A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism

Etelcalcetide (AMG 416)

Amgen Protocol Number 20150238

NCT #: NCT03299244

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Investigator's Agreement

I have read the attached protocol entitled: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride with Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects with Secondary Hyperparathyroidism, dated **27 November 2018**, and agree to abide by all provisions set forth therein.

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I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy, Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride with Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects with Secondary Hyperparathyroidism

Study Phase: 3

Indication: Hemodialysis Subjects with Secondary Hyperparathyroidism (SHPT)

Primary Objective: To demonstrate that treatment with etelcalcetide (AMG 416) is not inferior to treatment with cinacalcet for lowering serum intact parathyroid hormone (PTH) levels by > 30% from baseline among subjects with chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) who require management with hemodialysis.

Secondary Objective: To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) **measured at the central laboratory,** and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dl **measured at the central laboratory** during the efficacy assessment phase (EAP).

Safety Objectives:

- Assess the safety and tolerability of etelcalcetide compared to cinacalcet
- Evaluation of antibody formation to etelcalcetide

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

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

Primary Endpoint: The primary endpoint of the study is achievement of a > 30% reduction from baseline in mean predialysis serum PTH level during the EAP of the study (EAP is defined as weeks 20 to 27, inclusive).

Key Secondary Endpoint(s):

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

Other Secondary Endpoints

- Percent change from baseline in mean predialysis serum cCa **measured by the central laboratory** during the EAP
- Achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

Safety Endpoints

- Incidence of cCa < 8.3 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 8.0 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 7.5 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of treatment-emergent symptomatic hypocalcemia during the study

- Incidence of antibody formation to etelcalcetide
- Nature, frequency, severity, and relationship of treatment-emergent adverse events.

Exploratory Endpoints

[redacted]

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

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

Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet.

Sample Size: Approximately 660 subjects will be randomized in this study (approximately 330 subjects in each of the 2 treatment arms).

Summary of Subject Eligibility Criteria: The study seeks to enroll subjects (≥ 18 years of age at the time of signing the informed consent) who are receiving maintenance hemodialysis 3 times weekly for at least 3 months, with adequate hemodialysis with a delivered Kt/V ≥ 1.2 or urea reduction ratio (URR) ≥ 65% within 4 weeks prior to screening laboratory assessments.

Subjects must have SHPT as defined by 1 central laboratory screening predialysis serum PTH value > 500 pg/mL **(53.00 pmol/L)** and one serum cCa value ≥ 8.3 mg/dL **(2.07 mmol/L)** within 2 weeks prior to randomization. Eligible subjects cannot have received cinacalcet during the 3 months preceding the first screening laboratory assessment. For subjects currently receiving vitamin D sterols, the vitamin D dose must have no more than a maximum dose change of 50% within the 4 weeks prior to screening laboratory assessments, maintain stable through randomization, and be expected to maintain stable doses for the duration of the study, except for adjustments allowed per protocol or for safety reasons. Subjects receiving calcium supplements must have no more than a maximum dose change of 50% within 2 weeks before screening laboratory assessments are obtained, and the dose must remain unchanged through randomization. Subjects receiving phosphate binders must have had no more than a maximum of 50% dose change within 2 weeks before screening laboratory assessments are obtained, and the dose must remain stable thereafter throughout the study except as noted in the protocol or for safety reasons.

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.1.

Investigational Product: The investigational products (IPs) used in this study will include etelcalcetide (Amgen IP), cinacalcet (non-Amgen IP), and placebo. Placebo will be provided with either intravenous (IV) or oral tablets.

Amgen Investigational Product Dosage and Administration: Subjects who are randomized to treatment with etelcalcetide will be treated with IV IP 3 times weekly at the end of each dialysis session and oral placebo tablets daily for 26 weeks. The starting dose of IV IP is 5 mg and will be titrated by the Interactive Voice Response (IVR)/Interactive Web Response (IWR) system to target predialysis [redacted] The minimum IV IP dose is 2.5 mg,

and the maximum dose is 15 mg. The dose of the IV IP may be increased in increments of 2.5 mg or 5 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL **(31.80 pmol/L)** and cCa values remain ≥ 8.3 mg/dL **(2.07 mmol/L)** based on results **measured by the central laboratory** obtained the previous **or current** week.

Non-Amgen Investigational Product Dosage and Administration: Subjects who are randomized to treatment with oral cinacalcet will be treated with oral IP daily and three times weekly IV doses of placebo at the end of each dialysis session, for 26 weeks. The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] The minimum oral IP dose is 25 mg, and the maximum dose is 100 mg. The dose of oral IP may be increased in increments of 25 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL **(31.80 pmol/L)** and cCa values remain ≥ 8.3 mg/dL **(2.07 mmol/L)** based on results **measured by the central laboratory** obtained the previous **or current** week.

Procedures: After signing the informed consent form, subjects will enter the screening period (up to 8 weeks). Screening evaluations will include review of inclusion/exclusion criteria, demographics, medical history, prior and concomitant medications, physical examination, electrocardiogram, and reporting of serious adverse events. Blood samples will be collected for pharmacokinetics (PK), hematology, chemistry, PTH, and for all females of childbearing potential a serum pregnancy test. Kt/V or URR assessment will be performed at screening unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available. At the day 1 visit, baseline assessments will be performed and eligible subjects will be enrolled and randomized 1:1 to either etelcalcetide or cinacalcet into the 26-week treatment period and should receive the first dose of IP within 1 day of randomization. Randomization will be stratified by PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L),** screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L), both measured by the central laboratory**, and country (China versus non-China). Assessments during the treatment period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started and will be scheduled based on the day 1 date. Subjects will complete the study at the follow-up visit 30 days (± 3 days) after the last dose of IP. IP will be dosed to achieve predialysis [redacted] but maintaining cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**. Doses of IP will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before **or week of** dose adjustment. **Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3); however, IV IP dose cannot be resumed or increased without an available cCa result from the central laboratory for the prior or current week.** Dosing with IP may be suspended, and dosing resumed at a lower dose according to protocol-defined rules for low predialysis PTH (based on central laboratory values) or cCa values, for symptomatic hypocalcemia, or for other drug-related adverse events**. Corrected Calcium results from the local laboratory can only be used for the management of safety concerns and for suspension of IP; results must not be used for resumption or titration of IP. A local cCa and central laboratory cCa, must not be collected at the same time.**

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2). The dosing schema is provided in Table 3.

Statistical Considerations: The primary objective of the study is to determine whether etelcalcetide is non-inferior to cinacalcet in achievement of a > 30% reduction from baseline in mean predialysis PTH during the EAP. Etelcalcetide will be considered non-inferior to cinacalcet if the upper bound of the 2-sided 95% confidence interval (CI) of the treatment difference (cinacalcet – etelcalcetide) is smaller than 12% (see Section 10.2). If this criterion is met, the 2 key secondary endpoints will be tested sequentially. The superiority testing for the endpoint of achievement of a > 50% reduction from baseline in mean predialysis serum PTH during the EAP will be carried out first. Only if the result achieves statistical significance, the secondary endpoint of achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the

EAP will be tested for superiority. The other secondary endpoints that will formally tests if both key secondary endpoints are statistically significant. To control for the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used for the testing of the other secondary endpoints.

The primary analysis will be conducted upon achieving the Primary Completion milestone. At the time of the Primary Analysis, the study will be unblinded and all endpoints will be evaluated. The primary analysis of all primary and secondary endpoints will be conducted on the Full Analysis Set (FAS).

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, and treatment-emergent adverse events of interest will also be provided. Proportion of subjects (with 95% confidence interval) with the following will be provided:

- cCa < 8.3 mg/dL **measured by the central laboratory**
- cCa < 8.0 mg/dL **measured by the central laboratory**
- cCa < 7.5 mg/dL **measured by the central laboratory**
- treatment-emergent symptomatic hypocalcemia adverse events during the study will be presented by treatment group.

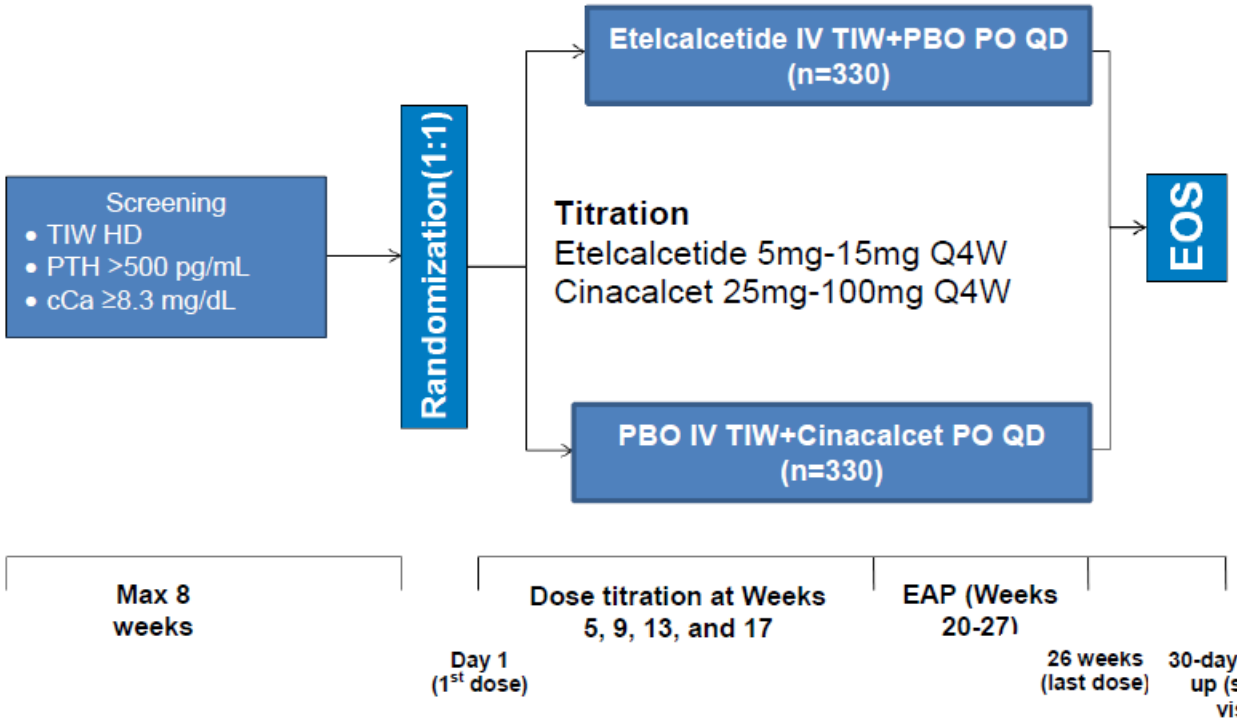
Laboratory parameters (hematology, chemistry anti-drug antibodies), blood pressure, pulse rate, and weight will also be analyzed.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version/Date:	Version 5/20 March 2015

Figure 1. Study Design and Treatment Schema



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

Study Glossary

Abbreviation or Term	Definition/Explanation
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
[redacted]	
CaR	calcium-sensing receptor
cCa	corrected calcium
CCAS	cCa Completer Analysis Set
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
C_{max}	maximum observed plasma concentration
[redacted]	
CYP	Cytochrome P-450 system
D_2	Ergocalciferol
D_3	Cholecalciferol
DILI	drug induced liver injury
EAP	efficacy assessment phase
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Follow-up	defined as the date when the last subject completes the last protocol-specified assessment in the study
End of Study	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for **evaluation in the study at the follow-up visit (30 days after last dose [± 3 days]) or the last assessment is collected for the primary endpoint, whichever is later**
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOS	end-of-study

Abbreviation or Term	Definition/Explanation
eSAE	electronic Serious Adverse Event
ESRD	end-stage renal disease
ET	Early termination
Etelcalcetide	AMG 416
FAS	Full Analysis Set
GCP	Good Clinical Practice
HIV	**Human Immunodeficiency Virus**
HPT	Hyperparathyroidism
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
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.
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
IRB/IEC	institutional review board/independent ethics committee
IV	Intravenous
MBD	Mineral and Bone Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NASH	Nonalcoholic Steatohepatitis
NKF-K/DOQI	National Kidney Foundation- Kidney Disease Outcomes Quality Initiative
P	phosphorus
PCAS	PTH Completer Analysis Set
PK	Pharmacokinetics
PPAS	Per Protocol Analysis Set
PTH	parathyroid hormone
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHPT	Secondary Hyperparathyroidism

Abbreviation or Term	Definition/Explanation
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 first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TBL	total bilirubin
TIW	three times per week
ULN	Upper limit of normal
URR	urea reduction ratio
US	United States

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1. OBJECTIVES

1.1 Primary

- To demonstrate that treatment with etelcalcetide (AMG 416) is not inferior to treatment with cinacalcet for lowering serum intact parathyroid hormone (PTH) levels by > 30% from baseline among subjects with chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) who require management with hemodialysis.

