/day.

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

The study endpoints are defined in Section 10.1.1.

With:

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.

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Subjects will remain on cinacalcet treatment for 28 weeks after enrollment 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.

The study endpoints are defined in Section 10.1.1.

3.1.1 Subjects from Study 20130356

Eligible subjects will complete the 20-week treatment period in study 20130356 and either continue or start cinacalcet treatment in this study. Eligible subjects will not complete the safety follow-up period in Study 20130356, beginning the extension study at the week 20 end of investigational product (EOIP) study visit. Week 20 in study 20130356 and day 1 in Study **20140159** will be the same visit. Eligible subjects will complete **20140159** day 1 assessments (Section 7.1) and confirm eligibility in IVRS prior to dispensing IP on day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm **in Study 20130356** will begin cinacalcet treatment on day 1 **in Study 20140159** if their iPTH is ≥ 300 pg/mL and cCa is ≥ 8.8 mg/dL at week 19 of study 20130356. Eligible subjects from the cinacalcet arm in 20130356 will continue cinacalcet treatment on day 1 if their iPTH is ≥ 150 pg/mL and cCa is ≥ 8.4 mg/dL at week 19 of study 20130356. Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in Section 6.2.3.

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

Section: 3.1.2 Subjects From Study 20110100

Heading

Add:

3.1.2 Subjects from Study 20110100

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Section: 3.1.2 Subjects From Study 20110100

Add:

Eligible subjects will complete the Week 26 End of Study visit for Study 20110100 and restart cinacalcet treatment in this study on Day 1. Eligible subjects will be screened during the safety follow-up period in Study 20110100, they will be required to have their 20140159 Day 1 visit and their 20110100 End of Study visit at the same time point. Week 26 in Study 20110100 and day 1 in this study will be the same visit. Subjects will complete day 1 assessments (Section 7.1) and confirm eligibility in IVRS prior to dispensing IP on day 1.

Eligible subjects from 20110100 will restart cinacalcet treatment based on their dry weight at the time of enrollment in the 20140159 study and age at the time of enrollment in the 20110100 study.

Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in Section 6.2.3.1.2.

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

Section: 3.2 Number of Sites

Paragraph 1

Replace:

This study will be conducted at approximately 50 sites in North America, Europe, Russia, Latin America, and Australia.

With:

This study will be conducted at approximately **60** sites in North America, Europe, Russia, Latin America, and Australia.

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Section: 3.3 Number of Subjects

Paragraph 2

Replace:

This study is open to subjects who complete the 20-week treatment period in study 20130356. There may be up to 48 subjects enrolled in this study.

With:

This study is open to subjects who complete the 20-week treatment period in study 20130356 **or the Week 26 End of Study visit in Study 20110100**. There may be up to **78** subjects enrolled in this study.

Section: 4. Study Eligibility

Paragraph 2, sentence 2

Add:

Subjects who were ≤ 18 years old at week 20 in the 20130356 study are eligible to enter this Study 20140159 even if they have already turned 18 years of age or are due to turn 18 years of age during their planned participation in the 20140159 study.

Section: 4.1.1 Inclusion Criteria

Replace:

101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any day 1 study-specific activities/procedures being initiated.

102 Completed treatment through week 20 in the parent study, 20130356

103 Dry weight ≥ 12.5 kg at day 1

104 Dialysate calcium concentration ≥ 2.5 mEq/L at day 1

Subjects Randomized to the 20130356 Standard of Care Arm Only

105 iPTH value ≥ 300 pg/mL (week 19 in 20130356)

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106 Corrected calcium value \geq 8.8 mg/dL (week 19 in 20130356)

With:

101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any day 1 study-specific activities/procedures being initiated.

102 Dialysate calcium concentration \geq 2.5 mEq/L at day 1

All subjects from 20130356

103 Completed treatment through week 20 in the 20130356 study

104 Dry weight \geq 12.5 kg at day 1 of Study 20140159

Subjects Randomized to the 20130356 Standard of Care Arm Only

105 iPTH value \geq 300 pg/mL (week 19 in 20130356)

106 Corrected calcium value \geq 8.8 mg/dL (week 19 in 20130356)

All Subjects from 20110100

107 Completed Week 26 End of Study visit in the 20110100 study

108 Dry weight \geq 7 kg at day 1 of Study 20140159

Section: 4.1.2 Exclusion Criteria

First paragraph

Replace:

Study 20130356

With:

Studies 20130356 or 20110100

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Section: 4.1.2 Exclusion Criteria

Exclusion Criteria 201

Replace:

201 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s), other than Amgen Study 20130356.

With:

201 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s), other than Amgen Studies 20130356 **or 20110100**.

Section: 4.1.2 Exclusion Criteria

Exclusion Criteria 211

Replace:

211. Subject has an ongoing adverse event from Study 20130356 that is considered related to IP and:

- Is \geq CTCAE (v 4.0) grade 3, and/or
- Considered clinically significant in the opinion of the investigator

With:

211. Subject has an ongoing adverse event from Studies 20130356 **or 201101100** that is considered related to IP and:

- Is \geq CTCAE (v 4.0) grade 3, and/or
- Considered clinically significant in the opinion of the investigator

Section: 4.1.2 Exclusion Criteria

Exclusion Criteria 212

Replace:

212 Central laboratory values (cCa, iPTH) were not obtained/are not available for week 19 in the 20130356 study

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With:

212 Central laboratory values (cCa, iPTH) were not obtained/are not available for

- **20130356** week 19 **or**
- **20140159** Screening **visit for subjects from 20110100** study

Section: 4.1.2 Exclusion Criteria

After exclusion criteria 216

Replace:

At Day 1 Study Visit-Subjects Randomized to the 20130356 Cinacalcet Arm Only

With:

At Day 1 Study Visit-Subjects **Rolling Over from 20130356 Cinacalcet Arm or from**
20110100 Study

Section: 4.1.2 Exclusion Criteria

Exclusion Criteria 217

Replace:

217 Cinacalcet dose withheld > 1 month

With:

217 Cinacalcet dose withheld **for \geq last 4 weeks of treatment in studies 20130356**
and 201101100.

Section: 5 Subject Enrollment

Paragraph 2

Replace:

Subjects will retain the unique subject identification number received in the parent Study 20130356. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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With:

Subjects will retain the unique subject identification number received in Studies 20130356 or **20110100**. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Section: 5.1 Screening

Paragraph 1

Replace:

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. The informed consent can be signed up to (\pm 3 days) prior to day 1 (eg, at week 19 in 20130356).

With:

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. The informed consent can be signed up to **1 week** (\pm 3 days) prior to **20140159** day 1.

Section: 5.2 Enrollment

Paragraph 1

Replace:

Following confirmation that subjects met eligibility criteria in Section 4, the subject will be registered in the interactive voice response/interactive web response (IVR/IWR) system. The subject will be considered enrolled in the extension study and assigned a cinacalcet dose based on the treatment arm and/or last dose received in Study 20130356.

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With:

Following confirmation that subjects met eligibility criteria in Section 4, the subject will be registered in the interactive voice response/interactive web response (IVR/IWR) system.

The subject will be considered enrolled in the extension study:

- **20130356 subjects will be** assigned a cinacalcet dose based on the treatment arm and/or last dose received in Study 20130356.
- **20110100 subjects will be assigned a cinacalcet dose based on their dry weight at the time of enrollment in the 20140159 study and age at time of enrollment in the 20110100 study.**

Section: 6.1 Standard of Care

Paragraph 2

Replace:

Standard of care therapy that is commercially available will not be provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for obtaining supplies of these therapies.

With:

Standard of care therapy that is commercially available will not **usually** be provided or reimbursed by Amgen (except if required by local regulation). The Investigator will be responsible for obtaining supplies of these therapies **unless they are provided by Amgen.**

Section: 6.2.3 Dosage, Administration, and Schedule

Paragraph 2

Replace:

The protocol-specified doses (PSD) for use in this study are: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg. Subjects who are assigned doses of 10 or 15 mg/day will require administration of 2 or 3 capsules respectively per dose. Subjects who are assigned doses of 60 - 180 mg/day will require administration of 2 - 6 tablets per dose. For those subjects unable to swallow tablets, capsules may be dispensed.

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The maximum dose of cinacalcet that will be administered at any time during the study will be 2.5 mg/kg/day based on the subject's day 1 dry weight or 180 mg daily, whichever is lower.

With:

The subject will be considered enrolled in the extension study:

- **Subjects \geq 6 years of age:** 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg.
 - Subjects **from 20130356 may receive capsules for any dose which is an exact multiple of 5 mg.** Subjects who are assigned doses of 60 - 180 mg/day will require administration of 2 - 6 tablets per dose. For those subjects unable to swallow tablets, capsules may be dispensed.
 - The maximum dose of cinacalcet that will be administered at any time during the study will be 2.5 mg/kg/day based on the subject's day 1 dry weight **in Study 20140159** or 180 mg daily, whichever is lower.
- **Subjects < 6 years of age:** 1, 2.5, 5, 7.5, 10, 15, 30 and 60 mg. **Subjects from Study 20110100 will start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at the 20140159 Day 1 timepoint and age at time of enrollment in 20110100 study, rounded down to the lowest PSD.**
 - **Subjects assigned dose of 10-60 mg/day will require that more than 1 capsule per dose be sprinkled on soft food or used to create the liquid suspension for administration.**
 - **Subjects enrolling into 20140159 from 20110100 would have a maximum dose of 2.5 mg/kg/day based on the Day 1 dry weight or 60 mg daily, whichever is lower.**

Section: 6.2.3 Dosage, Administration, and Schedule

Paragraphs 4 and 5

Replace:

Subjects will be required to return all unused medication, including empty bottles, at each study visit. Site staff will confirm that the previously assigned medication bottle has been returned prior to dispensing a new bottle of IP.

If no ionized calcium values are available at the time of a study visit, a new bottle of IP investigational product will not be dispensed to the subject. Once the calcium value has been obtained, IP may be dispensed as appropriate.

With:

Subjects will be required to return all unused medication, including empty bottles, at each study visit. Site staff will confirm that the previously assigned medication bottle(s)

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have been returned prior to dispensing a new bottle(s) of IP. **In the event unused medications or empty bottles have been permanently misplaced, contact Amgen prior to dispensing new bottle(s) of IP.**

If no ionized calcium values are available at the time of a study visit, a new bottle of IP will not be dispensed to the subject. Once the **ionized** calcium value has been obtained **and in accessible range**, IP may be dispensed as appropriate.

Section: 6.2.3.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting,
Permanent Discontinuation

Paragraph 1

Replace:

Dosage adjustments, titrations, and withholding/restarting rules will be the same as the parent Study 20130356.

With:

Dosage adjustments, titrations, and withholding/restarting rules will be the same as the parent studies.

Section: 6.2.3.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting,
Permanent Discontinuation

Heading

Add:

6.2.3.1.1 Subjects from Study 20130356

Section: 6.2.3.1.1 Subjects from Study 20130356

Replace:

On day 1, subjects from the SOC arm in 20130356 will receive the initial dose of cinacalcet as defined in Section 6.2.3.1.1

Subjects from the cinacalcet arm will follow the dose titration rules outlined in Table 1 in Section 6.2.3.1.2. If subjects from the cinacalcet arm in 20130356 are on a dose

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withhold at day 1, the iPTH and cCa restart values (iPTH > 100 pg/mL and cCa > 8.4 mg/dL) must be reached prior to resuming cinacalcet in the current extension study. Subjects from the cinacalcet arm, who have had their dose withheld for > 1 month at the time of day 1 in this extension study will not be eligible for this study.

With:

On day 1 of **Study 20140159**, subjects from the SOC arm in 20130356 will receive the initial dose of cinacalcet as defined in Section 6.2.3.1.1.1

Subjects from the cinacalcet arm will follow the dose **adjustments** outlined in **Table 1** in Section **6.2.3.1.1.1**. If subjects from the cinacalcet arm in 20130356 are on a dose withhold at **20140159** day 1, the iPTH and cCa restart values (iPTH > 100 pg/mL and cCa > 8.4 mg/dL) must be reached prior to resuming cinacalcet in the current extension study. Subjects from the cinacalcet arm, who have had their dose withheld for > 1 month at the time of **20140159** day 1 will not be eligible for this study.

Section: 6.2.3.1.1.1 Dosage Adjustments

Paragraph 1

Replace:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, rounded down to the lowest PSD. Subjects from the cinacalcet arm will start cinacalcet dosing on day 1 at the same dose of cinacalcet they received at the completion of the treatment period (week 20) in the parent study or titrate based on the Table 1 in Section 6.2.3.1.2. The initial dose of cinacalcet will be assigned to subjects restarting cinacalcet after withholding the dose for more than 14 days during the study.