1.2 Secondary

- To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) **measured by the central laboratory** and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dL **measured by the central laboratory** during the efficacy assessment phase (EAP).

1.3 Safety

- Assess the safety and tolerability of etelcalcetide compared to cinacalcet
- Evaluation of antibody formation to etelcalcetide

1.4 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease Background of SHPT

SHPT occurs commonly among patients with CKD, and it is an integral component of the syndrome of CKD- Mineral and Bone Disorder (MBD). Persistently elevated levels of PTH in serum or plasma are the cardinal biochemical feature of SHPT, affecting 40% to 50% of patients receiving dialysis regularly in the US (USRDS, 2009). SHPT is associated with important disturbances in calcium and P metabolism including hyperphosphatemia, pathological changes in bone described collectively as renal osteodystrophy, soft-tissue and vascular calcification, left ventricular hypertrophy, and cardiovascular events (Alem et al, 2000; Block et al, 2000; Bro and Olgaard, 1997; Diaz-Corte and Cannata-Andia, 2000; Moe, 2001; Salusky and Goodman, 1996; Slatopolsky et al, 1980; USRDS, 2009). PTH values not only serve as a useful index of disease severity, but also can be used to monitor evolution of the disorder over time and the response to treatment. The importance of managing SHPT chronically is highlighted in clinical practice guidelines promulgated by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) and the International Society of

Nephrology Kidney Disease Improving Global Outcomes ([KDIGO®] KDIGO, 2009; K/DOQI, 2003).

Adoption of hemodialysis in Asia, particularly in China, has rapidly expanded, and recent data describe emerging hemodialysis practice patterns and outcomes. Retrospective studies of Chinese hemodialysis patients showed that mineral metabolism control in China remains an unmet medical need (Bieber et al, 2014; Kong, 2012).

Treatment guidelines for SHPT cover several therapeutic strategies used to lower elevated plasma PTH levels and to manage SHPT among patients with CKD (Locatelli et al, 2008; KDIGO, 2009; Saliba and El-Haddad, 2009). Traditionally, most have employed treatment with vitamin D sterols such as calcitriol or synthetic vitamin D analogues. Vitamin D therapies are only partially effective for controlling serum PTH levels among patients with SHPT, and values often remain elevated despite ongoing treatment.

An alternative approach is directed toward enhancing signal transduction through the calcium-sensing receptor (CaR) in parathyroid tissue, thereby suppressing PTH. These compounds are called calcimimetic agents, and they include cinacalcet, which is taken daily by mouth, and the investigational medication being evaluated in this study, etelcalcetide, which is administered intravenously three times per week (TIW) at the end of each hemodialysis treatment. Calcimimetics reduce PTH secretion from the parathyroid glands and consequently lower serum PTH levels. Reductions in serum calcium concentrations are also observed and are an expected physiological consequence of PTH reduction. As such, treatment is initiated with small doses that are subsequently titrated upwards as needed to achieve meaningful reductions in serum PTH levels only if serum calcium concentrations remain unchanged or decrease modestly. PTH and calcium laboratory values are routinely drawn to measure the effectiveness of cinacalcet, and to titrate the dose as appropriate.

2.2 Amgen Investigational Product Background

2.2.1 Etelcalcetide

Etelcalcetide is a novel peptide that has been shown in pharmacological studies to be a potent and selective allosteric activator of the CaR, lowering the threshold of receptor activation by calcium, the natural ligand. As such, it inhibits PTH secretion by the parathyroid tissue. The CaR was shown in cellular studies to be the molecular target of etelcalcetide. Pharmacological activity of etelcalcetide requires formation of a disulfide bond between cysteine 482 in the human CaR and the D-cysteine of etelcalcetide.

Disulfide exchange of the D-cysteine of etelcalcetide also leads to biotransformed products in the blood.

Etelcalcetide has been studied in three 26-week phase 3 studies, 2 placebo-controlled trials (20120229 and 20120230), and 1 active-controlled trial (20120360). In Study 20120229, 74% of etelcalcetide subjects achieved > 30% reduction from baseline in mean PTH during the EAP versus 8.3% of placebo subjects ($p < 0.001$). In Study 20120230, 75.3% of etelcalcetide subjects achieved this endpoint versus 9.6% of placebo subjects ($p < 0.001$). Similarly, the proportion of etelcalcetide subjects who achieved mean predialysis [redacted] during the EAP was significantly higher in the etelcalcetide group than in the placebo group ($p < 0.001$) in both Studies 20120229 and 20120230. In Study 20120229, 49.6% of subjects in the etelcalcetide group and 5.1% of subjects in the placebo group achieved this endpoint, and 53.3% of subjects in the etelcalcetide group and 4.6% of subjects in the placebo group achieved this endpoint in Study 20120230. The events that occurred with a greater frequency among subjects in the etelcalcetide group compared with subjects in the placebo group (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo) were blood calcium decreased (63.8% etelcalcetide; 10.1% placebo), muscle spasms (11.5% etelcalcetide; 6.6% placebo), diarrhea (10.7% etelcalcetide; 8.6% placebo), nausea (10.7% etelcalcetide; 6.2% placebo), vomiting (8.9% etelcalcetide; 5.1% placebo), headache (7.6% etelcalcetide; 6.0% placebo), and hypocalcemia (7.0% etelcalcetide; 0.2% placebo).

An additional phase 3 study (20120360) was performed to compare the therapeutic efficacy of etelcalcetide and cinacalcet for lowering serum PTH concentrations among subjects with CKD and SHPT receiving maintenance hemodialysis. A higher observed percentage of subjects in the etelcalcetide group (77.9%) had a > 30% reduction from baseline in serum PTH during the EAP compared with the cinacalcet group (63.9%). The estimated treatment difference (cinacalcet - etelcalcetide) was -10.48% (95% confidence interval [CI]: -17.45%, -3.51%). Because the upper bound of the 95% CI is < 12% (the prespecified margin for noninferiority), etelcalcetide is noninferior to cinacalcet in the proportion of subjects with a > 30% reduction from baseline in serum PTH during the EAP. Additionally, etelcalcetide was superior to cinacalcet on the proportion of subjects achieving a > 50% and a > 30% reduction from baseline in mean predialysis serum PTH during the EAP. There was no significant difference in the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment, as

measured by a patient-reported outcome instrument. The most common (> 10% in either treatment group) adverse events (etelcalcetide, cinacalcet) were asymptomatic decreased blood calcium (68.9%, 59.8%), nausea (18.3%, 22.6%), vomiting (13.3%, 13.8%), and diarrhea (6.2%, 10.3%). Symptomatic hypocalcemia was reported for 17 subjects (5.0%) in the etelcalcetide group and 8 subjects (2.3%) in the cinacalcet group.

Please refer to the etelcalcetide Amgen Investigator Brochure for additional detailed information about the chemistry, toxicology, preclinical pharmacology, pharmacokinetics (PK), safety, and clinical experience of etelcalcetide.

2.3 Non-Amgen Medicinal Product Background

2.3.1 Cinacalcet

Cinacalcet is a first-in-class calcimimetic agent that functions as an allosteric modulator of the CaR on the surface of parathyroid cells, increasing the sensitivity of the CaR to extracellular calcium ions.

Cinacalcet has been approved by the Food and Drug Administration in the United States for the treatment of SHPT in patients with CKD on dialysis, for the treatment of hypercalcemia in subjects with parathyroid carcinoma, and for the treatment of severe hypercalcemia in patients with primary HPT who are unable to undergo parathyroidectomy. Cinacalcet also has received marketing authorization under the name of Sensipar, Mimpara, or Regpara, in 6 countries in Asia, Australia, Canada, multiple countries in Europe, parts of Latin America, several countries in the Middle East, New Zealand, and Russia. As of 07 September 2012, cinacalcet has been approved in 60 countries. Please refer to the cinacalcet package insert for the exact approved indication(s) in each of these regions.

In adult humans, the maximum observed plasma concentration (C_{max}) of cinacalcet is achieved between 2 to 6 hours after oral doses, which corresponds temporally with the nadir in plasma PTH. After absorption, cinacalcet concentrations in serum decrease in a biphasic fashion with a terminal half-life of 30 to 40 hours. Steady-state drug levels are achieved within 7 days, and serum calcium concentrations remain constant over the 24-hour dosing interval once stable serum drug levels are achieved in patients with CKD on hemodialysis. Cinacalcet is metabolized extensively by multiple hepatic cytochrome P-450 (CYP) enzymes, and < 1% of the parent drug is excreted in the urine. No unique metabolites of cinacalcet have been identified in humans (original NDA 21-688, Study 980233).

An extensive phase 3 program was completed by Amgen in adult non-transplant subjects with end-stage renal disease (ESRD), demonstrating that treatment with cinacalcet resulted in concurrent reductions in PTH, calcium, P, and Ca x P, among dialysis subjects with inadequately controlled SHPT as defined by baseline plasma PTH > 300 pg/mL (31.8 pmol/L). The incidence of serious adverse events was 31% and 29% among subjects assigned randomly to treatment with cinacalcet or placebo. The most common adverse events were nausea (31% versus 19%) and vomiting (27% versus 15%) among subjects assigned to treatment with cinacalcet compared with placebo. Post-hoc analyses of phase 3 clinical trial data demonstrated that treatment with cinacalcet enabled a significantly greater proportion of adult subjects on dialysis with SHPT to achieve National Kidney Foundation- Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI)™ recommended targets for PTH, calcium, P, and Ca x P compared with treatment using traditional therapies for SHPT (Moe et al, 2005).

Please refer to the Cinacalcet package insert for Sensipar/Mimpara/Regpara for additional detailed information about the chemistry, toxicology, preclinical pharmacology, PK, safety, and clinical experience of cinacalcet.

2.4 Rationale

Sub-optimal adherence and compliance with oral medication regimens that include cinacalcet are common among patients managed with hemodialysis. This is due in part to a high daily pill burden and gastrointestinal intolerance in such individuals, and the overall complexity of the drug treatment strategies used to manage them clinically. Etelcalcetide is administered intravenous (IV) at the end of each hemodialysis session, and thus provides the opportunity to circumvent the shortcomings of oral therapies and to achieve greater drug adherence/compliance for managing SHPT.

This current study is designed to assess the efficacy and safety of a novel therapeutic agent, IV etelcalcetide, compared with the other calcimimetic agent (oral cinacalcet), for the treatment of SHPT in CKD subjects on hemodialysis. The data from this study will be used to support registration of etelcalcetide in China and other countries.

2.5 Clinical Hypotheses

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

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

3. EXPERIMENTAL PLAN

3.1 Study Design

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

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

Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L),** screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25mmol/L) measured by the central laboratory**, and country (China versus non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet.

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.

3.2 Number of Sites

The study is planned to be conducted at approximately 120 centers in China **mainland**, Taiwan, South Korea, Hong Kong, Malaysia, and India. Other countries **and/or regions** may be added as needed.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 660 subjects will be randomized in this study (approximately 330 subjects in each of the 2 treatment arms). Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Randomized subjects who subsequently withdraw from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The maximum duration of study participation for a subject will be approximately 9 months; which includes an 8-week screening period, a 26-week treatment period, and a 30-day follow-up safety visit that is considered the end-of-study (EOS) visit.

3.5.2 End of Study

Primary Completion: The primary completion date is when the last subject is assessed or receives an intervention for evaluation in the study at the follow-up visit (30 days after last dose [± 3 days]) or the last assessment is collected for the primary endpoint, whichever is later.

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

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response (IVR)/Interactive Web Response (IWR) system.

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided informed consent prior to performing any study-related activities/procedures.

102 Male or female subjects ≥ 18 years of age or older at the time of signing informed consent.

103 Subject must be receiving maintenance hemodialysis 3 times weekly for at least 3 months, with adequate hemodialysis with a delivered Kt/V ≥ 1.2 or urea reduction ratio (URR) ≥ 65% within 4 weeks prior to screening laboratory assessments. The Kt/V formula used for a subject must be the formula used during routine care prior to screening.