With:

On day 1, the subject's ionized calcium must be at or above threshold (i.e. ≥ 1.13 mmol/L for subjects less than 2 years of age, ≥ 1.05 mmol/L for subjects 2 years of age and above) prior to initiation of treatment. The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at **20140159** day 1, rounded down to

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the lowest PSD. Subjects from the cinacalcet arm will start cinacalcet dosing on **20140159** day 1 at the same dose of cinacalcet they received at the completion of the treatment period (week 20) in Study **20130356** or titrate based on the Table 1 in Section 6.2.3.1.1.1. The initial dose of cinacalcet will be assigned to subjects restarting cinacalcet after withholding the dose for more than 14 days during the study.

Section: 6.2.3.1.1.1 Dose Adjustments

Replace:

Monthly dose titrations will be assessed at Day 1, Weeks 4, 8, 12, etc as outlined in the Schedule of Assessments (Section 7.1). Cinacalcet doses will be titrated up or down one PSD or maintained monthly and confirmed by the IVR/IWR system using the corrected serum calcium and iPTH values obtained from the central laboratory the week prior to the dose titration visit, as well as assessments of symptoms of hypocalcemia and ionized calcium values obtained on the day of the titration visit, as outlined in Table 1 below.

Dose increases can occur only once a month.

Table 1. Monthly Dose Titration Rules

	↑ one PSD (if all criteria met)	Maintain Dose (if all criteria met)	↓ one PSD (if any criteria met)	withhold* (if any criteria met)
Corrected Calcium (central laboratory)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0 - < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)
Ionized Calcium	≥ 1.05 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L
iPTH	≥ 300 pg/mL (≥ 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)
Symptoms of Hypocalcemia	None	None	Not Applicable	Yes

*restart one PSD below last dose when corrected calcium is > 8.4 mg/dL, iPTH is > 100 pg/mL, ionized calcium is > 1.05 mmol/L and symptoms of hypocalcemia have resolved.

If the central laboratory corrected calcium value is < 8.0 mg/dL at any time during the trial, the dose of cinacalcet is to be withheld until the central laboratory corrected calcium

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value is > 8.4 mg/dL, at which time the dose may be restarted at one PSD below the previous dose received, provided that the iPTH is > 100 pg/mL, the ionized calcium is > 1.05 mmol/L, and the subject has no symptoms of hypocalcemia. Subjects receiving the lowest PSD (2.5 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 2.5 mg/day.

6.2.3.1.1.3 Dose Adjustments

Administration of cinacalcet may be withheld at any time during the study based on the ionized calcium, local laboratory total calcium values, and/or if the subject has signs/symptoms of hypocalcemia. The dose may be decreased based on the ionized calcium, as described in Table 2 below.

Table 2: Dose Adjustments for Safety

	↓ one PSD (if any criteria met)	withhold* (if any criteria met)
Total calcium (local laboratory)	Not Applicable	< 8.0 mg/dL (< 2.0 mmol/L)
Ionized Calcium	≥ 1.00 - < 1.05 - mmol/L	< 1.00 mmol/L
Symptoms of Hypocalcemia	Not Applicable	Yes

*restart one PSD below last dose when ionized calcium is > 1.05 mmol/L and symptoms of hypocalcemia have resolved.

If at any time the subject has a local total calcium value of < 8.0 mg/dL, the dose of investigational product must be withheld until an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained, at which time the dose may be resumed at one PSD below the previous dose. If a local laboratory measurement is used it must be documented in the subject's source record and recorded in the electronic case report form (eCRF).

In addition, if subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of cinacalcet is to be withheld. The dose may be restarted when treatment with the concomitant medication has completed and an ionized calcium of > 1.05 mmol/L or a central lab corrected calcium of > 8.4 mg/dL are obtained, at which time the dose may be resumed either at one PSD below the previous dose or at the initial dose if the criteria in Section 6.2.3.1.4 are met.

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With:

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, and 27), the dose may be maintained, reduced or withheld based upon the criteria in Table 1.

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- Central laboratory corrected calcium value is > 8.4 mg/dL
- iPTH is > 100 pg/mL
- Ionized calcium is > 1.05 mmol/L
- Subject has no symptoms of hypocalcemia
- Subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of > 1.05 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (2.5 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 2.5 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

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If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table 1. Dose Adjustment Rules: Monthly, Weekly and Withholding in Children 6-18 years of age

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16, 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27)			Dose Withholding for Safety at Anytime (Monthly, Weekly or Unscheduled)
	↑ one PSD (if all criteria met)	Maintain Dose (if all criteria met)	↓ one PSD** (if any criteria met)	withhold* (if any criteria met)	Maintain Dose (if all criteria met)	↓ one PSD** (if any criteria met)	withhold* (if any criteria met)	
Corrected Calcium (central laboratory)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0 - < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0 - < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)
Ionized Calcium	≥ 1.05 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	< 1.00 mmol/L
Total Calcium (local laboratory)	N/A	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)
iPTH	≥ 300 pg/mL (≥ 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	≥ 150 pg/mL (≥ 15.9 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes

*restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > 100 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

**if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased per dose adjustment procedures of that visit.

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Section: 6.2.3.1.2 Subjects From 20110100

Heading:

Add:

6.2.3.1.2 Subjects from 20110100

Section: 6.2.3.1.2 Subjects From 20110100

Add:

In order to start dosing, all subjects from Study 20110100 must have:

- **Ionized calcium prior to initiation of treatment on day 1 in this study**
 - **≥ 1.13 mmol/L if age < 2 years**
 - **≥ 1.05 mmol/L if ≥ 2 years**
- **iPTH value ≥ 150 pg/mL within 7 days of day 1**
- **Corrected calcium value within 7 days of day 1**
 - **≥ 9.4 mg/dL if age < 2 years**
 - **≥ 8.8 mg/dL if age ≥ 2 years**
- **Phosphorus value within 7 days of day 1**
 - **≥ 5.0 mg/dL (1.25 mmol/L) if age < 1 year**
 - **≥ 4.5 mg/dL (1.13 mmol/L) if age ≥ 1 year**

Section: 6.2.3.1.2.1 Subjects < 2 Years of Age

Heading

Add:

6.2.3.1.2.1 Subjects < 2 Years of Age

Section: 6.2.3.1.2.1 Subjects < 2 Years of Age

Paragraph 1

Replace:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial

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cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, rounded down to the lowest PSD.

With:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, **in the 20140159 study** rounded down to the lowest PSD.

Section: 6.2.3.1.2.1 Subjects < 2 Years of Age

After paragraph 1

Add:

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the criteria in Table 2.

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- **Central laboratory corrected calcium value is > 9.0 mg/dL**
- **iPTH is > 150 pg/mL**
- **Ionized calcium is > 1.13 mmol/L**
- **Subject has no symptoms of hypocalcemia**
- **Subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.**

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of >1.13 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (1 mg) who require a dose reduction will have their dose withheld until the criteria for

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maintaining or increasing the dose are met, at which time they will restart dosing at 1 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table 2. Dose Adjustment Rules: Monthly, Weekly and Withholding in Subjects < 2 Years Old

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19)			Dose Withholding for Safety at Anytime (Monthly, Weekly or Unscheduled)
	↑ one PSD (if <u>all</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	Maintain Dose (if <u>all</u> criteria met)	↓ one PSD** (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)	withhold* (if <u>any</u> criteria met)
Corrected Calcium (central laboratory)	≥ 9.0 mg/dL (≥ 2.25 mmol/L)	≥ 9.0 mg/dL (≥ 2.25 mmol/L)	≥ 8.6 - < 9.0 mg/dL (≥ 2.15 - < 2.25 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)	≥ 9.0 mg/dL (≥ 2.25 mmol/L)	≥ 8.6 - < 9.0 mg/dL (≥ 2.15 - < 2.25 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)
Ionized Calcium	≥ 1.13 mmol/L	≥ 1.13 mmol/L	≥ 1.08 - < 1.13 mmol/L	< 1.08 mmol/L	≥ 1.13 mmol/L	≥ 1.08 - < 1.13 mmol/L	< 1.08 mmol/L	< 1.08 mmol/L
Total Calcium (local laboratory)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)	Not Applicable	< 8.6 mg/dL (< 2.15 mmol/L)	< 8.6 mg/dL (< 2.15 mmol/L)
iPTH	≥ 300 pg/mL (≥ 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes

*restart one PSD below last dose when cCa is > 9.0 mg/dL, iPTH is > 150 pg/mL, ionized calcium is > 1.13 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved

**if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased.

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Section: 6.2.3.1.2.2 Subjects \geq 2 Years of Age

Heading

Add:

Subjects \geq 2 Years of Age

Section: 6.2.3.1.2.2 Subjects \geq 2 Years of Age

Paragraph 1

Replace:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, rounded down to the lowest PSD.

With:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1 **in the 20140159 study**, rounded down to the lowest PSD.

Section: 6.2.3.1.2.2 Subjects \geq 2 Years of Age

After paragraph 1

Add:

Dose adjustments for subjects receiving cinacalcet will be assessed at each weekly visit during the treatment period. The daily dose of cinacalcet may only be increased at monthly titration visits (week 4, 8, 12, 16, 20, and 24); it can't be increased at any other time during the treatment period. At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the criteria in Table 3.

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

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- Central laboratory corrected calcium value is > 8.4 mg/dL
- iPTH is > 150 pg/mL
- Ionized calcium is > 1.05 mmol/L
- Subject has no symptoms of hypocalcemia
- Subject doesn't have any ongoing adverse event(s) which warrant withholding of cinacalcet.

If a subject dose is being withheld, ionized calcium levels should be assessed weekly until an ionized calcium of >1.05 mmol/L is obtained, at which point, cCa and iPTH should be assessed by the central laboratory.

Once all the restart criteria above are met, cinacalcet may be restarted at one PSD below the previous dose received. Subjects receiving the lowest PSD (1 mg) who require a dose reduction will have their dose withheld until the criteria for maintaining or increasing the dose are met, at which time they will restart dosing at 1 mg/day.

If subjects require temporary administration of concomitant medications that are known to prolong the QTc interval, are CYP3A4 inhibitors, or are CYP2D6 substrates, the administration of IP is to be withheld. The dose may be restarted at one PSD below the previous dose once the treatment with the concomitant medication has completed and all of the restart criteria above are met.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

If any of the criteria for dose decrease are met between scheduled study visits, the dose of cinacalcet is to be suspended until the next visit at which time the dose will be decreased per dose adjustment procedures of that visit.

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Table . Dose Adjustment Rules: Monthly, Weekly and Withholding in Subjects ≥ 2 years old

	Monthly Dose Titration Visit Rules (Weeks 4, 8, 12, 16, 20, 24)				Weekly Dose Adjustment Visit Rules (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27)			Dose Withholding for Safety at Anytime (Monthly, Weekly or Unscheduled)
	↑ one PSD (if all criteria met)	Maintain Dose (if all criteria met)	↓ one PSD** (if any criteria met)	withhold* (if any criteria met)	Maintain Dose (if all criteria met)	↓ one PSD** (if any criteria met)	withhold* (if any criteria met)	withhold* (if any criteria met)
Corrected Calcium (central laboratory)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0 - < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	≥ 8.4 mg/dL (≥ 2.1 mmol/L)	≥ 8.0 - < 8.4 mg/dL (≥ 2.0 - < 2.1 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)
Ionized Calcium	≥ 1.05 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	≥ 1.05 mmol/L	≥ 1.00 - < 1.05 mmol/L	< 1.00 mmol/L	< 1.00 mmol/L
Total Calcium (local laboratory)	N/A	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	N/A	N/A	< 8.0 mg/dL (< 2.0 mmol/L)	< 8.0 mg/dL (< 2.0 mmol/L)
iPTH	≥ 300 pg/mL (≥ 31.8 pmol/L)	≥ 150 - < 300 pg/mL (≥ 15.9 - < 31.8 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	≥ 150 pg/mL (≥ 15.9 pmol/L)	≥ 100 - < 150 pg/mL (≥ 10.6 - < 15.9 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)	< 100 pg/mL (< 10.6 pmol/L)
Symptoms of Hypocalcemia	None	None	N/A	Yes	None	N/A	Yes	Yes
Other AE that warrants IP dose withhold	None	None	N/A	Yes	None	N/A	Yes	Yes

*restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > 150 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia, and other AE that warrants IP dose withholding have resolved.

**if any lab values that warrant a dose decrease are received between regularly scheduled visits, the subject dose should be suspended until the next visit, at which time the dose will be decreased per dose adjustment procedures of that visit.

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Section: 6.2.3.1.3 Missed Doses

Paragraph 1

Replace:

If a subject misses > 14 consecutive doses of cinacalcet for any reason, including temporary dose withholding due to the administration of concomitant medications as noted above, they will be restarted at their initial dose of cinacalcet (0.20 mg/kg/day based on dry weight at day 1) when administration of IP resumes per the dose titration guidelines outlined in Table 1.

With:

If a subject misses > 14 consecutive doses of cinacalcet for any reason, including temporary dose withholding due to the administration of concomitant medications as noted above, they will be restarted at their initial dose of cinacalcet (0.20 mg/kg/day based on dry weight at day 1) when administration of IP resumes per the dose titration guidelines outlined in Table 1, **Table 2, and Table 3.**

Section: 6.2.3.2 Measures of Compliance with Cinacalcet Administration

Paragraph 2

Replace:

Electronic patient diaries (eDiary) and pill counts will be reconciled and utilized in this study to document subject compliance with daily administration of cinacalcet therapy. The data entered into the eDiary will be available to the investigator and/or study coordinator on a daily basis to enable ongoing reviews of subject compliance. The eDiary and pill counts data collected will be reviewed with the subject and/or their parent(s) or legal guardian(s) by the investigator and/or study coordinator during the weekly study visits.

With:

Electronic patient diaries (eDiary) and **IP accountability information** will be reconciled and utilized in this study to document subject compliance with daily administration of cinacalcet therapy. The data entered into the eDiary will be available to the investigator and/or study coordinator on a daily basis to enable ongoing reviews of subject compliance. The eDiary and **IP accountability** data collected will be reviewed with the

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subject and/or their parent(s) or legal guardian(s) by the investigator and/or study coordinator during the weekly study visits.

Section: 6.2.3.3 Overdose

Paragraph 3

Replace:

Once hypocalcemia and any symptoms associated with the overdose have resolved, subjects may resume cinacalcet administration at their previously assigned dose.

With:

Once hypocalcemia and any symptoms associated with the overdose have resolved, subjects resume cinacalcet administration dose. **To resume dosing, the subject must meet the dosing restart criteria for his/her respective age group as specified in Sections 6.2.3.1.1, 6.2.3.1.2.1, and 6.2.3.1.2.2.**

Section: 6.3.1 Criteria for Permanent Discontinuation of Amgen IP and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Paragraph 2

Replace:

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen IP and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

With:

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen IP and other protocol-required therapies should be withheld (**see section 6.3.2**) or permanently discontinued, as deemed appropriate for the safety of the subject.

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Section: 7.1 Schedule of Assessments

Table 4. Schedule of Assessments

Replace:

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[illegible][illegible][illegible]

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Section: 7.1 Schedule of Assessments

Table 4. Schedule of Assessments, Footnotes 2 and 3

Replace:

2 - These procedures are required for the 20130356 EOIP visit and 20140159 day 1 visit. These procedures will be performed once at the site and applied to both study visits.

With:

2 - These procedures are required for the 20130356 EOIP **and 20110100 EOS** visit and 20140159 day 1 visit. These procedures will be performed once at the site and applied to both study visits.

3 - Biomarker Assessments and 25 (OH) Vit D are not required for subjects previously enrolled in 20110100. If baseline FGF23 is not collected at Day 1, it must not be collected at week 28.

Section: 7.2 General Study Procedures

Paragraph 2

Replace:

The duplicate study assessments from the end of investigational product (EOIP) visit in the parent study, 20130356, and from the day 1 visit will be collected once for both studies as described in Section 7.2.2.

With:

The duplicate study **assessments will** be collected once for both studies as described in Section 7.2.2.

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Section: 7.2.2 Day 1

Paragraph 1

Replace:

The following day 1 procedures are also required for the EOIP study visit at week 20 for Amgen study 20130356. These procedures should not be duplicated and may be collected once and entered onto the appropriate eCRF once eligibility for this study has been confirmed:

With:

The following day 1 procedures are also required for the EOIP study visit at week 20 for Amgen study 20130356 **and Week 26 End of Study visit for Study 20110100 except where indicated.** These procedures should not be duplicated and may be collected once and entered onto the appropriate eCRF once eligibility for this study has been confirmed:

Section: 7.2.2 Day 1

Bullet 8, subbullet 6

Replace:

25 (OH) Vitamin D

With:

25 (OH) Vitamin D **(not required for subjects from 20110100)**

Section: 7.2.2 Day 1

Bullet 8, subbullet 8

Replace:

Bone specific alkaline phosphatase (BALP), cross-linked N-telopeptides of type 1 collagen (NTx), type 1 collagen cross-linked telopeptide (CTx), amino terminal propeptide of type 1 collagen (P1NP), FGF23

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With:

Bone specific alkaline phosphatase (BALP), cross-linked N-telopeptides of type 1 collagen (NTx), type 1 collagen cross-linked telopeptide (CTx), amino terminal propeptide of type 1 collagen (P1NP), FGF23 **(not required for subjects from 20110100).**

Section: 7.2.2 Day 1

Bullet 9

Replace:

Medical history (including ongoing AEs/SAEs from the parent study, 20130356)

With:

Medical history (including ongoing AEs/SAEs from Studies, 20130356 **and 20110100**)

Section: 7.2.3 Treatment

Bullet 2, subbullet 2

Replace:

Pill counts

With:

Counts **of returned bottles of tablets/capsules/suspension**

Section: 7.2.4 End of Investigational Product

Bullet 4, subbullet 2

Replace:

Pill counts

With:

Counts **of returned bottles of tablets/capsules/suspension**

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Section: 7.2.4 End of Investigational Product

Bullet 8, subbullet 4

Replace:

25 (OH) Vitamin D

With:

25 (OH) Vitamin D **(not required for subjects from 20110100)**

Section: 7.2.4 End of Investigational Product

Bullet 8, subbullet 7

Replace:

BALP, NTx, CTx, P1NP, FGF23

With:

BALP, NTx, CTx, P1NP, FGF23 **(not required for subjects from 20110100)**

Section: 7.2.6 End of Study Visit

Bullet 9, subbullet 4

Replace:

25 (OH) Vitamin D

With:

25 (OH) Vitamin D **(not required for subjects from 20110100)**

Section: 7.3.2 Demographic Data

Replace:

Demographic data including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. These data will be transferred from the parent Study 20130356.

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With:

Demographic data including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. These data will be transferred from the **Studies 20130356 and 20110100**.

Section: 7.3.3 Medical and Surgical History

Replace:

The subject's complete medical and surgical history will be reviewed on day 1. The investigator or designee will collect a complete medical and surgical history for conditions that started within 5 years of the date of enrollment, including information on the subject's concurrent conditions. Ongoing adverse events and serious adverse events in the parent Study 20130356 will be entered as concurrent conditions on the medical history form. This information will be recorded on the medical history eCRF for subjects enrolled into the study.

With:

The subject's complete medical and surgical history will be reviewed on day 1. The investigator or designee will collect a complete medical and surgical history for conditions that started within 5 years of the date of enrollment, including information on the subject's concurrent conditions. Ongoing adverse events and serious adverse events in **Studies 20130356 and 20110100** will be entered as concurrent conditions on the medical history form. This information will be recorded on the medical history eCRF for subjects enrolled into the study.

Section: 7.3.8 Electronic Patient Diary

Paragraph 1, sentence 2

Replace:

The eDiary will collect date, time and number of capsules/tablets of cinacalcet taken each day.

With:

The eDiary will collect date, time and **amount** of cinacalcet taken each day.

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Section: 7.3.8 Electronic Patient Diary

Paragraph 1, Sentence 9

Replace:

The investigator and/or study coordinator will also reconcile any discrepancies between the eDiary and the pill count during the weekly study visits.

With:

The investigator and/or study coordinator will also reconcile any discrepancies between the eDiary and the **IP accountability data** during the weekly study visits.

Section: 7.3.11 Laboratory Assessments

Table 4 Analytes, last row of table

Replace:

BALP, NTx, CTx, P1NP, 25(OH) Vitamin D, FGF23

With:

BALP, NTx, CTx, P1NP, 25(OH) Vitamin D, FGF23 (not required for subjects from 20110100)
--

Section: 7.3.12 Home Healthcare

Paragraph 1

Replace:

Subjects receiving peritoneal dialysis may not have to be seen routinely by the investigator at the clinical site on a weekly basis. These subjects will be required to be seen in the clinic every 2 weeks, including the week prior to the monthly dosing titration visit at a minimum during the trial. The investigator may utilize their site staff or a qualified home healthcare service provider to conduct the procedures required for remaining weekly study visits, subject to the investigator's direction and oversight.

With:

Subjects receiving peritoneal dialysis may not have to be seen routinely by the investigator at the clinical site on a weekly basis. These subjects will be required to be

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seen in the clinic every 2 weeks, including the week prior to the monthly dosing titration visit **and those visits where central laboratory samples are collected**, at a minimum during the trial. The investigator may utilize their site staff or a qualified home healthcare service provider to conduct the procedures required for remaining weekly study visits, subject to the investigator's direction and oversight.

Section: 9.2 Reporting of Adverse Events

Paragraph 1

Replace:

Ongoing adverse events and serious adverse events in the parent Study 20130356, will be entered as a concurrent condition on the Medical History eCRF.

With:

Ongoing adverse events and serious adverse events in Studies 20130356 **or 20110100**, will be entered as a concurrent condition on the Medical History eCRF.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events

Paragraph 1

Replace:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur from the date of the first dose through 30 days after the last day of the dosing interval of IP or end of study visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

With:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur from the date of the first dose through 30 days after the last day of the dosing interval of IP or end of study visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the **serious adverse event form**.

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Section: 10.1.3 Covariates and Subgroups

Replace:

The primary, secondary, and safety endpoints will be summarized by parent study baseline age group (6 to < 12 years old and 12 to < 18 years old as supportive analyses.

With:

The primary, secondary, and safety endpoints will be summarized by baseline age group (6 to < 12 years and 12 to < 18 years **for Study 20130356; 28 days to < 2 years and 2 to < 6 years for Study 20110100**) as supportive analyses.

Section: 10.2 Sample Size Considerations

Replace:

This is an extension study of Study 20130356. The sample size of approximately 48 for the parent study will result in a maximum of 48 subjects.

With:

This is an extension study of Studies 20130356 **and 20110100**. The sample size may be up to **78** subjects.

Section: 10.3.1 Interim Analysis

Paragraph 1

Replace:

An interim analysis will be conducted. The timing of the interim analysis will be dependent on the completion of the parent study. There is no formal statistical testing. The analysis for all endpoints will be descriptive in nature.

With:

An interim analysis will be conducted. The timing of the interim analysis will be dependent on the completion of the Study **20130356**. There is no formal statistical testing. The analysis for all endpoints will be descriptive in nature. **There are no plans to change the conduct of the study based on interim analysis results.**

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Section: 10.4.1 General Considerations

Paragraph 4

Add:

All summaries will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, overall) and Study 20110100.

Section: 10.4.2 Primary Endpoint

Paragraph 1, sentence 3

Delete:

The incidence will be categorized and summarized by parent study treatment group and overall.

Section: 10.4.3 Secondary Endpoints

Paragraph 1, Sentence 4

Replace:

Summary statistics will be provided for serum cCa and phosphorus values at day 1 to week 11, and week 28 within the study population and within each age group by previous treatment group in the parent study and overall. No imputation of missing data will be utilized.

With:

Summary statistics will be provided for serum cCa and phosphorus values at day 1 to week 11, and week 28. No imputation of missing data will be utilized.

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Section: 10.4.4 Safety Endpoints

Paragraphs 2, 3, 4, and 5

Replace:

Adverse Events

All treatment-emergent adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary. The subject incidence of all treatment-emergent adverse events, serious adverse events, treatment-related adverse events, and serious treatment-related adverse events will be tabulated by system organ class and preferred term in descending order of frequency by parent study treatment group. Tables of treatment-emergent adverse events, fatal adverse events, serious adverse events, and adverse events leading to withdrawal from IP or from study will be tabulated by preferred term by parent study treatment group.

Laboratory Data, Blood Pressure, and Heart Rate

Descriptive statistics for values, changes and percent changes of selected laboratory parameters from first dose of IP date will be presented by parent study treatment group at each measurement time point during the study. In addition, shift tables will summarize grades using CTCAE (version 4) by worst grades between baseline and any visit up to the end of the study for selected hematology and chemistry parameters.

The incidence of hypocalcemia after the first dose of IP will be summarized using descriptive statistics by parent study treatment group. Hypocalcemia will be defined in two ways, with the subject incidence of corrected serum calcium of < 7.5 mg/dL and < 8.4 mg/dL both being summarized. Subject incidence of ionized calcium value < 1.05 mmol/L and <1.00 mmol/L will be summarized. Blood pressure (systolic and diastolic) and heart rate will be summarized at each time point.