104 Dialysate calcium concentration must be ≥ 2.5 mEq/L (1.25 mmol/L) and stable for at least 4 weeks prior to screening laboratory assessments, and must remain ≥ 2.5 mEq/L (1.25 mmol/L) for the duration of the study.

105 Subject must have SHPT as defined by one central laboratory screening predialysis serum PTH value > 500 pg/mL **(53.00 pmol/L)**, within 2 weeks prior to randomization.

106 Subject currently receiving vitamin D sterols must have had no more than a maximum dose change of 50% within the 4 weeks prior to screening laboratory assessments, remain stable through randomization, and be expected to maintain stable doses for the duration of the study, except for adjustments allowed per protocol or for safety reasons.

107 Subject must have 1 screening predialysis serum cCa laboratory value ≥ 8.3 mg/dL **(2.07 mmol/L)** measured within 2 weeks prior to randomization.

108 A subject receiving calcium supplements must have had no more than a maximum dose change of 50% within 2 weeks prior to screening laboratory assessments and remain stable through randomization.

109 A subject receiving phosphate binders must have had no more than a maximum dose change of 50% within the 2 weeks prior to screening laboratory assessments, remain stable through randomization, and be expected to maintain stable dose for the duration of the study, except for adjustments allowed per protocol or for safety reasons.

4.1.2 Exclusion Criteria

201 Currently receiving treatment in another investigational device or drug study, or ≤ 30 days since ending treatment on another investigational device or drug study(s). Other investigational procedures while participating in this study are excluded.

202 Subject has received etelcalcetide in a prior clinical trial of etelcalcetide.

203 Subject has received cinacalcet during the 3 months prior to the first screening laboratory assessments.

204 Subject has known sensitivity to any of the products or components of either cinacalcet or etelcalcetide to be administered during dosing.

205 Subject has previously been randomized in this study.

206 Anticipated or scheduled parathyroidectomy during the study period.

207 Subject has received a parathyroidectomy within 6 months prior to dosing.

208 Anticipated or scheduled kidney transplant during the study period.

209 Subject has an unstable medical condition based on medical history, physical examination, and routine laboratory tests, or is otherwise unstable in the judgment of the Investigator.

210 Malignancy within the last 5 years of screening (except non-melanoma skin cancers or cervical carcinoma in situ).

211 Subject is unwilling or unable to avoid consumption of grapefruit juice during the study period.

212 Subject is pregnant or nursing, or planning to become pregnant or nurse during treatment or within 3 months after the last dose of etelcalcetide or 30 days after the last dose of cinacalcet.

213 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with investigational product (IP) through 3 months after the last dose of IP. Refer to Section 6.9 for additional information on pregnancy prevention and definition of woman of childbearing potential.

214 Subject has a history of symptomatic ventricular dysrhythmias or Torsades de Pointes.

215 Subject has a history of myocardial infarction, coronary angioplasty, or coronary arterial bypass grafting within the past 6 months prior to screening.

216 Subject has clinically significant abnormalities on prestudy clinical examination or abnormalities on the most recent central laboratory tests during the screening period prior to randomization according to the Investigator including but not limited to the following:

- serum albumin < 3.0 g/dL **(30 g/L)**
- serum magnesium < 1.5 mg/dL **(0.62 mmol/L)**
- serum transaminase (alanine transaminase [ALT] or serum glutamic pyruvic transaminase [SGPT], aspartate aminotransferase [AST] or serum glutamic oxaloacetic transaminase [SGOT]) > 3 times the upper limit of normal (ULN) at screening

Note: if results of serum transaminases are not available, Amgen should be notified prior to randomization; serum transaminases may be measured at the local laboratory

217 Subject likely not available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and Investigator's knowledge.

218 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.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). Specify

that all subjects or legally acceptable representatives must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

After signing the informed consent, subjects must be randomized within 8 weeks. Subjects screening laboratory assessments may be repeated up to 2 times beyond the initial screening assessments within the 8-week screening period. If a subject fails to meet all eligibility criteria in the initial 8-week screening period (including 3 attempts at meeting laboratory criteria), the 8-week screening period may be repeated once.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria via the IVR/IWR system. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned using IVR/IWR. 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.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Randomization/Treatment Assignment

Subjects will be randomized by IVR/IWR in a 1:1 ratio to either TIW IV etelcalcetide (and daily oral placebo tablets) or daily oral cinacalcet tablets (and TIW IV placebo) in a double-blind, double-dummy manner, and should receive the first dose of IP within 1 day of randomization. Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China). The total duration of treatment will be 26 weeks. IP will be dosed to achieve predialysis [redacted] Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

Randomization should occur on the same day as enrollment and the date is to be documented in the subject's medical record and on the enrollment eCRF. The randomization number will be provided to the Investigator (or designee) by accessing the

IVR/IWR and receiving the IP assignment (box number). Details for this procedure will be provided in the IVR/IWR manual.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen IP used in this study is etelcalcetide.

The non-Amgen IP used in this study is cinacalcet.

Note: Ancillary device(s) (ie, medical device(s) not under study) are described in Section 6.6.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Etelcalcetide

Etelcalcetide will be manufactured and packaged by Amgen Inc. or its designee, and distributed using Amgen clinical IP distribution procedures. The active pharmaceutical ingredient (API) in etelcalcetide is an 8-amino acid synthetic peptide prepared as a hydrochloride salt.

Etelcalcetide investigational drug product is supplied as a sterile, preservative-free, aqueous solution containing 10 mg etelcalcetide free base, [redacted] sodium chloride and [redacted] succinic acid, in a single-use 3 mL glass vial. The drug product vial contains 2 mL of clear, colorless solution with etelcalcetide concentration of 5 mg/mL. The solution is ready to administer and has pH between 3.0 and 3.6. The recommended storage condition for etelcalcetide liquid drug product is 2°C to 8°C.

Etelcalcetide placebo will be presented in identical containers and stored/packaged in the same manner as etelcalcetide.

6.2.1.1 Dosage, Administration, and Schedule

Intravenous IP will be administered by dialysis site staff by bolus injection into the venous line of the dialysis circuit at the end of each TIW hemodialysis session just prior to or during rinse-back. At least 150 mL of rinse-back volume should be administered after injection of IP to ensure that IP reaches the systemic circulation.

If rinse back is completed and IP was not administered, then IP may be administered intravenously followed by at least 10 mL saline flush volume.

The end of hemodialysis treatment is defined as the time at which the prescribed hemodialysis treatment has been completed (ie, remaining time on dialysis is zero) unless hemodialysis treatment is discontinued early; in this case the end of hemodialysis is when the arterial flow is stopped (eg, arterial line is clamped or disconnected to discontinue treatment), whichever occurs first.

If a regularly scheduled hemodialysis session is missed and subsequently rescheduled, IV IP should be administered at the rescheduled hemodialysis session. If an additional hemodialysis treatment is needed intermittently (eg, fourth treatment during a week for ultrafiltration) then an additional dose of IP will not be administered during the extra dialysis session.

Intravenous IP must only be administered intravenously; it must not be administered via any other route.

Intravenous IP must not be administered concurrently with any other IV medications.

The quantity, IP administration date/time, and kit number of IV IP are to be recorded on each subject's eCRF.

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

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results **from the central laboratory** obtained during the prior **or current** week.

Subjects will be treated with IV IP three times weekly at the end of hemodialysis, for 26 weeks. The starting dose of IV IP is 5 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL**(2.07 mmol/L).** The minimum IV IP dose is 2.5 mg, and the maximum dose is 15 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1 unless any of the following criteria are met:

- subject has missed 3 or more IV doses during the prior 3 weeks
- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- **most recent** predialysis serum cCa < 8.3 mg/dL **(2.07 mmol/L)** during the prior **or current** week
- **most recent** predialysis [redacted] during the prior **or current** week

Table 1. Investigational Product Dosing Algorithm Based on PTH

PTH (pg/mL)	IV IP Dose If Current Dose < 10mg	IV IP Dose If Current Dose 10 mg	**IV IP Dose If Current Dose 12.5 mg**	Oral IP Dose
PTH > 450 **(47.70 pmol/L)**	Increase dose by 2.5 mg	Increase dose by 5 mg	**Increase dose by 2.5 mg**	Increase dose by 25 mg
300 **(31.80 pmol/L)** < PTH ≤ 450 **(47.70 pmol/L)**	Increase dose by 2.5 mg	Increase dose by 2.5 mg	**Increase dose by 2.5 mg**	Increase dose by 25 mg
PTH ≤ 300 **(31.80 pmol/L)**	Maintain dose	Maintain dose	**Maintain dose**	Maintain dose
PTH < 100 **(10.60 pmol/L)**	If 2 consecutive values at least 1 week apart, suspend dose	If 2 consecutive values at least 1 week apart, suspend dose	**If 2 consecutive values at least 1 week apart, suspend dose**	If 2 consecutive values at least 1 week apart, suspend dose

IP = investigational product; IV = intravenous; PTH = parathyroid hormone

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3); however, IV IP dose cannot be resumed or increased without an available cCa result from the central laboratory for the prior or current week.

If an overdose of the IV IP has been administered to/taken by the subject, subjects should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum cCa levels.

See Section 6.2.3 and Section 6.2.4 for details on dose suspensions, reductions, and resumptions.

6.2.2 Non-Amgen Investigational Product Cinacalcet

Cinacalcet tablets are manufactured by Kyowa Hakko Kirin Co., Ltd at strengths of 25 mg and packaged by Amgen Inc. or its designee. Cinacalcet placebo tablets will be presented in identical dosage form images (ie, will be presented in the same size and color of actives) and containers (eg, bottle size, color, and shape). Additional details regarding cinacalcet and its placebo will be provided in the IPIM.

6.2.2.1 Dosage, Administration, and Schedule

Oral IP should be taken by the subject with food, at approximately the same time on a daily basis during the 26-week duration of the study treatment period. The oral IP should be taken by the subject at least 12 hours before the PTH laboratory assessment.

If ≤ 7 consecutive daily doses of the oral IP were missed, because of reasons unrelated to those described in Section 6, the subject should be instructed to resume dosing at the IVR/IWR assigned dose. The subject must not attempt to make up for any missed doses.

The quantity, start date, stop date, and box number of oral IP are to be recorded on each subject's eCRF. When the oral IP is returned by the subject during a study visit (see Pill Count in Dose Schema in **Figure 1**) the investigator or responsible person will determine the level of compliance with the administration of the oral IP. The subject's IP accountability (eg, amount used/amount expected to be used in interval between visits) will be recorded on the compliance forms provided in the IPIM. This may require the review of subject's diaries (if used), subject interviews, or other methods.

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

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results obtained during the prior **or current** week.

Subjects will be treated with oral IP daily, for 26 weeks. The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**. The minimum oral IP dose is 25 mg, and the maximum IP dose is 100 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1. unless any of the following criteria are met:

- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- **most recent** predialysis serum cCa < 8.3 mg/dL **(2.07 mmol/L)** during the prior **or current** week
- **most recent** predialysis [redacted] during the prior **or current** week

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3), but oral IP dose cannot be resumed or increased without an available cCa result from the central laboratory from the prior or current week.

If an overdose of the oral IP has been administered to/taken by the subject, subjects should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum cCa levels.

See Section 6.2.3 and Section 6.2.4 for details on dose suspensions, reductions, and resumptions.

6.2.3 Suspension and Reduction of Oral and Intravenous Investigational Product

Dosing with IP may be temporarily suspended by the Investigator or by the IVR/IWR at any time if ANY of the criteria below apply. IP dosing may resume only after ALL criteria contributing to suspension of IP dosing are resolved.

- two consecutive predialysis central laboratory PTH < 100 pg/mL **(10.60 pmol/L)** at least 1 week apart (see Section 6.2.3.1)
- cCa is < 7.5 mg/dL **(1.87 mmol/L)** (see Section 6.2.3.2 **measured by either the central or local laboratory**
- subject experiences symptomatic hypocalcemia (see Section 6.2.3.3)
- there is any other ongoing adverse event that, in the opinion of the Investigator, necessitates suspension of IP dosing

The site will immediately enter the information in IVR/IWR and electronic data capture (EDC) system when a dose suspension rule is invoked and the reason for missed or suspended doses is recorded on the subject eCRF. Even when dosing with IP is suspended per protocol, all scheduled assessments should be completed.