Medications of Interest

Use of vitamin D sterols and phosphate binders during study will be tabulated by parent study treatment group.

With:

Adverse Events

All treatment-emergent adverse events occurring during the study will be coded using the latest version of the MedDRA dictionary. The subject incidence of all

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treatment-emergent adverse events, serious adverse events, treatment-related adverse events, and serious treatment-related adverse events will be tabulated by system organ class and preferred term in descending order of frequency. Tables of treatment-emergent adverse events, fatal adverse events, serious adverse events, and adverse events leading to withdrawal from IP or from study will be tabulated by preferred term.

Laboratory Data, Blood Pressure, and Heart Rate

Descriptive statistics for values, changes and percent changes of selected laboratory parameters from first dose of IP date will be presented at each measurement time point during the study. In addition, shift tables will summarize grades using CTCAE (version 3) by worst grades between baseline and any visit up to the end of the study for selected hematology and chemistry parameters.

The incidence of hypocalcemia after the first dose of IP will be summarized using descriptive statistics. Hypocalcemia will be defined in two ways, with the subject incidence of corrected serum calcium of < 7.5 mg/dL and < 8.4 mg/dL both being summarized. Subject incidence of ionized calcium value < 1.05 mmol/L and < 1.00 mmol/L will be summarized. Blood pressure (systolic and diastolic) and heart rate will be summarized at each time point.

Medications of Interest

Use of vitamin D sterols and phosphate binders during study.

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Amendment 3

Protocol Title: 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

Amgen Protocol Number (cinacalcet HCl) 20140159

Amendment Date: 16 March 2016

Rationale:

The protocol is being amended to allow not only subjects who complete the 20-week treatment period Study 20130356 or reach study termination or the week 26 End of Study visit in Study 20110100 or reach study termination to be eligible to receive 28 weeks of treatment with cinacalcet in this single-arm extension study. It is also being amended to include additional secondary efficacy and exploratory endpoints. Specifically:

- Added subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the 20-week treatment period in 20130356 or following Study 20130356 termination and within 1 week of day 1 of 20140159.
- Clarified that subjects who are in Study 20130356 study, the end of study (EOS) procedures for an individual subject will occur at the same time as the end of investigational product (EOIP) visit for subjects enrolling in Study 20140159.
- Clarified that for subjects enrolled in Study 20140159 at the time of 20110100 study termination, the 2-week safety follow-up period in 20110100 will not apply for these subjects and the EOS procedures for an individual subject will occur at the time as the EOIP visit for subjects enrolling in Study 20140159.
- Added the EOIP visit in study 20130356 and day 1 in Study 20140159 will be the same visit unless there is an administrative delay. Eligible subjects will complete day 1 of 20140159 assessments.
- Clarified the initial dose of cinacalcet for eligible subjects from the cinacalcet arm in 20130356 who meet eligibility on day 1 for Study 20140159.
- Clarified the initial dose of cinacalcet for eligible subjects from Study 20110100 on day 1 of Study 20140159.
- Added eligible 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 the early termination visit. The early termination/EOS visit in study 20110100 and Day 1 in Study 20140159 will be the same visit unless there is

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an administrative delay and that 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 day 1 based on dosing instructions

- Added inclusion criteria for all subjects with > 14 days between the last study visit in Study 20130356 or 20110100 and screening for Study 20140159 who are prescribed anti-convulsant medication must be on a stable dose
- Added inclusion criteria for all subjects from 20130356 study. Subjects must have completed treatment through week 20 in the 20130356 study or on study at time of Study 20130356 termination
- Added inclusion criteria for subjects randomized to the 20130356 Standard of Care Arm Only must have an iPTH value ≥ 300 pg/mL (within 1 week of day 1 in Study 20140159) and corrected calcium value ≥ 8.8 mg/dL within 1 week of Day 1 in Study 20140159
- Added inclusion criteria for all subjects from the 20110100 study. Subjects must have completed Week 26 End of Study visit in the, 20110100 study or on study at time of Study 20110100 termination
- Added exclusion criteria that subjects with a new onset of seizure or worsening of pre-existing seizure disorder would not be eligible to enroll in the study
- Added exclusion criteria for all subjects with > 14 days between the last study visit in Study 20130356 or 20110100 and the screening visit in Study 20140159
- Revised the Dose Adjustments sections for clarity.
- Added secondary endpoints for the 20140159 study only
- Added secondary endpoints for the combined 20130356, 20110100 and 20140159 studies
- Added exploratory endpoints for the 20140159 study only
- Added exploratory endpoints for the combined 20130356, 20110100 and 20140159 studies
- Added the definition of Efficacy Analysis Set
- Clarified the interim analyses that may be conducted
- Clarified the primary analysis of all endpoints will be conducted after all subjects completed the week 32 End of Study visit or early terminated the study and clarified the secondary analysis of the primary endpoint
- Clarified the analysis of the secondary endpoints
- Clarified safety endpoints in 20140159 study only and combined 20130356, 20110100, and 20140159 studies will be summarized by treatment group in parent studies and overall
- Administration, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

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Description of Changes:

Section: Global

Change:

Minor corrections throughout (eg, correcting typographical and formatting errors)

Section: Global

Replace:

22 July 2015

With:

16 March 2016

Section: Title Page

Added:

Amendment 3: 16 March 2016

Section: Synopsis, Secondary Endpoints

Replace:

Secondary Endpoints:

- Percent change from day 1 in intact parathyroid hormone (iPTH) to week 11 and week 28
- Serum corrected calcium (cCa) values at day 1, week 11, and week 28
- Serum phosphorus values at day 1, week 11, and week 28

With:

Secondary Endpoints:

Study 20140159 only

- **Achievement of $\geq 30\%$ reduction from baseline to mean intact parathyroid hormone (iPTH) during weeks 11 and 15 (standard of care [SOC] arm of Study 20130356 only)**
- **Achievement of $\geq 30\%$ 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)**
- **Change in corrected total serum calcium from baseline to mean value during weeks 23 and 28**

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- Change in serum phosphorus from baseline to mean value during weeks 23 and 28
- Achievement of a mean iPTH ≤ 300 pg/mL during weeks 23 and 28
- ~~Percent change from day 1 in intact parathyroid hormone (iPTH) to week 11 and week 28~~
- Serum corrected calcium (cCa) ~~at baseline values at day 1, week 11, and week 28~~
- Serum phosphorus ~~at baseline values at day 1, week 11, and week 28~~

Combined Studies 20130356, 20110100, and 20140159

- Achievement of $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15
- Achievement of $\geq 30\%$ 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

Section: Synopsis Exploratory Endpoints

Replace:

Exploratory Endpoint:

- Growth velocity from day 1 to end of study
- Change in Tanner stage from day 1 to end of study

With:

Exploratory Endpoints:

Study 20140159 only

- Growth velocity from baseline to end of study (EOS)
- Change in Tanner stage from baseline to EOS

Combined Studies 20130356, 20110100, and 20140159

- Growth velocity from day 1 of cinacalcet treatment to EOS
- Change in Tanner stage from day 1 of cinacalcet treatment to EOS
- ~~Growth velocity from day 1 to end of study~~
- ~~Change in Tanner stage from day 1 to end of study~~

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Section: Protocol Synopsis, Summary of Subject Eligibility Criteria

Replace:

Summary of Subject Eligibility Criteria: Subjects who complete the 20-week treatment period in Study 20130356 or the week 26 End of Study visit in Study 20110100 will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, followed by a 4-week safety follow-up. Subjects must also meet the inclusion and exclusion criteria for this extension study in order to be eligible. Subjects must provide written informed consent (parents or guardian) and assent, where appropriate, according to local regulations specific to the procedures in this study.

- Subjects enrolled in the standard of arm of Study 20130356 will be eligible for the extension study if the iPTH \geq 300 pg/mL and the cCa \geq 8.8 mg/mL at the week 19 visit. Eligible subjects from the cinacalcet arm in Study 20130356 will continue cinacalcet treatment following the dosing rules described in Section 6.2.3.
- Eligible subjects from 20110100 study will restart cinacalcet treatment as described in Section 6.2.3.1.

With:

Summary of Subject Eligibility Criteria: Subjects who complete the 20-week treatment period in ~~Study 20130356~~ **or reach study termination in Study 20130356** or the week 26 End of Study visit in ~~Study 20110100~~ **or reach study termination in Study 20130356** will be eligible to receive 28 weeks of treatment with cinacalcet in this extension study, followed by a 4-week safety follow-up. Subjects must also meet the inclusion and exclusion criteria for this extension study in order to be eligible. Subjects must provide written informed consent (parents or guardian) and assent, where appropriate, according to local regulations specific to the procedures in this study.

- Subjects enrolled in the ~~standard of care~~ **SOC** arm of Study 20130356 will be eligible for the extension study if the iPTH **is** \geq 300 pg/mL and the cCa **is** \geq 8.8 mg/mL **within 7 days of day 1 in Study 20140159** ~~at the week 19 visit.~~
- Eligible subjects from the **cinacalcet arm of** ~~in~~ Study 20130356 will **restart or** continue cinacalcet treatment following the dosing rules described in Section **6.2.3.1.1** ~~6.2.3.~~
- Eligible subjects from **Study** 20110100 ~~study~~ will **restart or continue** cinacalcet **following the dosing rules** ~~treatment~~ as described in Section **6.2.3.1.2** ~~6.2.3.1.~~

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Section: Protocol Synopsis, Procedures

Replace:

Procedures: Informed consent, and assent where applicable, for this study should be presented during the studies 20130356 or 20110100. The informed consent, including assent as appropriate, will be obtained prior to execution of any study procedures for this extension study. Where the Screening and day 1 assessments for Study 20140159 overlap with visits in the 20130356 or 20110100 studies, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments, eg, 20130356 week 19 and 20140159 Screening. The subject visits and assessments for this study will occur from baseline through to the end of study. Assessments during this study will include:

- Collection of blood samples for the evaluation of blood chemistry, hematology, calcium, iPTH, and bone biomarkers
- Physical assessments including vital signs (ie, blood pressure, heart rate)
- 12-lead electrocardiogram (ECG) at baseline and week 32 (if the subject ends the study prior to week 32, the 12-lead ECG will be performed at the last study visit)
- Assessments for symptoms of hypocalcemia
- Recording of adverse events, concomitant medications, and IP compliance

Subjects from 20130356: Subjects who complete the 20-week treatment period in Study 20130356 will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects in the 20130356 Standard of Care (SOC) group will receive the initial dose of cinacalcet based on the subject's dry weight at baseline, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects from the 20130356 SOC group will follow the same cinacalcet titration schedule as subjects who received cinacalcet in Study 20130356. Subjects will continue in the extension study on cinacalcet at the completion of the treatment period (week 20) in 20130356 study following the dose adjustments outlined in Section 6.2.3.1.1.1. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg has not been reached and they meet the titration criteria defined in Section 6.

Subjects from 20110100: Subjects who complete the Week 26 End of Study visit will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159 and age at time of enrollment to 20110100,

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0.20 mg/kg/day, rounded down to the nearest PSD. Subjects will follow the dose adjustments outlined in Section 6.2.3.1.1.1. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg has not been reached and they meet the titration criteria defined in Section 6.

Weekly monitoring of ionized calcium will be required for all subjects through the end of the treatment period, week 28.

Cinacalcet doses will be calculated by the site staff and confirmed by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6. The titration tables are based on cCa and iPTH values from the central laboratory collected one week before dose titration. Final dose assignment will be based on the ionized calcium obtained on the day of titration. An assessment of symptomatic hypocalcemia will also be performed on the day of titration. Additional weekly dose adjustments for safety are permitted as described in Section 6.2.3.1.1.1. The maximum dose assigned for all subjects will be 2.5 mg/kg/day (based on dry weight at day 1) not to exceed a dose of 180 mg/day for subjects from 20130356 and 60 mg/day for subjects from 20110100.

With:

Procedures: Informed consent, and assent where applicable, for this study should be presented during the Studies 20130356 or 20110100. The informed consent, including assent as appropriate, will be obtained prior to execution of any study procedures for this extension study. Where the Screening and day 1 assessments for Study 20140159 overlap with visits in the 20130356 or 20110100 studies, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments, eg, 20130356 week 49 ~~end of investigational product (EOIP)~~ and 20140159 Screening. The subject visits and assessments for this study will occur from baseline through to the end of study. Assessments during this study will include:

- collection of blood samples for the evaluation of blood chemistry, hematology, calcium, iPTH, and bone biomarkers
- physical assessments including vital signs (ie, blood pressure, heart rate)
- 12-lead electrocardiogram (ECG) at baseline and week 32 (if the subject ends the study prior to week 32, the 12-lead ECG will be performed at the last study visit)
- assessments for symptoms of hypocalcemia
- recording of adverse events, concomitant medications, and IP compliance

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Subjects from **Study 20130356**: Subjects who complete the 20-week treatment period in Study 20130356 **or are still on study at the time of Study 20130356 termination**, will be eligible to receive cinacalcet treatment in the current study.

- **Subjects from the SOC group in 20130356**: After confirming eligibility, subjects in the 20130356 SOC group will receive the initial dose of cinacalcet based on the subject's dry weight at **day 1 baseline in Study 20140159**, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects from the 20130356 SOC group will follow the same cinacalcet titration schedule as subjects who received cinacalcet in Study 20130356.
- **Subjects from the cinacalcet group in 20130356**: After confirming eligibility, subjects from the cinacalcet group will continue to receive cinacalcet at the same dose as EOIP visit if there are ≤ 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159. If the cinacalcet dose has been withheld or missed for > 14 days at the time of day 1 of Study 20140159, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159. ~~Subjects will continue in the extension study on cinacalcet at the completion of the treatment period (week 20) in 20130356 study following the dose adjustments outlined in Section 6.2.3.1.1.1.~~ Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg **(based on 20140159 day 1 dry weight), not exceeding 180 mg**, has not been reached and they meet the titration criteria defined in Section 6.

Subjects from 20110100: Subjects who complete the week 26 End of Study visit **or are still on study at the time of Study 20110100 termination**, will be eligible to receive cinacalcet treatment in the current study. After confirming eligibility, subjects will **continue to receive cinacalcet at the same dose as EOIP visit if there are ≤ 14 days between the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159.** If the cinacalcet dose has been withheld or missed for > 14 days at the time of day 1 of Study 20140159, subjects will receive the initial dose of cinacalcet based on the subject's dry weight at time of enrollment to 20140159 and age at time of enrollment to 20110100, 0.20 mg/kg/day, rounded down to the nearest PSD. Subjects will follow the dose adjustments outlined in **Section 6.2.3.1.1**. Subjects in this group will be eligible to receive dose titrations during the extension study if the maximum dose of 2.5 mg/kg **(based on 20140159 day 1 dry weight), not exceeding 60 mg**, has not been reached and they meet the titration criteria defined in Section 6.

During the 20140159 study:

Weekly monitoring of ionized calcium will be required for all subjects through the end of the treatment period, week 28.

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Cinacalcet doses will be calculated by the site staff and confirmed by the interactive voice response/interactive web response (IVR/IWR) system following the titration tables in Section 6. The titration tables are based on cCa and iPTH values from the central laboratory collected one week before dose titration. Final dose assignment will be based on the ionized calcium obtained on the day of titration. An assessment of symptomatic hypocalcemia will also be performed on the day of titration. Additional weekly dose adjustments for safety are permitted as described in Section 6.2.3.1. The maximum dose assigned for all subjects will be 2.5 mg/kg/day (based on dry weight at day 1 in **Study 20140159**) not to exceed a dose of 180 mg/day for subjects from 20130356 and 60 mg/day for subjects from 20110100.

Section: Protocol Synopsis, Statistical Considerations

Replace:

Statistical Considerations: There is no formal statistical testing for this study. The analysis of the primary and secondary endpoints will be descriptive in nature.

For categorical variables, the number and percentage of subjects in each category will be reported. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, where applicable). All summaries will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, overall) and Study 20110100.

With:

Statistical Considerations: There is no formal statistical testing for this study. The analysis of the primary and secondary endpoints will be descriptive in nature.

For categorical variables, the number and percentage of subjects in each category will be reported. Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, where applicable). All summaries ~~ies~~ **tables** will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, ~~overall~~) and **Study 20110100 and overall, unless otherwise specified.**

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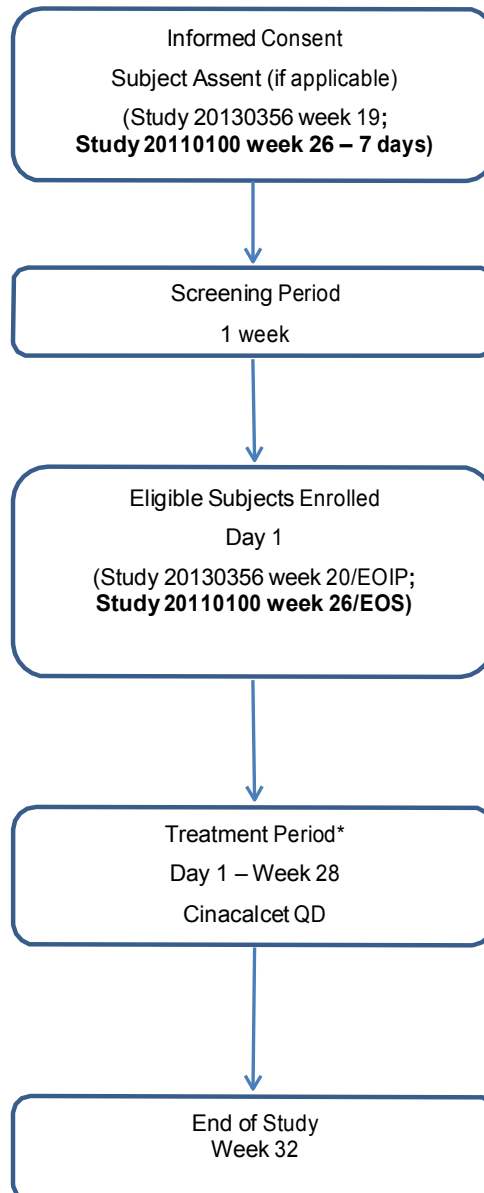
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Section: Study Design and Treatment Schema

Replace:

Study Design and Treatment Schema



The initial dose of cinacalcet assigned will be based on the dosing in the originating parent study. Refer to Section 6 of the protocol for additional details.

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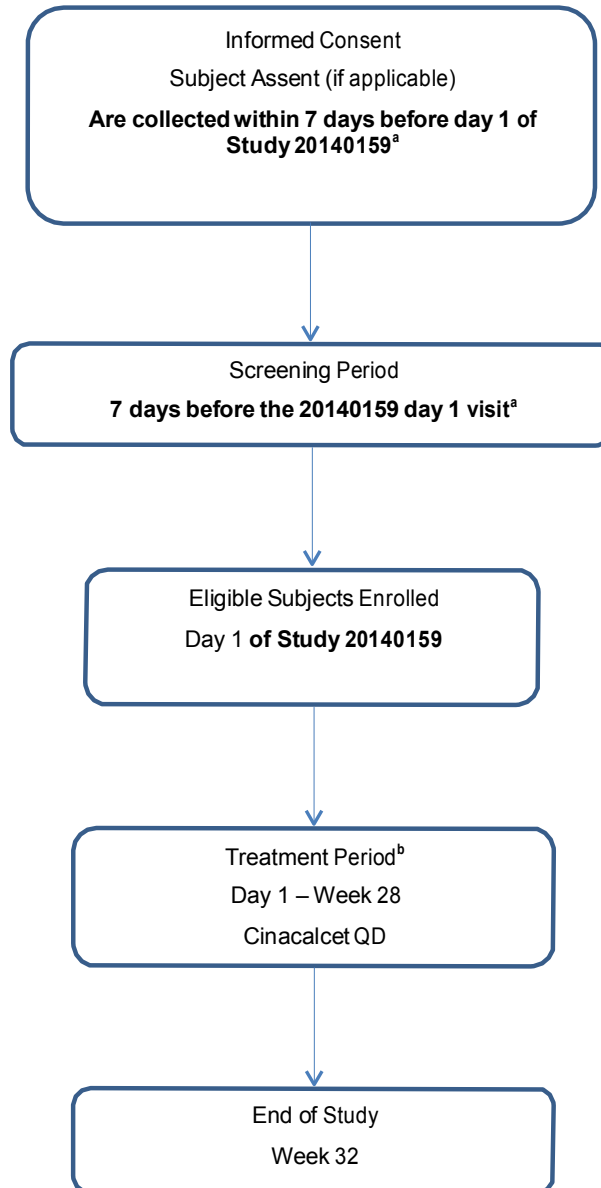
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With:

Study Design and Treatment Schema



^a When it is not possible to perform a study visit at the specified time point, the visit may be performed within ± 3 days.

^b The initial dose of cinacalcet assigned will be based on the dosing in the originating parent study. Refer to Section 6 of the protocol for additional details.

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Section: List of Abbreviations

Delete

LSP	Lactation Surveillance Program
PSP	Pregnancy Surveillance Program

Add:

sNDA	Supplemental New Drug Application
------	-----------------------------------

Section: 2.5.1 Amgen Study 20130356

Replace:

Amgen Study 20130356 is a phase 3 randomized, multicenter, open-label, controlled study. In Study 20130356, cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 6 and < 18 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. Approximately 48 subjects are planned to be randomized into the study to one of two treatment arms in a 1:1 allocation ratio; daily oral administration of cinacalcet in addition to SOC or SOC. Once randomized, the expected treatment period in 20130356 is 20 weeks with a 4-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the 20-week treatment period in 20130356 or following Study 20130356 termination and within 1 week of day 1 of 20140159. The 4-week safety follow-up period in 20130356 will not apply for these subjects.

With:

Amgen **Study** 20130356 is a phase 3 randomized, multicenter, open-label, controlled study. In **Study** 20130356, cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 6 and < 18 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. Approximately 48 subjects are planned to be randomized into the study to one of two treatment arms in a 1:1 allocation ratio; daily oral administration of cinacalcet in addition to SOC or SOC **only**. Once randomized, the expected treatment period in 20130356 is 20 weeks with a 4-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the 20-week treatment period in 20130356 or following Study 20130356 termination **and within 7 days** of day 1 of 20140159 **unless there is an administrative delay. The end of study (EOS) procedures for an individual subject will occur at the same time as the end of investigational product (EOIP)**

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visit for subjects enrolling in Study 20140159. The 4-week safety follow-up period in 20130356 will not apply for these subjects.

Section: 2.5.2 Amgen Study 20110100

Replace:

Amgen Study 20110100 is a phase 2, multicenter, open-label, single-arm study. In Study 20110100 cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 28 days and < 6 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. The expected treatment period in 20110100 is 24 weeks of daily oral administration of cinacalcet in addition to SOC with a 2-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the Week 26 End of Study visit.

With:

Amgen Study 20110100 is a phase 2, multicenter, open-label, single-arm study. In Study 20110100 cinacalcet is being evaluated in pediatric subjects enrolled between the ages of 28 days and < 6 years, with SHPT and CKD receiving either hemodialysis or peritoneal dialysis. The expected treatment period in 20110100 is 24 weeks of daily oral administration of cinacalcet in addition to SOC with a 2-week safety follow-up period. Subjects who are eligible for and enroll in the 20140159 extension study will do so at the completion of the **week 26 End of Study visit or at Study 20110100 termination and within 7 days of day 1 of 20140159 unless there is an administrative delay. For subjects enrolled in the 20140159 extension study at the time of 20110100 study termination, the 2-week safety follow-up period in 20110100 will not apply for these subjects and EOS procedures for an individual subject will occur at the time as the EOIP visit for subjects enrolling in Study 20140159.**

Section: 3.1.1 Subjects from Study 20130356

Replace:

Eligible subjects will complete the 20-week treatment period in study 20130356 and either continue or start cinacalcet treatment in this study. Eligible subjects will not complete the safety follow-up period in Study 20130356, beginning the extension study at the week 20 end of investigational product (EOIP) study visit. Week 20 in Study 20130356 and day 1 in Study 20140159 will be the same visit. Eligible subjects

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will complete 20140159 day 1 assessments (Section 7.1) and confirm eligibility in IVRS prior to dispensing IP on day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm in Study 20130356 will begin cinacalcet treatment on day 1 in Study 20140159 if their iPTH is ≥ 300 pg/mL and cCa is ≥ 8.8 mg/dL at week 19 of Study 20130356. Eligible subjects from the cinacalcet arm in 20130356 will continue cinacalcet treatment on day 1 if their iPTH is ≥ 150 pg/mL and cCa is ≥ 8.4 mg/dL at week 19 of Study 20130356. Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in Section 6.2.3.