During a hospitalization or when hemodialysis is provided in a location other than the Investigator's site, both oral and IV IPs should be suspended **When hemodialysis is provided in a location other than the Investigator's site, the visit should not be registered in the IVR/IWR. The reasons for missed doses should be recorded on the subject eCRF.**

6.2.3.1 Low Predialysis Serum PTH

If a subject has 2 consecutive central laboratory predialysis serum PTH results obtained at least 1 week apart that are both < 100 pg/mL **(10.60 pmol/L)**, then the Investigator will be notified by the IVR/IWR that dosing of both the IV and oral IPs should be suspended.

Intact PTH monitoring will continue per the protocol. Once PTH is ≥ 150 pg/mL **(15.90 pmol/L)** and the **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**, the Investigator will be notified by the IVR/IWR that dosing with the IV and oral IPs may resume at a 2.5 mg lower dose for the IV, and at a 25 mg lower dose for the oral.

If a subject was receiving the 2.5 mg IV dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 2.5 mg dose level when PTH is > 300 pg/mL **(31.80 pmol/L)**, and the most recent predialysis **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**.

If a subject was receiving the 25 mg oral dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 25 mg dose level when PTH is > 300 pg/mL **(31.80 pmol/L),** and the most recent predialysis **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**.

6.2.3.2 Low Predialysis Serum Corrected Calcium

Administration of etelcalcetide or ingestion of cinacalcet, both potent agonists of the CaR, may result in rapid and sustained suppression of PTH levels.

Management of subjects with rapid and sustained reductions in PTH includes careful monitoring of serum calcium by the Investigator. Supplementation with oral calcium and/or increasing the dialysate calcium concentration may be instituted by the Investigator if serum cCa is below the lower limit of the reference range or there is a rapid large reduction in serum calcium, especially in subjects with PTH > 700 pg/mL **(74.20 pmo/L)** and markedly elevated serum alkaline phosphatase (ALP) at baseline. Increased calcium supplementation may only be needed on a temporary basis until mineral balance is re-established at the reduced PTH level.

The following guidance is provided for the management of serum cCa below the lower limit of the reference range with any change to therapy based on Investigator clinical judgment. If **the** cCa **measured by either the central or local laboratory is** < 8.3 mg/dL **(2.07 mmol/L)**, the following options may be taken by the Investigator:

- May increase oral calcium intake
- May increase dialysate calcium concentration
- May initiate or increase active vitamin D analogues if other therapies are ineffective

If **the** cCa **measured by either the central or local laboratory** is < 7.5 mg/dL **(1.87 mmol/L)** or the subject experiences symptomatic hypocalcemia**, in addition to the above actions, do the following:**

- Suspend dosing with IP, and at the next hemodialysis session following notification of the low serum calcium result, draw a confirmatory predialysis serum cCa sample **and send to the central laboratory**.
- Obtain weekly predialysis **central laboratory** serum cCa. Once predialysis serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)** and any hypocalcemic symptoms have resolved the IVR/IWR will provide instructions to resume dosing. For the oral IP, the dose should be reduced by 25 mg or at the minimum dose of 25 mg, whichever is greater. For the IV IP, the dose should be reduced by 5 mg or at the minimum dose of 2.5 mg, whichever is greater. Resume routine laboratory monitoring per Table 2, the Schedule of Assessments. Refer to Section 7.2 for central laboratory samples to be submitted.

An unscheduled collection of cCa from the central laboratory can be done at any time for safety. A cCa collected and measured by the local laboratory can only be done for the management of safety concerns. If the cCa measured by the local laboratory is < 7.5 mg/dL (1.87 mmol/L), IP must be suspended and

can only be resumed once the cCa measured by the central laboratory is ≥ 8.3 mg/dL (2.07 mmol/L) (see Section 6.2.5).

6.2.3.3 Symptomatic Hypocalcemia

The clinical signs and symptoms of hypocalcemia include increased neuromuscular excitability, manifested as paresthesias of the fingers, toes, and circumoral region. In more extreme cases, there may be muscle cramping, carpopedal spasm, laryngospasm, and seizures. Symptoms reflect not only the degree of hypocalcemia, but also the acuteness of the fall in serum calcium concentration. Signs of latent tetany include Chvostek's sign (twitching of the upper lip after tapping on the facial nerve below the zygomatic arch) and Trousseau's sign (carpal spasm after inflating a cuff on the upper arm above systolic blood pressure for 2 to 3 minutes). Various mental disturbances, such as irritability, depression, and even psychosis, have been attributed to hypocalcemia. Cardiac effects of hypocalcemia include a prolonged QT interval and, rarely, ventricular tachyarrhythmia's or congestive heart failure which may be fatal.

Common symptoms of hypocalcemia include paresthesias (fingertips, toes, or perioral), fatigue, muscle cramps, irritability or anxiety, tetany (eg, carpopedal spasm, laryngospasm), Chvostek's sign, seizures, and prolonged QT interval.

If symptomatic hypocalcemia is suspected, calcium levels should be closely monitored, and corrective measures should be undertaken by the Investigator. Calcium supplementation can be provided by IV infusion (eg, a calcium gluconate) and/or oral calcium supplementation.

Suppressed levels of serum magnesium can be associated with refractory hypocalcemia. Serum magnesium should be closely monitored in subjects with hypocalcemia, and magnesium supplements should be provided as needed.

If dosing with IP is suspended for symptomatic hypocalcemia, dosing may resume at a lower dose once symptomatic hypocalcemia has resolved when the central laboratory cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**, and once the Investigator has notified the IVR/IWR.

6.2.3.4 Adverse Event

If the adverse event is deemed not related to IP by the Investigator, dosing with IP may resume at the same dose once the clinical adverse event, which led to suspension of dosing, has resolved or has stabilized.

If the adverse event was deemed to be IP related by the Investigator but not related to PTH < 100 pg/mL **(10.60 pmol/L)**, cCa < 7.5 mg/dL **(1.87 mmol/L)** or symptomatic hypocalcemia, dosing with IP may resume once the adverse event has resolved or stabilized **and the central laboratory serum cCa is ≥ 8.3 mg/dL (2.07 mmol/L)** with the dose reduced. For the oral product, the dose should be reduced by 25 mg (if the dose was already at 25 mg, the dose of 25 mg should be resumed). For the IV product, the dose should be reduced by 5 mg or at the minimum dose of 2.5 mg, whichever is greater.

During a hospitalization or when hemodialysis is provided in a location other than the Investigator's site, both oral and IV IPs should be suspended.

6.2.4 Resumption of Investigational Product After Repeated Missed Doses

If more than 14 consecutive days of IP are missed (eg, extended hospitalization for an adverse event unrelated to IP, vacation), a central laboratory cCa must be obtained prior to restarting IP. Only after the **central laboratory** cCa is ≥ 8.3 mg/dL **(2.07 mmol/L)** should dosing with IP resume. Intravenous IP dosing will be restarted by the IVR/IWR at 5 mg and oral IP dose at 25 mg. If the subject's last IV dose was 2.5 mg, then the subject should resume IV dosing at the 2.5 mg dose level.

6.2.5 cCa measured by the local laboratory

A cCa can only be collected and measured by the local laboratory for the management of safety concerns and/or suspension of IP. All cCa results measured by the local laboratory will be recorded on the eCRF. If the cCa is < 7.5 mg/dL (1.87 mmol/L) or the subject experiences symptomatic hypocalcemia, refer to Section 6.2.3.2for further management. The IP can only be resumed once the cCa measured by the central laboratory is ≥ 8.3 mg/dL (2.07 mmol/L).

A local laboratory cCa and central laboratory cCa must not be collected at the same time.

If the local laboratory cCa is < 7.5 mg/dL (1.87 mmol/L), suspend IP by registering a suspension in IVR/IWR with the reason of adverse event related to IP or symptomatic hypocalcemia depending on the clinical assessment.

6.3 Other Protocol-required Therapies

Dialysate calcium must remain ≥ 2.5 mEq/L (1.25 mmol/L) for the duration of the study.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, 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). **Note: If the central laboratory is unable to perform the analysis of the hepatic laboratory tests (as discussed with Amgen during screening) then those tests should be measured by the local laboratory.**

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

IP should be discontinued permanently by the Investigator 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 x ULN or International Normalized Ratio (INR) > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

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

- **AND no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:**
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on subject 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.

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

For subjects that do not meet the criteria for permanent withholding of IP outlined above, IP should be withheld if ANY of the following criteria are met, and the subject should be evaluated for DILI:

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

Baseline AST or ALT value	AST or ALT elevation
Any	> 8 x ULN at any time
Any	> 5 x ULN but < 8 x ULN for ≥ 2 weeks
Any	> 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule

AST = aspartate aminotransferase; ALT = alanine transaminase; ULN = upper limit of normal

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

If IPs are 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 6.4.3).

6.4.3 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, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then IP should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, including calcium supplements, phosphate binders, active vitamin D sterols, vitamin D supplements except for those listed in Section 6.8. These medications will not be provided by Amgen.

Medication use at screening and then at every study visit including Early Termination will be recorded and categorized by general, vitamin D supplement, active vitamin D sterol, calcimimetics, calcium supplements, or phosphate binder. Dialysate calcium will be collected at screening and anytime there is a change. For previous cinacalcet use, specific reasons for discontinuation will be captured.

Concomitant therapies are to be collected in the eCRF from informed consent through the EOS. Therapy name, indication, dose, unit, frequency, route, start date and stop date should be recorded.

6.5.1 Calcium Supplements

Subjects receiving calcium supplements must have had no more than a maximum dose change of 50% within the 2 weeks prior to screening laboratory assessments and remain stable through randomization. Except during the screening period, calcium supplement therapy may be adjusted as needed based on Investigator clinical judgment.

6.5.2 Phosphate Binders

Subjects receiving phosphate binders must have had no more than a maximum dose change of 50% within the 2 weeks prior to screening laboratory assessments, remain stable through randomization, and be expected to maintain stable dose for the duration of the study except as defined in the protocol (see Section 6.5.6.2).

Changing the type of phosphate binder is discouraged during the study and should only occur if unavoidable (eg, drug shortage). Should a change in type of phosphate binder be required, equivalent doses should be prescribed to maintain stable clinical effects to the extent possible.

6.5.3 Active Vitamin D Sterols

Subjects receiving an active vitamin D sterol must have had no more than a maximum dose change of 50% within the 4 weeks prior to screening laboratory assessments, remain stable through randomization, and be expected to maintain stable dose for the duration of the study, unless a change in dose is appropriate and consistent with the guidance in this protocol.

However, changes to the dose of active vitamin D sterols are permitted by the Investigator for reasons of safety with respect to the management of increased or decreased cCa as defined in the protocol (see Section 6.2.3.2 and Section 6.5.6.1).

Changing the type of active vitamin D sterol is emphatically discouraged during the study and should only be considered, if unavoidable under uncommon circumstances such as

drug shortage or drug availability. Should a change in type of active vitamin D sterol become necessary, equivalent doses should be prescribed to maintain consistent clinical and biochemical responses to the extent possible. The doses provided should be regarded as approximately equivalent doses to guide conversion between type and/or dosage form.