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

With:

Eligible subjects will complete the 20-week treatment period in Study 20130356, or reach Study 20130356 termination and either continue, restart, or start cinacalcet treatment in this study. Eligible subjects will not complete the safety follow-up period in Study 20130356, beginning the extension study at the **20130356 week 20 end of investigational product (EOIP) study visit**. **The EOIP visit Week 20 in Study 20130356 and day 1 in Study 20140159 will be the same visit unless there is an administrative delay.** Eligible subjects will complete **day 1 of 20140159 day 1 assessments** (Section 7.1) and confirm eligibility in **the interactive voice response (IVR) system before** prior to dispensing IP on day 1.

Eligible subjects from 20130356 who were randomized to the SOC arm in Study 20130356 will begin cinacalcet treatment on day 1 in Study 20140159 if their iPTH is ≥ 300 pg/mL and cCa is ≥ 8.8 mg/dL **during screening in Study 20140159 at week 19 of study 20130356**. Eligible subjects from the cinacalcet arm in 20130356 will continue cinacalcet treatment on 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 > 14 days at the time of day 1 of Study 20140159, the subject will resume dosing at the starting dose level once all restart criteria are met at week 19 of study 20130356.**

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

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Subjects will complete day 1 assessments (Section 7.1) and confirm eligibility in IVR system prior to dispensing IP on day 1.

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 day 1 **in Study 20140159**, not to exceed a dose of 180 mg/day.

Section: 3.1.2 Subjects from Study 20110100

Replace:

Eligible subjects will complete the week 26 End of Study visit for Study 20110100 and restart cinacalcet treatment in this study on day 1. Eligible subjects will be screened during the safety follow-up period in Study 20110100, they will be required to have their 20140159 day 1 visit and their 20110100 End of Study visit at the same time point. Week 26 in Study 20110100 and day 1 in this study will be the same visit. Subjects will complete day 1 assessments (Section 7.1) and confirm eligibility in IVRS prior to dispensing IP on day 1.

Eligible subjects from 20110100 will restart cinacalcet treatment based on their dry weight at the time of enrollment in 20140159 study and age at the time of enrollment in the 20110100 study. Cinacalcet dosing will follow the dose titration, dose withhold, and restarting rules defined in Section 6.2.3.1.2.

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

With:

Eligible subjects will complete the ~~Week 26~~ End of Study visit **or early termination visit** for Study 20110100 and **continue or** restart cinacalcet treatment in this study on day 1 **based on dosing instructions outlined in Section 6.2.3**. Eligible subjects **completing the full treatment period in Study 20110100** will be screened during the safety follow-up period in Study 20110100 **and they** will be required to have their 20140159 day 1 visit and their 20110100 **week 26** End of Study visit at the same **visit** time point. **Eligible 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 the 20110100 early termination visit. The early**

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termination/EOS visit in Study 20110100 and day 1 in Study 20140159 will be the same visit unless there is an administrative delay.

Subjects will complete day 1 assessments (Section 7.1) and confirm eligibility in IVR **system before being** dispensed IP on day 1.

Eligible subjects will continue cinacalcet treatment on 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 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. Eligible subjects from 20110100 will restart cinacalcet treatment based on their dry weight at the time of enrollment in 20140159 study and age at the time of enrollment in the 20110100 study.

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 day 1 in Study 20140159, not to exceed a dose of 60 mg/day.

Section: 3.3 Number of Subjects

Replace:

This study is open to subjects who complete the 20-week treatment period in Study 20130356 or the Week 26 End of Study visit in Study 20110100. There may be up to 78 subjects enrolled in this study.

With:

This study is open to subjects who complete the 20-week treatment period in Study 20130356 **or reach study termination in Study 20130356** or the week 26 End of Study visit in Study 20110100 **or reach study termination in Study 20110100**. There may be up to 78 subjects enrolled in this study.

Section: 4 Subject Eligibility

Replace:

Subjects from the cinacalcet arm in Amgen Study 20130356, who are on a dose withhold at the completion of week 20 in Amgen Study 20130356, may enroll in this

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study if they meet eligibility criteria but will not restart dosing until the criteria for restarting dosing, defined in Section 6.2.3, are met.

Subjects who were ≤ 18 years old at week 20 in the 20130356 study are eligible to enter this Study 20140159 even if they have already turned 18 years of age or are due to turn 18 years of age during their planned participation in the 20140159 study.

With:

Subjects from the cinacalcet arm in ~~Amgen~~ of Study 20130356 **or subjects in Study 20110100** who had their are on a dose withheld at the completion of week 20 **EOIP visit in Amgen Study 20130356**, may enroll in this study if they meet eligibility criteria but will not restart dosing until the criteria for restarting dosing, defined in Section 6.2.3, are met.

Subjects who were ≤ 18 years old at week 20 in the 20130356 study **or at the time of study termination**, are eligible to enter this Study 20140159 even if they have already turned 18 years of age or are due to turn 18 years of age during their planned participation in the 20140159 study.

Section: 4.1.1 Inclusion Criteria

Replace:

- 101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any day 1 study-specific activities/procedures being initiated.
- 102 Dialysate calcium concentration ≥ 2.5 mEq/L at day 1

All subjects from 20130356

- 103 Completed treatment through week 20 in the 20130356 study
- 104 Dry weight ≥ 12.5 kg at day 1 of Study 20140159

Subjects Randomized to the 20130356 Standard of Care Arm Only

- 105 iPTH value ≥ 300 pg/mL (week 19 in 20130356)
- 106 Corrected calcium value ≥ 8.8 mg/dL (week 19 in 20130356)

All Subjects from 20110100

- 107 Completed week 26 End of Study visit in the, 20110100 study
- 108 Dry weight ≥ 7 kg at day 1 of Study 20140159

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With:

All Subjects

- 101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any Study 20140159 day 1 study-specific activities/procedures being initiated.
- 102 Dialysate calcium concentration ≥ 2.5 mEq/L at day 1

All subjects with > 14 days between the last study visit in Study 20130356 or Study 20110100 and screening for Study 20140159

- 103 **Subjects on anti-convulsant medication must be on a stable dose**

All subjects from 20130356

- 104 Completed treatment through week 20 in the 20130356 study **or on study at the time of Study 20130356 termination**
- 105 Dry weight ≥ 12.5 kg at day 1 of Study 20140159

Subjects Randomized to the 20130356 Standard of Care Arm Only

- 106 iPTH value ≥ 300 pg/mL (**within 7 days of day 1 in Study 20140159**) (~~week 19 in 20130356~~)
- 107 Corrected calcium value ≥ 8.8 mg/dL **within 7 days of day 1 in Study 20140159** (~~week 19 in 20130356~~)

All Subjects from 20110100

- 108 Completed **week 26 End of Study visit** in the, 20110100 study **or on study at the time of Study 20110100 termination**
- 109 Dry weight ≥ 7 kg at day 1 of Study 20140159

Section: 4.1.2 Exclusion Criteria

General

Studies 20130356 or 20110100

Added:

Studies 20130356 or 20110100

- 211 **A new onset of seizures or worsening of pre-existing seizure disorder All Subjects with > 14 days between the last study visit in Study 20130356 or Study 20110100 and the screening visit in Study 20140159 will have the following exclusion criteria applied during screening and day 1:**

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- 212 Unstable chronic heart failure defined as worsening pulmonary edema or other signs and symptoms as per investigator assessment during screening
- 213 Received therapy with commercial cinacalcet after the last study visit in Study 20130356 or Study 20110100 before day 1 of Study 20140159
- 214 Scheduled date for kidney transplantation from a known living donor that makes completion of the study unlikely
- 215 Either new or recurrent cardiac ventricular arrhythmias requiring a change in treatment within 10 days prior to screening visit or day 1 of Study 20140159 screening
- 216 Hepatic impairment indicated by elevated levels of hepatic transaminase or bilirubin (aspartate aminotransferase [AST] $\geq 1.5 \times$ upper limit of normal [ULN] OR alanine aminotransferase [ALT] $\geq 1.5 \times$ ULN OR total bilirubin $\geq 1 \times$ ULN per institutional laboratory range) during screening

Section: 4.1.2 Exclusion Criteria

General

Studies 20130356 or 20110100

Replace:

- 208 If sexually active, subject is not willing to use highly effective contraception during treatment and for at least 9 days after the end of treatment.

With:

- 208 If sexually active, subject is not willing to use **acceptable** highly effective contraception during treatment and for at least 9 days after the end of treatment.

At Day 1 Study Visit-All Subjects

- 212 Central laboratory values (cCa, iPTH) were not obtained/are not available for
- 20130356 week 19 or
 - 20140159 Screening visit for subjects from 20110100 study

With:

All Subjects – At Day 1 Study Visit – All Subjects

- 217 Central laboratory values (cCa, iPTH) were not obtained/are not available at day 1 in Study 20140159
- ~~20130356 week 19 or~~
 - ~~20140159 Screening visit for subjects from 20110100 study~~

Delete:

At Day 1 Study Visit-Subjects Rolling Over from 20130356 Cinacalcet Arm or from 20110100 Study

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217 ~~Cinacalcet dose withheld for \geq last 4 weeks of treatment in studies 20130356 and 201101100.~~

218 If sexually active, subject is not willing to use highly effective contraception during treatment and for at least 9 days after the end of treatment.

Section: 5.1 Screening

Replace:

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. The informed consent can be signed up to (\pm 3 days) prior to 20140159 day 1.

With:

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. The informed consent can be signed up to **7 days** (\pm 3 days) prior to 20140159 day 1.

Section: 5.2 Enrollment

Replace:

The subject will be considered enrolled in the extension study:

- 20130356 subjects will be assigned a cinacalcet dose based on the treatment arm and/or last dose received in Study 20130356.
- 20110100 subjects will be assigned a cinacalcet dose based on their dry weight at the time of enrollment in the 20140159 study and age at time of enrollment in the 20110100 study.

With:

The subject will be considered enrolled in the extension study:

- 20130356 subjects will be assigned a cinacalcet dose based on the treatment arm and/or last dose received in Study 20130356 **following the dosing instructions in Section 6.2.3**
- 20110100 subjects will be assigned a cinacalcet dose based on ~~enrollment the last dose received at the EOIP visit in Study 20110100 study~~ **following the dosing instructions in Section 6.2.3** ~~their dry weight at the time of enrollment in the 201401159 study and the age at the time of.~~

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Section: 6.2.3 Dosage, Administration, and Schedule

Replace:

- Subjects ≥ 6 years of age: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg.
 - Subjects from 20130356 may receive capsules for any dose which is an exact multiple of 5 mg. Subjects who are assigned doses of 60 - 180 mg/day will require administration of 2 - 6 tablets per dose. For those subjects unable to swallow tablets, capsules may be dispensed.
- Subjects < 6 years of age: 1, 2.5, 5, 7.5, 10, 15, 30 and 60 mg. Subjects from Study 20110100 will start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at the 20140159 day 1 timepoint and age at time of enrollment in 20110100 study, rounded down to the lowest PSD.
 - Subjects assigned dose of 10-60 mg/day will require that more than 1 capsule per dose be sprinkled on soft food or used to create the liquid suspension for administration.
 - Subjects enrolling into 20140159 from 20110100 would have a maximum dose of 2.5 mg/kg/day based on the subject's day 1 dry weight or 60 mg daily, whichever is lower.

With:

- Subjects ≥ 6 years of age: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg. **Subjects from Study 20130356 will either continue to receive cinacalcet at the same dose as at the EOIP visit if ≤ 14 days have passed between last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159. If > 14 days have passed, subjects will start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at Study 20140159 day 1 time point and age at time of enrollment in Study 20130356, rounded down to the lowest PSD.**
- Subjects from Study 20130356 may receive capsules for any dose which is an exact multiple of 5 mg. Subjects who are assigned doses of 60 **to** 180 mg/day will require administration of **two to six 30 mg** tablets per dose. For those subjects unable to swallow tablets, capsules may be dispensed.
- **Subjects < 6 years of age:** 1, 2.5, 5, 7.5, 10, 15, 30 and 60 mg. Subjects from Study 20110100 will **either continue to receive cinacalcet at the same dose as at the EOIP visit if ≤ 14 days have passed between last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159. If > 14 days have passed, subjects will** start cinacalcet in Study 20140159 at 0.20 mg/kg/day based on the subject's dry weight at the 20140159 day 1 time point and age at time of enrollment in 20110100 study, rounded down to the lowest PSD.
 - Subjects assigned **a dose between** 10 **to** 60 mg/day will require more than 1 capsule per dose be sprinkled on soft food or used to create the liquid suspension for administration.
 - Subjects enrolling into 20140159 from 20110100 would have a maximum dose of 2.5 mg/kg/day based on the subject's **20140159** day 1 dry weight or 60 mg daily, whichever is lower.