6.5.4 Nutritional Vitamin D

If prescribed by the individual Investigator, subjects may receive nutritional vitamin D (ergocalciferol [D_2] or cholecalciferol [D_3]) without restriction. Examples of nutritional vitamin D compounds are provided below:

- cholecalciferol
- ergocalciferol
- renal multivitamins that contain D2 or D3

6.5.5 Allowed Treatments and/or Procedures During a Study Period

- Subjects should be on maintenance hemodialysis treatment with a prescription for dialysis 3 times per week. Dialysis duration and membrane may be modified to maintain adequate hemodialysis treatment (eg, Kt/V ≥ 1.2 or URR > 65%). If a subject requires a significant change in hemodialysis prescription to maintain adequate hemodialysis (eg, permanent change from TIW), then the subject will be discontinued from treatment with IP, and every effort will be made to continue to follow the subject through the duration of the study.
- Intermittent additional hemodialysis treatment (eg, for ultrafiltration) or changes in hemodialysis schedule (eg, missed/rescheduled treatments or shifts in schedule) are not considered significant changes in hemodialysis treatment prescription.
- Subjects must have a prescribed dialysate calcium concentration ≥ 2.5 mEq/L (1.25 mmol/L) stable for at least 4 weeks prior to screening laboratories, and the dialysate calcium concentration must be maintained ≥ 2.5 mEq/L (1.25 mmol/L) throughout the study.
- Medications used to treat hemodialysis-related symptoms or comorbid conditions should be reported as concomitant medications whenever administered to the subject.
- Medications administered at each dialysis session (eg, heparin, diphenhydramine) should be reported on the eCRF with a frequency of 3 times per week unless a change in dose or frequency occurs. The following medications used in the delivery of hemodialysis should not be reported on the eCRF as concomitant medication:
    - local anesthetic for cannulation
    - saline prime for the dialysis circuit
    - saline or hypertonic saline for management of intradialytic hypotension
    - oxygen

6.5.6 Management of Laboratory Values

6.5.6.1 Management of Elevated Serum Corrected Calcium or Symptomatic Hypercalcemia

The following guidance is provided for the management of serum cCa above the upper limit of the reference range. If a subject has 2 consecutive central laboratory cCa > 10.6 mg/dL **(2.64 mmol/L)**, then doses of active vitamin D sterol, oral calcium intake, and/or dialysate calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L), unless otherwise permitted by Amgen.

If a subject has a central laboratory cCa > 11.0 mg/dL **(2.74 mmol/L)** or develops symptomatic hypercalcemia, then any active vitamin D sterol and oral calcium intake (including calcium-based phosphate binders) may be reduced or discontinued, and dialysate calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L). Common signs and symptoms of hypercalcemia include: nausea, vomiting or constipation, fatigue or weakness, musculoskeletal pain, hypertension, impaired concentration, confusion or lethargy.

6.5.6.2 Management of Serum Phosphorous

Serum P will be monitored locally in accordance with the dialysis unit's standard operating procedures during the study. It is recommended that phosphate binder dose remain stable throughout the study. At the Investigator's clinical discretion and based on dialysis unit routine monitoring tests, phosphate binder dose may be adjusted consistent with the following guidance:

- If 2 consecutive local predialysis serum P values are > 5.5 mg/dL **(1.78 mmol/L)** and not amenable to modification via dietary counseling, then the dose of phosphate binder may be increased.
- If 2 consecutive local predialysis serum P values are < 3.0 mg/dL **(0.97 mmol/L)**, then the dose of phosphate binder may be decreased.

6.6 Medical Devices

The following medical devices for the IV infusion of IP (eg, inline filters, IV administration set, infusion pump) will not be provided by Amgen, as routine hemodialysis tubing should be used. The Investigator will be responsible for obtaining supplies of these devices.

Other medical devices, which are not considered test articles, may be used in the conduct of this study as part of standard care (eg, syringes, sterile needles, alcohol prep

pads). These devices that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 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 a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes IP.

6.8 Any Product Complaint(s) Associated With an IP(s) or Non-IP(s) or Device(s) Supplied by Amgen are to be Reported According to the Instructions Provided in the IPIM Excluded Treatments, Medical Devices, and/or Procedures During Study Period

6.8.1 Excluded Treatments and/or Procedures During Study Period

The following treatments will be prohibited during the study:

- Treatment with commercial cinacalcet is prohibited during the study through the last study visit (ie, the 30-day follow-up visit). Treatment during the study with other medications known to be associated with hypocalcemia is strongly discouraged. Cinacalcet must not have been taken for at least 3 months prior to the first screening laboratory assessments.
- Use of grapefruit juice is prohibited during the study. Changes in medications, including herbal medications, that are strong inhibitors or inducers of the enzymes CYP3A4 and CYP1A2 (eg, erythromycin, clarithromycin, ketoconazole, itraconazole) are permitted throughout the study at the Investigator's discretion. The investigator should monitor subject cCa closely if these medications are initiated, discontinued, or the dose is changed.
- Cinacalcet is a strong inhibitor of CYP2D6. Therefore, subjects receiving concomitant therapy with medications that are predominantly metabolized by the enzyme CYP2D6 and have a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine, and most tricyclic antidepressants) should be monitored closely during initiation and titration of the IP. Please refer to the product insert for additional details.

6.9 Pregnancy Prevention Requirements

Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with IP through 3 months after the last dose of IP. Acceptable methods of effective birth control include not having intercourse (true sexual abstinence, hormonal birth control methods (oral, intravaginal, transdermal,

injectable, or implantable), intrauterine devices, intrauterine hormonal-releasing system, surgical contraceptive methods (vasectomized partner with medical assessment of the surgical success of this procedure or bilateral tubal ligation/occlusion), or 2 barrier methods (each partner must use one barrier method and the female partner must use spermicide with the barrier method. The male partner must use a condom and the female partner must choose either a diaphragm, OR cervical cap, OR contraceptive sponge. A female condom is not an option because there is a risk of tearing when both partners use a condom. The two-barrier is acceptable in countries where spermicide is not available). Females of non-childbearing potential:

- Female subjects not of childbearing potential are defined as any female who:
- Is post-menopausal by history, defined as:
    - Age ≥ 55 years with cessation of menses for 12 or more months, OR
    - Age < 55 years but no spontaneous menses for at least 2 years, OR
    - Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrhoeic (eg, spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

OR

- Underwent bilateral oophorectomy OR
- Underwent hysterectomy OR
- Underwent bilateral salpingectomy

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 2 can only be performed after obtaining a signed informed consent. This includes any discontinuation of the subject's medication for the purpose of participation in this study.

It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits **unless discussed with Amgen**.

Dosing schema is provided in **Figure 1**

Initial IP dosing must start with a Monday through Friday hemodialysis treatment; initial dosing may not start with a Saturday hemodialysis treatment. Assessments during the treatment period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started, whenever possible.

The start of hemodialysis treatment is defined as when arterial flow is started. The end of hemodialysis treatment is defined as when the prescribed hemodialysis time is completed (ie, remaining time on dialysis is zero) unless hemodialysis treatment is discontinued early; in this case the end of hemodialysis is when the arterial flow is stopped (eg, arterial line is clamped or disconnected to discontinue treatment).

Procedures performed prior to hemodialysis should occur prior to the start of hemodialysis. Procedures performed after hemodialysis should be performed after the end of hemodialysis.

7.1 Schedule of Assessments

Table 2. Schedule of Assessments

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
IV investigational product administration		**Three times per week at the end of the hemodialysis session starting from day 1**																
Dose titration[b]						X				X				X				X
Informed Consent	X																	
Inclusion/Exclusion	X																	
Medical History	X																	
Demographics	X																	
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X																	
Assessment of Kt/V or URR[jL]	X																	
Randomization[c]		X																
Dispensation of oral IP bottle		X				X				X				X				X
Pill count				X		X		X		X		X		X		X		X
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior to dialysis																		
ECG[f]	X																	
Serum pregnancy test[g]	X	X											X					
Hematology	X																	
Chemistry	X																	
Albumin, Ca[i j]		X	X		X		X		X		X		X		X		X	
Phosphorus		X			X				X				X				X	
PTH	X	X	X		X		X		X		X		X		X		X	
PK[h]					X								X					
25(OH)D		X																
[redacted]																		
ADA		X											X					

Footnotes defined on the next page

Schedule of Assessments

Table 2. Schedule of Assessments

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
After dialysis																		
Pulse and blood pressure[ik]		X																
Height		X																
Weight		X																
PK (10-30 minutes postdose)[h]					X								X					

25(OH)D = 25-hydroxy vitamin D; ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted];
ECG = electrocardiogram; IP = investigational product; **HIV = Human immunodeficiency virus,** IV = intravenous; Kt/V = measure of dialysis adequacy;
PTH = parathyroid hormone, PK = pharmacokinetic;
TIW = three times per week; URR = urea reduction ratio

[a] Baseline assessments will be performed on the first day of dosing with IP (day 1). Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] The dose of IP may be increased or decreased at any time. The dose of either active IP will be titrated to target predialysis [redacted] but maintaining cCa ≥ 8.3 mg/dL **(2.07 mmol/L).** Doses of investigational product will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before dose adjustment.

[c] The first dose of IP should occur within 1 day after randomization.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol87mmol/L)**, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Subjects should remain supine or sitting for at least 10 minutes prior to recording the screening ECG, and be supine during the ECG. The screening predialysis ECG is a single recording.

[g] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[h] PK assessments can be done at any hemodialysis session during the treatment week. **Note: Per Section 7.4.2 this will not be drawn in subjects with a known history of HIV.**

[i] **To be measured by the central laboratory**

[j] **Chemistry will also include albumin and calcium**

[k] Subjects must be in a supine position in a rested and calm state for at least 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

[jL] Perform Kt/V or URR assessment at screening unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

Table 3 Schedule of Assessments Continued

				Treatment Period[a]							Follow-up		
Study Week (Study Day)	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[b]**	**30 days after last dose ± 3 days**	**Early Term**	**Dose Suspension**
IV investigational product administration				**Three times per week at the end of the hemodialysis session ending at week 26**									
Dose titration[c]													
Informed Consent													
Inclusion/ Exclusion													
Medical History													
Demographics													
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination											X	X	
Randomization													
Dispensation of oral IP bottle				X				X					
Pill count		X		X		X		X	X			X	
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]	X	X	X	X	X	X	X	X	X				
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status[f]									X			X	
Prior to dialysis													
ECG[g]										X		X	
Serum pregnancy test[h]							X				X	X	
Hematology											X	X	
Chemistry											X	X	
Albumin, Ca[i,j]	X		X		X		X		X	X			X[d]
Phosphorus			X				X		X	X			
PTH	X		X		X		X		X	X	X	X	
PK[k]									**X**		X		
25(OH)D													
ADA											X	X	
After dialysis													
Pulse and blood pressure[L]										X		X	
Height													
Weight										X		X	
PK (10-30 min post dose)[ik]									**X**				

Footnotes defined on the next page

ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted]; ECG = electrocardiogram; IP = investigational product; IV = intravenous; PTH = parathyroid hormone, PK = pharmacokinetic; TIW = three times per week

[a] Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] Week 27 assessments should be performed on the day of the first hemodialysis treatment after the last dose of IP.

[c] The dose of IP may be decreased at any time.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol87mmol/L),** a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Vital status will only be appropriately ascertained by sites for subjects who early terminated the study.

[g] Subjects should remain supine or sitting for at least 10 minutes prior and be supine during the ECG. The predialysis ECG is a single recording.

[h] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[i] **o be measured by the central laboratory.**

[j] **Chemistry will also include albumin and calcium**

[k] PK assessments can be done at any hemodialysis session during the treatment week.

[L] Subjects must be in a supine position in a rested and calm state 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

7.2 Study Procedures

After signing the informed consent form, potential subjects will be evaluated to determine whether they fulfill the entry requirements listed in Section 4.1. At screening, the subject should be reminded that participation in the study is contingent upon his or her screening test results. The screening period begins the day the subject signs the informed consent form, and ends when the subject is randomized to receive the first dose of IP or fails the enrollment criteria.

The procedures performed at each study visit are outlined above in Table 2. Details regarding each type of procedure are provided in subsequent sub-sections.

Refer to the applicable supplemental central laboratory, IVR/IWR system, and study manuals for detailed collection and handling procedures.

7.2.1 Screening Enrollment and/or Randomization

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written informed consent, the site will register the subject in IVR/IWR and screen the subject in order to assess eligibility for participation.

The screening period is up to 8 weeks. If a subject has not met all eligibility criteria at the end of the 8-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once as described in Section 7.2.2.

7.2.2 Re-screening

Screening assessments may be repeated up to 2 times during the 8-week screening period. Subjects who do not meet eligibility requirements during the screening period will be permitted to be re-screened once **as described in Section 5.**

7.2.3 Treatment

Procedures will be completed during the 26-week treatment period at the times designated in the Schedule of Assessments (Table 2). Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled and randomized 1:1 to either etelcalcetide or cinacalcet into the 26 week treatment period and should receive the first dose of investigational product within 1 day of randomization. Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening **central laboratory** serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory,** and country (China versus

non-China). The date of the first dose of IP is defined as day 1. Baseline assessments will be performed on the first day of dosing with IP (day 1). All subsequent study visits will be scheduled based on the day 1 date.