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Section: 6.2.3.1.1 Subjects From Study 20130356

Replace:

Subjects from the cinacalcet arm will follow the dose adjustments outlined in Table 1 in Section 6.2.3.1.1.1. If subjects from the cinacalcet arm in 20130356 are on a dose withheld at 20140159 day 1, the iPTH and cCa restart values (iPTH > 100 pg/mL and cCa > 8.4 mg/dL) must be reached prior to resuming cinacalcet in the current extension study. Subjects from the cinacalcet arm, who have had their dose withheld for > 1 month at the time of 20140159 day 1 will not be eligible for this study.

With:

Subjects from the cinacalcet arm **with ≤ 14 days between last dose of cinacalcet treatment in Study 20130356 and Study 20140159 day 1 will continue at the same dose as the last dose at EOIP and** will follow the dose adjustments outlined in Table 1 in Section 6.2.3.1.1.1. **Dose titration cannot occur until the week 4 visit per Table 1.** If subjects from the cinacalcet arm in 20130356 are on a dose **that was withheld or missed for > 14 days and ≤ 1 month at day 1 of Study 20140159** day 1, the iPTH and cCa restart values (iPTH > 100-150 pg/mL and cCa > 8.4 mg/dL) must be reached prior to resuming cinacalcet **will receive the initial dose of cinacalcet** in the current extension study **outlined in Table 1 in Section 6.2.3.1.1.1.**

Subjects from the cinacalcet arm **with > 1 month between the last dose of cinacalcet treatment in Study 20130356 and Study 20140159 day 1, will receive the initial dose of cinacalcet as defined in Section 6.2.3.1.1.1. To commence dosing, all subjects must have:** ~~who have had their dose withheld for > 1 month at the time of 20140159 day 1 will not be eligible for this study~~

- **ionized calcium ≥ 1.05 mmol/L prior to initiation of treatment on day 1 in this study**
- **iPTH value ≥ 300 pg/mL within 7 days of day 1**
- **corrected calcium value ≥ 8.8 mg/dL within 7 days of day 1**

Section: 6.2.3.1.1.1 Dosage Adjustments

Replace:

On day 1, the subject's ionized calcium must be at or above threshold (ie, ≥ 1.13 mmol/L for subjects less than 2 years of age, ≥ 1.05 mmol/L for subjects 2 years of age and above) prior to initiation of treatment. The initial dose of cinacalcet and all subsequent

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doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at 20140159 day 1, rounded down to the lowest PSD. Subjects from the cinacalcet arm will start cinacalcet dosing on 20140159 day 1 at the same dose of cinacalcet they received at the completion of the treatment period (week 20) in Study 20130356 or titrate based on the Table 1. The initial dose of cinacalcet will be assigned to subjects restarting cinacalcet after withholding the dose for more than 14 days during the study.

At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the criteria in Table 1.

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- iPTH is > 100 pg/mL

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

With:

~~On day 1, the subject's ionized calcium must be at or above threshold (ie, ≥ 1.13 mmol/L for subjects less than 2 years of age, ≥ 1.05 mmol/L for subjects 2 years of age and above) prior to initiation of treatment. The initial dose of cinacalcet and all subsequent~~
doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects from the SOC arm will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at **day 1 of Study 20140159** ~~day 1~~, rounded down to the lowest PSD.

~~Subjects from the cinacalcet arm will start cinacalcet dosing on~~ **with ≤ 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159 will start cinacalcet dosing** at the same dose of cinacalcet they received at the completion of the **EOIP visit** ~~treatment period (week 20) in Study 20130356 or~~ **and titrate follow weekly dose adjustment** based on the Table 1. **For subjects from the cinacalcet arm with > 14 days between the last dose of cinacalcet treatment in Study 20130356 and day 1 of Study 20140159, the initial dose of cinacalcet will be assigned to subjects restarting cinacalcet after withholding the dose for more than 14 days** **0.20 mg/kg/day, based on the subject's dry weight at**

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day 1 of 20140159, rounded down to the lowest PSD, will be assigned during the study.

At all weekly visits (including week 4, 8, 12, 16, 20, and 24), the dose may be maintained, reduced or withheld based upon the **dose adjustment** criteria in Table 1.

If any of the criteria for dose withholding are met at any time during the trial, including between scheduled study visits (ie, unscheduled), the dose of cinacalcet is to be withheld until all of the following criteria are met:

- iPTH is > **150** 100-pg/mL

If IP has been withheld or missed for ~~more than~~ > 14 days, the subject will resume dosing at the starting dose level once **(initial dose in parent Studies 20130356 or 20110100)** all restart criteria are met **based on dry weight at day 1 of Study 20140159**.

Section: Table 1 Footnote *

Replace:

* restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > 100 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

With:

* restart one PSD below last dose when cCa is > 8.4 mg/dL, iPTH is > **150** 100 pg/mL, ionized calcium is > 1.05 mmol/L, symptoms of hypocalcemia and other AE that warrants IP dose withholding have resolved.

Section: 6.2.3.1.2 Subjects from 20110100

Replace:

Subjects From 20110100

In order to start dosing, all subjects from Study 20110100 must have:

- Ionized calcium prior to initiation of treatment on day 1 in this study
 - ≥ 1.13 mmol/L if age < 2 years
 - ≥ 1.05 mmol/L if ≥ 2 years
- iPTH value ≥ 150 pg/mL within 7 days of day 1
- Corrected calcium value within 7 days of day 1

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- Phosphorus value within 7 days of day 1
 - ≥ 5.0 mg/dL (1.25 mmol/L) if age < 1 year
 - ≥ 4.5 mg/dL (1.13 mmol/L) if age ≥ 1 year

With:

Subjects From **Study 20110100**

For subjects where the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159 occurs within 14 days, in order to commence dosing, subjects from Study 20110100 will follow weekly dose adjustment criteria as outlined in Table 2 for age < 2 years and Table 3 for age ≥ 2 years. Dose titration cannot occur until week 4.

For subjects with > 14 days and < 1 month between the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, in order to commence start-dosing at the initial dose, all subjects from Study 20110100 must have meet restart criteria per weekly dose adjustment criteria as outlined in Table 2 for age < 2 years and Table 3 for age ≥ 2 years. Dose titration cannot occur until week 4.

- **Additionally the phosphorus value within 7 days of day 1 should be:**
 - ≥ 5.0 mg/dL (1.25 mmol/L) if age is < 1 year
 - ≥ 4.5 mg/dL (1.13 mmol/L) if age is ≥ 1 year

For subjects with > 1 month between EOS visit in Study 20110100 and day 1 of Study 20140159, in order to commence dosing, all subjects from Study 20110100 must have:

- ionized calcium prior to initiation of treatment on day 1 in this study
 - ≥ 1.13 mmol/L if age is < 2 years
 - ≥ 1.05 mmol/L if age is ≥ 2 years
- iPTH value ≥ 300 150pg/mL within 7 days of day 1
- Corrected calcium value within 7 days of day 1
- phosphorus value within 7 days of day 1
 - ≥ 5.0 mg/dL (1.25 mmol/L) if age is < 1 year
 - ≥ 4.5 mg/dL (1.13 mmol/L) if age is ≥ 1 year

Section: 6.2.3.1.2.1 Subjects < 2 Years of Age

Replace:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects will start at the initial cinacalcet dose of

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0.20 mg/kg/day, based on the subject's dry weight at day 1, in the 20140159 study rounded down to the lowest PSD.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

With:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system.

For subjects with > 14 days since the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, S subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1, in Study 20140159 rounded down to the lowest PSD.

For subjects with ≤ 14 days between the last dose of cinacalcet in Study 20110100 and Study 20140159 day 1, subjects will continue the same dose of cinacalcet they received at the completion EOIP visit or early termination visit at Study 20110100 termination and follow the weekly dose adjustments outlined in Table 2. Dose titration cannot occur until week 4. If subjects from the Study 20110100 are on a dose withhold at day 1 of Study 20140159, the iPTH and cCa restart values (iPTH > 150 pg/mL and cCa > 9.0 mg/dL) must be reached prior to resuming cinacalcet in the Study 20140159.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level (**initial dose in parent Studies 20130356 or 20110100**) once all restart criteria are met.

Section: 6.2.3.1.2.2 Subjects ≥ 2 Years of Age

Replace:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system. Subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1 in the 20140159 study, rounded down to the lowest PSD.

If IP has been withheld or missed for more than 14 days, the subject will resume dosing at the starting dose level once all restart criteria are met.

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With:

The initial dose of cinacalcet and all subsequent doses will be calculated by the site staff and confirmed by the IVR/IWR system.

For subjects with > 14 days since the last dose of cinacalcet treatment in Study 20110100 and day 1 of Study 20140159, subjects will start at the initial cinacalcet dose of 0.20 mg/kg/day, based on the subject's dry weight at day 1 in Study 20140159, rounded down to the lowest PSD.

For subjects with ≤ 14 days since the last dose of cinacalcet in Study 20110100 and day 1 of Study 20140159, subjects will continue cinacalcet based on the dose at the EOIP visit or early termination/EOS at study termination and follow the weekly dose adjustments outlined in Table 3. Dose titration cannot occur until week 4. If subjects from the Study 20110100 are on a dose that was withheld at day 1 of Study 20140159, the iPTH and cCa restart values (iPTH > 150 pg/mL and cCa > 8.4 mg/dL) must be reached before resuming cinacalcet in Study 20140159.

If IP has been withheld or missed for more than 14 days (initial dose in parent Studies 20130356 or 20110100), the subject will resume dosing at the starting dose level once all restart criteria are met.

Section: 6.2.3.1.3 Missed Doses

Replace:

If a subject misses > 14 consecutive doses of cinacalcet for any reason, including temporary dose withholding due to the administration of concomitant medications as noted above, they will be restarted at their initial dose of cinacalcet (0.20 mg/kg/day based on dry weight at day 1) when administration of IP resumes per the dose titration guidelines outlined in Table 1, Table 2, and Table 3.

With:

If a subject misses > 14 consecutive doses of cinacalcet for any reason, including temporary dose withholding due to the administration of concomitant medications as noted above, they will be restarted at their initial dose of cinacalcet (0.20 mg/kg/day based on dry weight at day 1 in Study 20140159) when administration of IP resumes per the dose titration guidelines outlined in Table 1, Table 2, and Table 3.

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Section: Table 4 Schedule of Assessments

Add:

Requirement to collect concomitant medications, liver function tests, and chemistry, hematology, 25(OH) Vit D at Screening, Week -1.

Note: When it is not possible to perform a study visit at the specified time point, the visit may be performed within ± 3 days

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[illegible][illegible][illegible][illegible]

2 - These procedures are required for the 20130356 EOIP and 20110100 EOS visit and 20140159 day 1 visit. These procedures will be performed once at the site and applied to both study visits.

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[illegible][illegible][illegible][illegible]

1 - Where the Screening and day 1 assessments for Study 20140159 overlap with visits in the Studies 20130356 or 20110100, these will be performed once at the site and applied to both study visits to minimize duplicate study assessments. ~~These procedures are required for the 20130356 week 19 visit and 20140159 screening visit. These procedures will be performed once at the site and applied to both study visits.~~

~~2 - These procedures are required for Study 20140159 screening visit if > 14 days since last study visit in Studies 20130356 or 20110100 for subjects impacted by study termination. These procedures are required for the 20130356 EOIP and 20110100 EOS visit and 20140159 day 1 visit. These procedures will be performed once at the site and applied to both study visits.~~

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Section: 7.2.2 Day 1

Replace:

The following day 1 procedures are also required for the EOIP study visit at week 20 for Amgen study 20130356 and Week 26 End of Study visit for Study 20110100 except where indicated. These procedures should not be duplicated and may be collected once and entered onto the appropriate eCRF once eligibility for this study has been confirmed:

With:

The following day 1 procedures are also required for the EOIP study visit ~~at week 20~~ for Amgen ~~s~~Study 20130356 and ~~week 26~~End of Study visit for Study 20110100 except where indicated. These procedures should not be duplicated and may be collected once **where study visits overlap** and entered onto the appropriate eCRF once eligibility for this study has been confirmed:

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 30 days.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program (PSP) within 24 hours of the investigator's knowledge of the event of a pregnancy.

Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The PSP will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 30 days.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event.

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With:

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of **cinacalcet** protocol-required therapies through **90** 30 days.

The pregnancy should be reported to Amgen's **Global Patient Safety** global Pregnancy Surveillance Program (PSP) within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (**Appendix C**). **Amgen Global Patient Safety** The PSP will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking **cinacalcet** protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of **cinacalcet** protocol-required therapies through **90** 30 days.

Any lactation case should be reported to Amgen's **Global Patient Safety** global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event.