The IP is to be administered after all pre-dose assessments have been completed on day 1. Administration of IV IP is to be administered 3 times per week at the end of each hemodialysis session as specified in Section 6.2.1. Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible. Oral IP should be taken by the subject with food at approximately the same time every day of the 26-week treatment period as described in Section 6.2.2. Week 27 assessments should be performed on the day of the first hemodialysis treatment after the last dose of IP. Concomitant medications, adverse events, and serious adverse events must be collected at every study visit.

7.2.4 Follow-up Visit

Subjects will complete the follow-up visit 30 days (± 3 days) after the last dose of IP. If a subject early terminates from IP or the study, the follow-up visit should also occur within 30 days (± 3 days) after the last dose of IP.

7.2.5 Early Termination of Investigational Product Visit

Subjects discontinuing IP prior to week 26 should return to the site for an early termination (ET) visit (refer to Table 2 and Table 3 for ET assessments) at the first hemodialysis treatment after the last dose of IP if at all possible, or at the earliest possible hemodialysis treatment. Additionally, every attempt should be made to complete a follow-up visit 30 days (± 3 days) from the last dose of IP.

After discontinuing IP, the subject may continue to participate in the study with varying levels of follow-up (refer to Section 8.1).

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in Section 7.1 and Section 7.2. Details regarding the collection, recording and reporting of adverse events and serious adverse events and/or other safety findings are provided in Section 9.

7.3.1 Informed Consent

All subjects/legally acceptable representatives must sign and personally date the IRB/IEC approved informed consent form before any study specific procedures are performed.

7.3.2 Medical History

Detailed medical history including parathyroidectomy **and known human immunodeficiency syndrome (HIV) status (yes/no)** will be obtained at screening. Specific details on cardiovascular history will also be collected

7.3.3 Demographics

Demographic data including age, sex, race, and ethnicity will be collected.

7.3.4 Physical Examination

A physical examination will be conducted post hemodialysis per standard of care. Any clinically significant findings noted at screening are to be detailed in the Medical History eCRF using the clinical diagnosis where applicable. Investigators are to check for any findings that would constitute study exclusion. Clinically significant findings noted at the 30-day safety follow-up or early termination visits should be entered on the events eCRF as appropriate.

7.3.5 Height and Weight

Height and weight will be collected and should be measured without shoes post hemodialysis.

7.3.6 Medication History

The subject's medications at screening (signing informed consent) will be recorded on the eCRF. If the subject is not taking any calcium supplements, phosphate binders, or vitamin D sterols at screening, then the last use should be recorded. If there is previous use of cinacalcet, then the most recent use should be recorded.

7.3.7 Concomitant Medication

All medications taken while on study should be recorded on the eCRF per Section 6.5.

Medications used to treat hemodialysis-related symptoms or comorbid conditions should be reported as concomitant medications whenever administered to the subject. The following medications used in the delivery of hemodialysis should not be reported on the eCRF as concomitant medication:

- local anesthetic for cannulation
- saline prime for the dialysis circuit

- saline or hypertonic saline for management of intradialytic hypotension
- oxygen

7.3.8 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, and heart rate will be measured after hemodialysis.

Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure and pulse rate assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF.

Record all measurements on the vital signs eCRF.

7.3.9 Electrocardiogram (ECG)

Pre-hemodialysis ECGs will be obtained using ECG equipment available at the site. Subject must be in supine position in a rested and calm state for at least 10 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. ECG abnormalities will be recorded in the Electrocardiogram eCRF.

The Primary Investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.3.10 Adverse Events and Disease Related Events

Serious adverse events that occur in a subject after signing the informed consent form through 30 days after the last dose of IP will be recorded in the eCRF. Non-serious adverse events will be recorded in the eCRF only if occurring after first dose of IP and through 30 days after the last dose of IP.

7.3.11 Pill Count

Subjects should bring the bottle(s) of cinacalcet/placebo for a pill count approximately 2 weeks after the dispensing visit, and then return the bottles(s) at the next dispensing visit approximately 2 weeks later for a final pill count for the dispensed bottles(s). The first pill count will occur at week 3. A pill count should also occur at an Early Termination visit.

7.3.12 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date should be obtained.

For any subject who terminates early, study sites will be expected to attempt to collect survival status at week 26, if appropriate based on the applicable local regulations.

7.4 Laboratory Assessments

All screening (except URR) and on-study laboratory samples will be processed and sent to the central laboratory. If screening samples for URR or Kt/V are required, they will be processed at the site's local laboratory. When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol/L),** a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/phosphorous sample is obtained on the same day. The results of this testing will be maintained in the source documents at the site. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. Please refer to the central laboratory manual for the complete listing of analytes run by the central laboratory. Blood samples will be obtained before IP administration (except for the post-dialysis PK samples). The date and time of sample collection will be recorded in the source documents at the site.

Table 4. outlines the specific analytes for serum chemistry, hematology, urinalysis, and other testing to be conducted on blood and urine samples by central, local**,** or core laboratories.

Table 4. Analytes Table

Chemistry	Hematology[c]	Other
Sodium	Hemoglobin	Antibodies[a]
Potassium	Hematocrit	Pregnancy test
Chloride	Platelets	Intact PTH
Bicarbonate	WBC	25-hydroxyvitamin D
Total protein	RBC	[redacted]
Albumin		
Calcium		Urea[b]
Corrected calcium (calculated)		
Magnesium		
Phosphorus		
Glucose		
Total bilirubin[c]		
Direct bilirubin[c]		
ALP		
LDH		
AST (SGOT)[c]		
ALT (SGPT)[c]		

ALP = serum alkaline phosphatase; ALT = alanine aminotransaminase; AST = aspartate transaminase; [redacted]; LDH = lactate dehydrogenase; PTH = parathyroid hormone; RBC = red blood cells; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; WBC = white blood cells

[a] These assays may be performed at a specialty laboratory

[b] Urea measurement to be performed locally for Kt/V or URR assessment at screening, unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

[c] **If the central laboratory result is not available, local laboratory values may be used to determine eligibility, but Amgen must be contacted prior to randomization.**

When albumin is < 4.0 g/dL **(40g/L)**, the calcium level will be corrected according to the following formula:

$$cCa\ (mg/dL) = total\ Ca\ (mg/dL) + (4 - albumin\ [g/dL]) \times 0.8.$$

7.4.1 Hepatitis Testing

Baseline hepatitis testing may be conducted if there is a clinically relevant increase in liver function tests of unknown etiology during the study or the increase meets the criteria for permanent discontinuation or conditional withholding of Amgen IP because of potential hepatotoxicity. For this purpose, a baseline sample will not be specifically stored for hepatitis testing but will be taken from the back-up baseline sample for

antibody testing. If needed, a hepatitis-screening panel (for hepatitis A, B, and C) will be performed.

7.4.2 Pharmacokinetic Sampling

Blood samples will be collected and assayed for etelcalcetide serum concentration. The PK samples will be analyzed only for those subjects assigned to etelcalcetide. PK assessments can be done at any hemodialysis session during the treatment week. **Subjects with a known history of HIV will not have samples drawn for PK analysis.**

Predialysis samples will be collected at weeks 4, 12, 26, and at the 30-day Safety Follow-up visit. Post-dialysis (10 to 30 minutes post-dose) blood samples will be collected at weeks 4,12, **and 26**.

7.5 Antibody Testing Procedures

Blood samples for antibody testing for the measurement of anti-etelcalcetide antibodies will be collected. Samples testing positive for binding antibodies may also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-etelcalcetide antibodies during the study.

More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects with a known history of HIV will not have samples drawn for antibody testing.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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 2) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 2) 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.

8.2 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 and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

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.

8.3 Reasons for Removal From Procedures, Treatment, or Study

8.3.1 Reasons for Removal From Treatment

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

- Protocol Specified Criteria
  - subject requires a significant permanent change in hemodialysis prescription to maintain adequate hemodialysis
  - subject receives a kidney transplant
  - subject undergoes a parathyroidectomy
- **Ineligibility determined**
- **Protocol deviation**
- **Noncompliance**
- Subject request
- **Adverse event**
- Death
- Lost to follow-up
- Decision by Sponsor (other than subject request, safety concern, lost to follow-up)

Subjects who are removed from protocol-required IP(s) will be approached by investigators to determine the amount of follow-up assessments but at a minimum for vital status at the week 26.

8.3.2 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 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical study 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 or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) 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.

For the purpose of this study **any** asymptomatic reductions in serum cCa below 7.5 mg/dL **(1.87 mmol/L) measured by either the central laboratory or the local laboratory** or asymptomatic reductions in serum cCa between 7.5 mg/dL **(1.87 mmol/L)** and < 8.3 mg/dL **(2.07 mmol/L), measured by either the central laboratory or the local laboratory,** that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as "blood calcium decreased." Symptomatic reductions in serum cCa < 8.3 mg/dL **(2.07 mmol/L) measured by either the central laboratory or the local laboratory** should be reported as "hypocalcemia", and the associated signs and symptoms should also be captured.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment because of an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study because of an adverse event, refer to Section 8 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 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 DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 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 after first dose of IP(s)/study treatment/protocol-required therapies through 30 days after the last dose of IP are reported using the Event CRF.

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),
- Severity (mild, moderate, severe),
- Assessment of relatedness to IP or other protocol-required therapies, and
- Action taken

The adverse event grading scale used will be the following:

- Mild: **Aware of sign or symptom, but easily tolerated**
- Moderate: **Discomfort enough to cause interference with usual activity**
- Severe: **Incapacitating with inability to work or do usual activity**

The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to 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.

9.2.1.2 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 after signing the informed consent form through 30 days after the last day of the dosing interval of IP 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 Event CRF.

If the EDC system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event

Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B. for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the electronic Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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 Event CRF.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

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 GCP.

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.

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. If serious adverse events are reported, the investigator is to report them 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.

9.2.2 Adverse Events of Interest

Based on the mechanism of action, pharmacological profile of etelcalcetide, potential class effects of etelcalcetide as a CaR agonist, and observations made during the nonclinical and clinical program, certain safety events were considered of special interest as follows: cardiac failure, Torsade de pointes-QT prolongation and ventricular arrhythmia, convulsions, hypersensitivity, hypocalcemia, a dynamic bone, hypophosphatemia, and infusion reactions.

9.2.3 Changes in Serum Calcium and Symptomatic Hypocalcemia

Serum cCa levels will be analyzed by the central laboratory throughout the study, and these results will be incorporated in the clinical database. **The cCa measured by the local laboratory and collected for the management of safety concerns will also be incorporated in the clinical database.** Per Section 6.2.3.2 dosing with IP will be suspended if a predialysis serum cCa < 7.5 mg/dL **(1.87 mmol/L)** value **from either the central or local laboratory** is observed. A repeat **central laboratory** serum cCa will be obtained prior to hemodialysis at the next hemodialysis session, to allow verification of the low serum cCa level. **Central laboratory** serum cCa will continue to be monitored per protocol if IP dosing is suspended for low serum cCa. Dosing may subsequently resume when **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)** and any hypocalcemic symptoms have resolved with the dose (1) reduced by 5 mg, or at the minimum dose of 2.5 mg, whichever is greater for IV IP, or (2) reduced by 25 mg, or at the minimum dose of 25 mg, whichever is greater for oral IP.

Investigators should assess subjects for the onset of signs and symptoms associated with low serum calcium (see Section 6.2.3.3) at each visit. **Any** asymptomatic reductions in serum cCa below 7.5 mg/dL **(1.87 mmol/L) from either the central or**

local laboratory or asymptomatic reductions in serum cCa between 7.5 mg/dL **(1.87 mmol/L)** and < 8.3 mg/dL **(2.07 mmol/L) from either the central or local laboratory** that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as "blood calcium decreased."

When signs and symptoms associated with low serum calcium are observed, "hypocalcemia" should be reported as the adverse event and the associated signs and symptoms should also be captured.

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 therapies report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of protocol-required therapies through 3 months after the last dose of IP.

The pregnancy should be reported to Amgen 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 follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while 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 3 months after the last dose of IP. Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C.). Amgen Global

Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

The primary endpoint of the study is achievement of a > 30% reduction from baseline in mean predialysis serum PTH level from baseline during the EAP of the study (EAP is defined as weeks 20 to 27, inclusive).

10.1.1.2 Key Secondary Endpoints

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

10.1.1.3 Other Secondary Endpoints

- Percent change from baseline in mean predialysis **measured by the central laboratory** serum cCa during the EAP
- Achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

10.1.1.4 Safety Endpoints

- Incidence of cCa < 8.3 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 8.0 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 7.5 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of treatment-emergent symptomatic hypocalcemia during the study
- Incidence of antibody formation to etelcalcetide
- Nature, frequency, severity, and relationship of treatment-emergent adverse events.

10.1.1.5 Exploratory Endpoints

[redacted]

[redacted]

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

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

10.1.2.2 PTH Completer Analysis Set

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

10.1.2.3 cCa Completer Analysis Set

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

10.1.2.4 Safety Analysis Set

The Safety Analysis Set consists of all randomized subjects who receive at least one dose of IP. Subjects will be analyzed according to randomized treatment unless the incorrect treatment is administered throughout the study period. Safety analyses will be performed using the Safety Analysis Set.

10.1.2.5 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) is defined as all randomized subjects who have no major protocol violations and have at least one post-dose PTH value and had at least 16 weeks exposure of IP. Subjects in the PPAS will be analyzed according to randomized treatment assignment.

10.1.3 Covariates and Subgroups

All analyses of primary and key secondary endpoints will be adjusted for the effect of the stratification factors of screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China). The primary and key secondary endpoints will be analyzed in the subgroups defined by the stratification factors.

10.2 Sample Size Considerations

The sample size calculations are based on the results of the global head-to-head study (20120360) and take into consideration sufficient power for both the primary and secondary endpoints. The non-inferiority margin is defined based on an Amgen EVOLVE trial (Study 20050182), which was a randomized, placebo-controlled trial. Using a similar subject population in the EVOLVE trial as intended to be recruited in this study, rates of 25% and 60% in the placebo and cinacalcet arms, respectively, were derived and the two-sided 95% CI for the treatment difference based on the large sample normal approximation is (31%, 39%). Half of the lower limit of the CI for the treatment difference (compared to placebo) is 15.5%. Taking a conservative approach, the non-inferiority margin is defined as 12%.

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

For the key secondary endpoint of achievement of >50% reduction from baseline in mean predialysis PTH during the EAP, 300 subjects per treatment group will provide approximately 84% power to detect a statistically significant difference between the treatment groups at the 5% significance level (two-sided), assuming a 52% and 40% response rate in subjects randomized to etelcalcetide and cinacalcet, respectively. For the key secondary endpoint of achievement of >30% reduction from baseline in mean predialysis PTH during the EAP (superiority analysis), 300 subjects per treatment group will provide about 72% power to detect a statistically significant difference between the treatment groups at the 5% significance level (two-sided), assuming a 68% and 58% response rate in subjects randomized to etelcalcetide and cinacalcet, respectively.

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

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (Section 5.2 and Section 9.2.1.2).

Amgen staff or designees from departments such as Biological Sample Management or Clinical Immunology who are responsible for tracking, assaying or analyzing biological samples during the conduct of study are considered unblinded to the treatment assignments in the study. These individuals will not have access to subject level clinical data.

10.4 Planned Analyses

10.4.1 Primary Analysis

The primary analysis will be conducted upon achieving the Primary Completion milestone. At the time of the Primary Analysis, the study will be unblinded and all endpoints will be evaluated.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

This is a phase 3 study to evaluate the efficacy of etelcalcetide as compared to cinacalcet. The primary objective is to determine if etelcalcetide is non-inferior to cinacalcet on achievement of a >30% reduction from baseline in mean predialysis serum PTH during the EAP. Etelcalcetide will be considered non-inferior if the upper bound of the two-sided 95% CI of the treatment difference (cinacalcet – etelcalcetide) is smaller than 12%. If this criterion is met, the 2 key secondary endpoints will be tested sequentially. The testing for the endpoint of achievement of a > 50% reduction from baseline in mean predialysis serum PTH during the EAP will be carried out first. Only if the result achieves statistical significance, the secondary endpoint of achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP will be tested. The other secondary endpoints will be formally tested if both key secondary endpoints are statistically significant. To control for the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used for testing of the other secondary endpoints. The primary analysis of all primary and secondary endpoints will be conducted on the FAS.

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

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

Descriptive statistics include number of observations, mean, median, standard deviation or standard error, minimum and maximum for continuous variables, and number and percent for categorical variables.

Descriptive statistics of plasma etelcalcetide at week 4 collected prior to dialysis will be summarized. The PK data collected may be pooled with other study data for further evaluation.

10.5.2 Primary Efficacy Endpoint

A Mantel-Haenszel (MH) method with adjustment for the 3 randomization stratification factors will be used to compute the 2-sided 95% CI for the difference between proportion of subjects who achieve > 30% reduction from baseline in mean predialysis serum PTH during the EAP between the cinacalcet and etelcalcetide groups. In the primary analysis, an imputation under the non-inferiority null method (Koch, 2008) will be applied to subjects who do not have PTH data during the EAP.

The following sensitivity **analysis** for the primary analysis on FAS will be conducted:

- For subjects without PTH data during the EAP, the mean of the last 2 predialysis PTH values obtained after day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. A similar imputation approach as the primary analysis will be applied to subjects without a post-baseline PTH value.

In addition, **supplementary analyses will be performed for primary endpoint using PCAS and PPAS.**

10.5.3 Secondary Efficacy Endpoints

Sequential testing of the following 2 key secondary efficacy endpoints will be performed if non-inferiority is demonstrated on the primary endpoint.

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

The endpoint of achievement of > 50% and > 30% reduction in mean predialysis serum PTH from baseline during the EAP will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. In these analyses, subjects will be considered as not achieving the endpoint if they do not have PTH data during the EAP (ie, nonresponder imputation). Sensitivity analysis will be conducted using multiple imputation method for both endpoints.

10.5.3.1 Other Secondary Efficacy Endpoints

The following secondary endpoints will be formally tested if both key secondary endpoints are statistically significant. To control the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used:

- percent change from baseline in mean predialysis **central laboratory** serum cCa during the EAP
- achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

A repeated measures mixed effects model will be used to compare the percent change from baseline in serum cCa levels during the EAP, and will include the randomization stratification factors. The difference between treatment groups will be presented with 95% CI. The analysis will be performed on the FAS and **supplementary** analysis will be performed using the cCa completer analysis set. The achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP will be analyzed by using CMH test stratified by the randomization stratification factors. The difference between treatments will be estimated and presented with a 95% confidence interval. These analyses will be performed on the FAS using the nonresponder imputation for those subjects without laboratory values during the EAP.

10.5.4 Safety Endpoints

All reported adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, high-level group term, and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, and treatment-emergent adverse events of interest will also be provided.

Proportion of subjects (with 95% confidence interval) with the following will be presented by treatment group:

- cCa < 8.3 mg/dL **measured by the central laboratory**
- cCa < 8.0 mg/dL **measured by the central laboratory** cCa < 7.5 mg/dL **measured by the central laboratory**
- treatment-emergent symptomatic hypocalcemia adverse event during the study **will be presented by treatment group.**

No formal statistical testing will be performed.

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 subject 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 IP(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 subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. Refer to ICH GCP guideline, Section 4.8.9.

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 IP.

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 eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- 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 ET and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP(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 whether to supply Amgen IP(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 eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF 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.

In this study, the IVR/IWR system captures the following data points and these are considered source data:

- Planned IP dose
- Treatment assignment
- Box ID/Kit number

eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

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 to include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- IP-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.
- Non-IP(s) documentation, 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor is responsible for verifying the eCRFs 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 research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

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 eCRFs, 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 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 or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, 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.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subject's 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 2), 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

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, the investigator will solicit input and assistance from Amgen staff as appropriate.

To coordinate dissemination of data from this study, Amgen may facilitate 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 of 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.
- 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.

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.

13. REFERENCES

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Amgen Standard Grading Scale as show below:

Grade	Definition
MILD	**Aware of sign or symptom, but easily tolerated**
MODERATE	**Discomfort enough to cause interference with usual activity**
SEVERE[a]	**Incapacitating with inability to work or do usual activity**

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severesevere

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 6.4 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 eCRF (eg, 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 9.2.1.2..

Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) because of potential DILI as specified in Sections 6.4.1 and 6.4.2 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

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic**. Note: Bilirubin (total and direct), ALT, and AST should be**

measured by the local laboratory if the central laboratory is unable to perform the analysis.

- 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 **plasma or** 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 PK 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 IP(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 eCRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20150238 AMG 416	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month___ Year_____

Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP/drug under study	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? AMG 416 No✓ Yes✓ / Cinacalcet No✓ Yes✓ / <Ptdevice> No✓ Yes✓ / <Ptdevice> No✓ Yes✓	**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20150238 AMG 416	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 416	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Cinacalcet	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

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 Day Month Year	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy 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 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

Page 1 of 1

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

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:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 3

Protocol Title: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism

Amgen Protocol Number (Etelcalcetide) 20150238

Amendment 3 Date: 27 November 2018

Rationale:

The rationale for the major changes in the study design is provided below:

- Language clarifying the use of central and local laboratory results has been inserted throughout the protocol to ensure that all laboratory analyses are processed at the appropriate laboratory.

Other changes to the protocol:

- Laboratory values have been updated to include the International System of Units (SI) units.
- Language on use of local hepatic laboratory results for eligibility and treatment of hepatic toxicities if central hepatic laboratory results are not available due to sample out of stability caused by shipping times has been included.
- Medical History has been revised to include that subjects will be asked their human immunodeficiency virus (HIV) status to enable compliance with local restrictions regarding laboratory analysis where appropriate.
- A PK sample has been added post-dose on week 26
- Adverse Event (AE) descriptions have been made consistent throughout the protocol
- The section on Drug Induced Liver Injury has been revised.
- Definitions for primary completion date and end of treatment criteria have been clarified.
- Study Efficacy endpoint analyses have been updated per ICH E9R1

Description of Changes:

Section: Header date

Replace:

Date: 16 February 2018

With:

Date: 27 November 2018

Section: Title page

Add:

NCT #: NCT03299244

Date:	04 December 2015
Amendment 1	07 February 2017
Amendment 2	16 February 2018
Amendment 3	**27 November 2018**

Replace:

[redacted]
Amgen, 1 Uxbridge Business Park
Sanderson Road
Uxbridge, Middlesex, UB8 1DH
United Kingdom
[redacted]

With:

[redacted]
Amgen, 1 Uxbridge Business Park
Sanderson Road
Uxbridge, Middlesex, UB8 1DH
United Kingdom
[redacted]

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride with Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects with Secondary Hyperparathyroidism, dated 16 February 2018, and agree to abide by all provisions set forth therein.

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 1 year after the study is completed, if there are changes that affect my financial disclosure status.

With:

I have read the attached protocol entitled: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride with Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects with Secondary Hyperparathyroidism, dated **27 November 2018**, and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis

Subsection: Secondary Objective

Replace:

Secondary Objective: To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dl during the efficacy assessment phase (EAP).

With:

Secondary Objective: To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH

from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) **measured at the central laboratory,** and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dl **measured at the central laboratory** during the efficacy assessment phase (EAP).

Subsection: Other Secondary Endpoints

Replace

- Percent change from baseline in mean predialysis serum cCa during the EAP
- Achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

With:

- Percent change from baseline in mean predialysis serum cCa **measured by the central laboratory** during the EAP
- Achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

Subsection: Safety Endpoints

Replace:

- Incidence of cCa < 8.3 mg/dL at any time during the study
- Incidence of cCa < 8.0 mg/dL at any time during the study
- Incidence of cCa < 7.5 mg/dL at any time during the study
- Incidence of treatment-emergent symptomatic hypocalcemia during the study

With

- Incidence of cCa < 8.3 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 8.0 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 7.5 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of treatment-emergent symptomatic hypocalcemia during the study

Subsection: Exploratory Endpoints

Replace:

[redacted]

Subsection: Study Design

Replace:

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

With:

Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central lab**, and country (China versus non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet.

Subsection: Summary of Subject Eligibility Criteria

Replace

Subjects must have SHPT as defined by 1 central laboratory screening predialysis serum PTH value > 500 pg/mL **(and** one serum cCa value ≥ 8.3 mg/dL within 2 weeks prior to randomization.

With:

Subjects must have SHPT as defined by 1 central laboratory screening predialysis serum PTH value > 500 pg/mL **(53.00 pmol/L)** and one serum cCa value ≥ 8.3 mg/dL **(2.07 mmol/L)** within 2 weeks prior to randomization.