Section: 10.1.1 Study Endpoints

Replace:

Secondary Endpoints:

- Percent change from day 1 in iPTH to week 11 and week 28
- Serum cCa values at day 1, week 11, and week 28
- Serum phosphorus values at day 1, week 11, and week 28

Exploratory Endpoint

- Growth velocity from day 1 to end of study
- Change in Tanner stage from day 1 to end of study

With:

Secondary Endpoints:

20140159 Study Only

- Percent change from day 1 in iPTH to week 11 and week 28
- Serum cCa values at day 1, week 11, and week 28

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- ~~Serum phosphorus values at day 1, week 11, and week 28~~
- Achievement of $\geq 30\%$ reduction from baseline to mean iPTH during weeks 11 and 15 (SOC arm of Study 20130356 only)
- Achievement of $\geq 30\%$ 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)
- Change in corrected total serum calcium from baseline to mean value during weeks 23 and 28
- Change in serum phosphorus from baseline to mean value during weeks 23 and 28
- Achievement of a mean iPTH ≤ 300 pg/mL during weeks 23 and 28
- Serum cCa at ~~baseline~~ day 1, week 11, and week 28
- Serum phosphorus at ~~baseline~~ day 1, week 11, and week 28

Combined 20130356, 20110100, and 20140159 Studies

- Achievement of $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH during weeks 11 and 15
- Achievement of $\geq 30\%$ 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 Endpoints:

Study 20140159 Only

- Growth velocity from baseline to EOS
- Change in Tanner stage from baseline to EOS

Combined Studies 20130356, 20110100, and 20140159

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

Exploratory Endpoint

- ~~Growth velocity from day 1 to end of study~~
- ~~Change in Tanner stage from day 1 to end of study~~

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Section: 10.1.2 Analysis Sets

Replace:

Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects with at least one assessment after day 1.

With:

Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects **in Study 20140159** with at least one assessment after day 1.

Added:

Efficacy Analysis Set

The Efficacy Analysis Set includes all enrolled subjects who received at least one dose of cinacalcet and have at least one assessment after day 1.

Section: 10.1.3 Covariates and Subgroups

Replace:

The primary, secondary, and safety endpoints will be summarized by baseline age group (6 to < 12 years and 12 to < 18 years for Study 20130356; 28 days to < 2 years and 2 to < 6 years for Study 20110100) as supportive analyses.

With:

The primary, secondary, and safety endpoints **may** will be summarized by baseline age group (6 to < 12 years and 12 to < 18 years for Study 20130356; 28 days to < 2 years and 2 to < 6 years for Study 20110100) as supportive analyses **upon availability of data in each subgroup.**

Section: 10.3.1 Interim Analysis

Replace:

An interim analysis will be conducted. The timing of the interim analysis will be dependent on the completion of the Study 20130356. There is no formal statistical testing. The analysis for all endpoints will be descriptive in nature.

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With:

Several interim analyses may be conducted. The first interim analysis will be performed to support the Supplemental New Drug Application (sNDA) for pediatric indication. Its scope of analysis will be limited to the planned analysis using 20140159 study data only. The rest of interim analyses may be performed to support further request from regulatory. The scope of these analyses will be specified in a separate statistical analysis plan of interim analysis. There is no plan to conduct formal statistical testing. An interim analysis will be conducted. The timing of the interim analysis will be dependent on the completion of the Study 20130356. There is no formal statistical testing. The analysis for all endpoints will be descriptive in nature.

Section: 10.3.2 Primary Analysis

Replace:

The general approach is to provide estimates for the primary and secondary endpoints for the study population.

The primary analysis of all endpoints will be conducted after the Primary Completion is achieved for this study.

With:

The general approach is to provide estimates for the primary and secondary endpoints for the study population.

The primary analysis of all endpoints will be conducted after all subjects have completed the week 32 EOS visit or terminated early from Study 20140159.

Section: 10.4.1 General Considerations

Replace:

There is no formal statistical testing for this study. The analysis for all endpoints will be descriptive in nature. No missing data imputation will be used.

All summaries will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, overall) and Study 20110100.

With:

There is no formal statistical testing for this study. The analysis for all endpoints will be descriptive in nature. ~~No missing data imputation will be used.~~

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All summary ~~ies~~ **tables** will be provided by study treatment group: Study 20130356 (SOC, SOC + cinacalcet, ~~overall~~) and Study 20110100 **and overall, unless otherwise specified.**

Section: 10.4.2 Primary Endpoint

Replace:

The primary analysis of the primary endpoint will be based on the Safety Analysis Set. The primary endpoint is subject incidence of events of interest (EOI; eg, hypocalcemia, convulsions, hypotension, worsening of heart failure, hypersensitivity, ischemic heart disease, QT prolongation/ventricular tachyarrhythmias, fracture, acute pancreatitis, drug-related hepatic disorders, nervous system disorders [excluding seizures], neoplastic events, and infection). The exact 95% confidence intervals (CI) of the overall incidence rates will be reported.

With:

The ~~primary~~ analysis of the primary endpoint will be based on the Safety Analysis Set. The primary **analysis of the primary** endpoint is subject incidence of events of interest (EOI; eg, hypocalcemia, convulsions, hypotension, worsening of heart failure, hypersensitivity, ischemic heart disease, QT prolongation/ventricular tachyarrhythmias, fracture, acute pancreatitis, drug-related hepatic disorders, nervous system disorders [excluding seizures], neoplastic events, and infection) **for data in the 20140159 study only. The secondary analysis of the primary endpoint is the incidence of events of interest adjusted by the amount of safety follow-up time for combined data from parent studies and data from the 20140159 study.** The ~~exact~~-95% confidence intervals (CI) of the overall incidence rates will be reported.

Section: 10.4.3 Secondary Endpoints

Replace:

The primary analysis will be based on FAS for all secondary endpoints. Summary statistics will be provided for percent change in iPTH, from day 1 to week 11 and week 28 within the study population and each age group by previous treatment group in the parent study and overall. No missing data imputation will be used. Summary statistics will be provided for serum cCa and phosphorus values at day 1 to week 11, and week 28. No imputation of missing data will be utilized.

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With:

The analysis of secondary endpoints will be based on the Efficacy Analysis Set. The approach for handling the missing data will be described for each endpoint in the statistical analysis plan. ~~primary analysis will be based on FAS for all secondary endpoints. Summary statistics will be provided for percent change in iPTH, from day 1 to week 11 and week 28 within the study population and each age group by previous treatment group in the parent study and overall. No missing data imputation will be used. Summary statistics will be provided for serum cCa and phosphorus values at day 1 to week 11, and week 28. No imputation of missing data will be utilized.~~

20140159 study only

The proportion of subjects who achieve a $\geq 30\%$ reduction from baseline of Study 20140159 to mean iPTH at weeks 11 and 15 and to mean iPTH at weeks 23 and 28 will be assessed for the SOC arm in Study 20130356 with a 95% CI.

Summary statistics will be provided for the percent change in mean iPTH from baseline in Study 20140159 during weeks 23 and 28 for the SOC group in Study 20130356.

Summary statistics will be provided for the change in corrected total serum calcium and change in serum phosphorus from baseline of Study 20140159 to mean value at weeks 23 and 28 by treatment group in the parent study.

The proportion of subjects who achieve a mean iPTH value of ≤ 300 pg/mL during weeks 23 and 28 will be provided by treatment group in the parent study with a 95% CI.

Summary statistics will be provided for serum cCa and phosphorus values at baseline to week 11 and week 28.

Combined 20130356, 20110100, and 20140159 Studies

The proportion of subjects who achieve a $\geq 30\%$ reduction from day 1 of cinacalcet treatment to mean iPTH at weeks 11 and 15 and to mean iPTH at weeks 23 and 28 will be provided by previous treatment group in the parent study with a 95% CI.

The percent change in iPTH, change in corrected serum calcium, and change in serum phosphorus from day 1 of cinacalcet treatment at each measurement time point will be summarized overall.

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Section: 10.4.4 Safety Endpoints

Added:

All safety endpoints in 20140159 study only and combined with their parent studies, will be summarized by treatment group in the parent studies and overall.

Replace:

Laboratory Data, Blood Pressure, and Heart Rate

The incidence of hypocalcemia after the first dose of IP will be summarized using descriptive statistics. Hypocalcemia will be defined in two ways, with the subject incidence of corrected serum calcium of < 7.5 mg/dL and < 8.4 mg/dL both being summarized. Subject incidence of ionized calcium value < 1.05 mmol/L and < 1.00 mmol/L will be summarized.

With:

Laboratory Data, Blood Pressure, and Heart Rate

The incidence of hypocalcemia after the first dose of IP will be summarized using descriptive statistics. Hypocalcemia will be defined in two ways, with the subject incidence of corrected serum calcium of < 7.5 mg/dL, **8.0 mg/dL**, and < 8.4 mg/dL both being summarized. Subject incidence of ionized calcium value < **0.94 mmol/L**, < 1.05 mmol/L, and < 1.00 mmol/L will be summarized.

Section: Appendix C Pregnancy and Lactation Notification Worksheets

Replace:

Footnotes on the Pregnancy and Lactation Notification Worksheets was removed.

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AtGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

8BECTORTYPE1N...FA»

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ E-mail _____

Institution _____

Address _____

Subject ID: _____ Subject Gender: ☐ Female ☐ Male Subject OOB: mm / dd / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm / dd / yyyy

Was the product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm / dd / yyyy
Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP: mm / dd / yyyy ☐ Unknown
Estimated date of delivery: mm / dd / yyyy ☐ Unknown ☐ N/A
If N/A, date of termination (actual or planned): mm / dd / yyyy
Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A
If yes, provide date of delivery: mm / dd / yyyy
Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A
Any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that identifies and reports to the appropriate regulatory authorities any potential fetal or maternal risks associated with the use of Amgen products. This information is provided to you for your information only and does not constitute a recommendation or endorsement of Amgen products. For more information, please contact your local Amgen representative.

Effective Date: March 27, 2011

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Print form

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country respective Safety Fax Line

SELECT OR TYPE IN A FAX LINE Enter fax number

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site# _____
Phone (____) _____ Fax (____) _____ Email _____
Institution _____
Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No
If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____
Did the subject Withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No
If No, provide stop date: mm ____ / dd ____ / yyyy ____
Infant date of birth: mm ____ / dd ____ / yyyy ____
Infant gender: ☐ Female ☐ Male
Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A
If any Adverse Event was experienced by the mother or the infant, provide brief details _____

Form completed by:

Print Name: _____ Title: _____
Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2.

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With:

AMGB1 Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE: N/A FAX:-

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name: _____ Site#: _____

Phone: _____ Fax: _____ Email: _____

Institution: _____

Address: _____

Subject ID#: _____ Subject Gender: ☒ Female ☐ Male Subject DOB: mm____/dd____/yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____dd____yyyy____

Was the Amgen product (or study drug) discontinued? ☒ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☒ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP: mm____/dd____/yyyy____ ☒ Unknown

Estimated date of delivery: mm____/dd____/yyyy____ ☒ Unknown ☐ N/A

If N/A, date of termination (actual or planned): mm____/dd____/yyyy____

Has the pregnant female already delivered? ☒ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm____/dd____/yyyy____

Was the infant healthy? ☒ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011

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AMGB1 Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm ____ / dd ____ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____ / dd ____ / yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____ / dd ____ / yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm ____ / dd ____ / yyyy ____

Infant date of birth: mm ____ / dd ____ / yyyy ____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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Date: 01 June 2016

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Superseding Amendment 3

Protocol Title: 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

Amgen Protocol Number (cinacalcet HCl) 20140159

EudraCT number 2014-003563-38

Superseding Amendment 3 01 June 2016
Date:

Rationale:

The purpose of the superseding protocol amendment is to correct administrative and typographical changes in [Section 10.4.4](#) Safety Endpoints.

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Description of Changes:

[Section: Global](#)

Replace:

16 March 2016

With:

01 June 2016

[Section: Title Page Date](#)

Added:

Superseding 3.1: 01 June 2016

[Section: 10.4.4 Safety Endpoints](#)

Replace:

Hypocalcemia will be defined in two ways, with the subject incidence of corrected serum calcium of < 7.5 mg/dL, 8.0 mg/dL, and < 8.4 mg/dL both being summarized. Subject incidence of ionized calcium value < 0.94 mmol/L, < 1.05 mmol/L, and < 1.00 mmol/L will be summarized.

With:

Hypocalcemia will be defined in two ways: with the subject incidence of corrected serum calcium of < 7.5 mg/dL, < 8.0 mg/dL, and < 8.4 mg/dL being summarized; **and with** subject incidence of ionized calcium value < 0.94 mmol/L, < 1.05 mmol/L, and < 1.00 mmol/L **being** summarized.

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