Subsection: Amgen Investigational Product Dosage and Administration

Replace:

The starting dose of IV IP is 5 mg and will be titrated by the Interactive Voice Response (IVR)/Interactive Web Response (IWR) system to target predialysis [redacted] The minimum IV IP dose is 2.5 mg, and the maximum dose is 15 mg. The dose of the IV IP may be increased in increments of 2.5 mg or 5 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL and cCa values remain ≥ 8.3 mg/dL based on results obtained the previous week.

With:

The starting dose of IV IP is 5 mg and will be titrated by the Interactive Voice Response (IVR)/Interactive Web Response (IWR) system to target predialysis [redacted] The minimum IV IP dose is 2.5 mg, and the maximum dose is 15 mg. The dose of the IV IP may be increased in increments of 2.5 mg or 5 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL **(31.80 pmol/L)** and cCa values remain ≥ 8.3 mg/dL **(2.07 mmol/L)** based on results **measured by the central laboratory** obtained the previous **or current** week.

Subsection: Non-Amgen Investigational Product Dosage and Administration

Replace:

The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] The minimum oral IP dose is 25 mg, and the maximum dose is 100 mg. The dose of oral IP may be increased in increments of 25 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL and cCa values remain ≥ 8.3 mg/dL based on results obtained the previous week.

With:

The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] The minimum oral IP dose is 25 mg, and the maximum dose is 100 mg. The dose of oral IP may be increased in increments of 25 mg at weeks 5, 9, 13, and 17, if PTH values remain > 300 pg/mL **(31.80 pmol/L)** and cCa values remain ≥ 8.3 mg/dL **(2.07 mmol/L)** based on results **measured by the central laboratory** obtained the previous **or current** week.

Subsection: Procedures

Replace:

Randomization will be stratified by PTH level (< 900 pg/mL, ≥ 900 pg/mL)**,** screening serum cCa (≥9.0 mg/dL, < 9.0 mg/dL)**,** and country (China versus non-China). Assessments during the treatment period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started and will be scheduled based on the day 1 date. Subjects will complete the study at the follow-up visit 30 days (± 3 days) after the last dose of IP. IP will be dosed to achieve predialysis [redacted] but maintaining cCa ≥ 8.3 mg/dL. Doses of IP will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before dose adjustment. Dosing with IP may be suspended, and dosing resumed at a lower dose according to protocol-defined rules for low predialysis PTH (based on central laboratory values) or cCa values, for symptomatic hypocalcemia, or for other drug-related adverse events**.**

With

Randomization will be stratified by PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L),** screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L),), both measured by the central laboratory**, and country (China versus non-China). Assessments during the treatment period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started and will be scheduled based on the day 1 date. Subjects will complete the study at the follow-up visit 30 days (± 3 days) after the last dose of IP. IP will be dosed to achieve predialysis [redacted]

[redacted] but maintaining cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**. Doses of IP will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before **or week of** dose adjustment. **Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3); however, IV IP dose cannot be resumed or increased without an available cCa result from the central laboratory for the prior or current week.** Dosing with IP may be suspended, and dosing resumed at a lower dose according to protocol-defined rules for low predialysis PTH (based on central laboratory values) or cCa values, for symptomatic hypocalcemia, or for other drug-related adverse events**. Corrected Calcium results from the local laboratory can only be used for the management of safety concerns and for suspension of IP; results must not be used for resumption or titration of IP. A local cCa and central laboratory cCa, must not be collected at the same time.**

Subsection: Statistical Considerations

Replace:

Proportion of subjects (with 95% confidence interval) with the following will be provided:

- cCa < 8.3 mg/dL
- cCa < 8.0 mg/dL
- cCa < 7.5 mg/dL
- treatment-emergent symptomatic hypocalcemia adverse events during the study will be presented by treatment group.

With:

Proportion of subjects (with 95% confidence interval) with the following will be provided:

- cCa < 8.3 mg/dL **measured by the central laboratory**
- cCa < 8.0 mg/dL **measured by the central laboratory**
- cCa < 7.5 mg/dL **measured by the central laboratory**

Subsection Study Design and Treatment Schema

Replace:

Study Design and Treatment Schema

With

Figure 1 Study Design and Treatment Schema

Section: Study Glossary

Replace:

End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s)

With:

End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for **evaluation in the study at the follow-up visit (30 days after last dose [± 3 days]) or the last assessment is collected for the primary endpoint, whichever is later**

Add:

HIV	**Human Immunodeficiency Virus**

Remove:

SECs	self-evident corrections

Section: 1.2 Secondary Objectives

Replace:

- To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dL during the efficacy assessment phase (EAP).

Add:

- To assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in serum PTH from baseline, proportion of subjects with > 30% decrease in serum PTH from baseline, percent change from baseline in mean predialysis albumin corrected calcium (cCa) **measured by the central laboratory** and achievement of mean predialysis serum phosphorus (P) ≤ 4.5 mg/dL **measured by the central laboratory** during the efficacy assessment phase (EAP).

Section: 2.2.1 Etelcalcetide

Replace:

Please refer to the etelcalcetide Amgen Investigator Brochure Edition 8 for additional detailed information about the chemistry, toxicology, preclinical pharmacology, pharmacokinetics (PK), safety, and clinical experience of etelcalcetide.

With:

Please refer to the etelcalcetide Amgen Investigator Brochure for additional detailed information about the chemistry, toxicology, preclinical pharmacology, pharmacokinetics (PK), safety, and clinical experience of etelcalcetide.

Section: 3.1 Study Design

Replace:

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

With:

Subjects will be stratified by screening serum PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China), and be randomized 1:1 to receive etelcalcetide or cinacalcet.

Section: 3.2 Number of Sites

Replace:

The study is planned to be conducted at approximately 120 centers in China, Taiwan, South Korea, Hong Kong, Malaysia, and India. Other countries may be added as needed.

With:

The study is planned to be conducted at approximately 120 centers in China **mainland**, Taiwan, South Korea, Hong Kong, Malaysia, and India. Other countries **and/or regions** may be added as needed.

Section: 4.1.1 Inclusion Criteria

Replace:

105 Subject must have SHPT as defined by one central laboratory screening predialysis serum PTH value > 500 pg/mL, within 2 weeks prior to randomization.

107 Subject must have 1 screening predialysis serum cCa laboratory value ≥ 8.3 mg/dL measured within 2 weeks prior to randomization.

With:

105 Subject must have SHPT as defined by one central laboratory screening predialysis serum PTH value > 500 pg/mL **(53.00 pmol/L)**, within 2 weeks prior to randomization.

107 Subject must have 1 screening predialysis serum cCa laboratory value ≥ 8.3 mg/dL **(2.07 mmol/L)** measured within 2 weeks prior to randomization.

Section: 4.1.2 Exclusion Criteria

Replace:

216 Subject has clinically significant abnormalities on prestudy clinical examination or abnormalities on the most recent central laboratory tests during the screening period prior to randomization according to the Investigator including but not limited to the following:

- serum albumin < 3.0 g/dL
- serum magnesium < 1.5 mg/dL

serum transaminase (alanine transaminase [ALT] or glutamic pyruvic transaminase [SGPT], aspartate aminotransferase [AST] or serum glutamic oxaloacetic transaminase [SGOT]) > 3 times the upper limit of normal (ULN) at screening

With:

216 Subject has clinically significant abnormalities on prestudy clinical examination or abnormalities on the most recent central laboratory tests during the screening period prior to randomization according to the Investigator including but not limited to the following:

- serum albumin < 3.0 g/dL **(30 g/L)**
- serum magnesium < 1.5 mg/dL **(0.62 mmol/L)**
- serum transaminase (alanine transaminase [ALT] or serum glutamic pyruvic transaminase [SGPT], aspartate aminotransferase [AST] or serum glutamic oxaloacetic transaminase [SGOT]) > 3 times the upper limit of normal (ULN) at screening

  Note: if results of serum transaminases are not available, Amgen should be notified prior to randomization; serum transaminases may be measured at the local laboratory

Section: 5.1 Randomization/ Treatment Assignment

Replace:

Subjects will be randomized by IVR/IWR in a 1:1 ratio to either TIW IV etelcalcetide (and daily oral placebo tablets) or daily oral cinacalcet tablets (and TIW IV placebo) in a double-blind, double-dummy manner, and should receive the first dose of IP within 1 day of randomization. Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL and country (China versus non-China). The total duration of treatment will be 26 weeks. IP will be dosed to achieve predialysis [redacted] Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

With:

Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China). The total duration of treatment will be 26 weeks. IP will be dosed to achieve predialysis [redacted] Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Replace:

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results obtained during the prior week.

Subjects will be treated with IV IP three times weekly at the end of hemodialysis, for 26 weeks. The starting dose of IV IP is 5 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL. The minimum IV IP dose is 2.5 mg, and the maximum dose is 15 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1 unless any of the following criteria are met:

- subject has missed 3 or more IV doses during the prior 3 weeks
- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- predialysis serum cCa < 8.3 mg/dL during the prior week
- predialysis [redacted] during the prior week

Table 1. Investigational Product Dosing Algorithm Based on PTH

PTH (pg/mL)	IV IP Dose If Current Dose < 10mg	IV IP Dose If Current Dose 10 mg	Oral IP Dose
PTH > 450	Increase dose by 2.5 mg	Increase dose by 5 mg	Increase dose by 25 mg
300 < PTH ≤ 450	Increase dose by 2.5 mg	Increase dose by 2.5 mg	Increase dose by 25 mg
PTH ≤ 300	Maintain dose	Maintain dose	Maintain dose
PTH < 100	If 2 consecutive values at least 1 week apart, suspend dose	If 2 consecutive values at least 1 week apart, suspend dose	If 2 consecutive values at least 1 week apart, suspend dose

IP = investigational product; IV = intravenous; PTH = parathyroid hormone

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

With:

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results **from the central laboratory** obtained during the prior **or current** week.

Subjects will be treated with IV IP three times weekly at the end of hemodialysis, for 26 weeks. The starting dose of IV IP is 5 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL **(2.07 mmol/L).** The minimum IV IP dose is 2.5 mg, and the maximum dose is 15 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1 unless any of the following criteria are met:

- subject has missed 3 or more IV doses during the prior 3 weeks
- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- **most recent** predialysis serum cCa < 8.3 mg/dL **(2.07 mmol/L)** during the prior **or current** week
- **most recent** predialysis [redacted] during the prior **or current** week

Table 1. Investigational Product Dosing Algorithm Based on PTH

PTH (pg/mL)	IV IP Dose If Current Dose < 10mg	IV IP Dose If Current Dose 10 mg	**IV IP Dose If Current Dose 12.5 mg**	Oral IP Dose
PTH > 450 **(47.70 pmol/L)**	Increase dose by 2.5 mg	Increase dose by 5 mg	**Increase dose by 2.5 mg**	Increase dose by 25 mg
300 **(31.80 pmol/L)** < PTH ≤ 450 **(47.70 pmol/L)**	Increase dose by 2.5 mg	Increase dose by 2.5 mg	**Increase dose by 2.5 mg**	Increase dose by 25 mg
PTH ≤ 300 **(31.80 pmol/L)**	Maintain dose	Maintain dose	**Maintain dose**	Maintain dose
PTH < 100 **(10.60 pmol/L)**	If 2 consecutive values at least 1 week apart, suspend dose	If 2 consecutive values at least 1 week apart, suspend dose	**If 2 consecutive values at least 1 week apart, suspend dose**	If 2 consecutive values at least 1 week apart, suspend dose

IP = investigational product; IV = intravenous; PTH = parathyroid hormone

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3); however, IV IP dose cannot be resumed or increased without an available cCa result from the central laboratory for the prior or current week.

Section 6.2.2.1 Dosage, Administration, and Schedule:

Replace:

Oral IP should be taken by the subject with food, at approximately the same time on a daily basis during the 26-week duration of the study treatment period. The oral IP should be taken by the subject at least 12 hours before the PTH assessment.

If ≤ 7 consecutive daily doses of the oral IP were missed, because of reasons unrelated to those described in Section 6, the subject should be instructed to resume dosing at the IVR/IWR assigned dose. The subject must not attempt to make up for any missed doses.

The quantity, start date, stop date, and box number of oral IP are to be recorded on each subject's eCRF. When the oral IP is returned by the subject during a study visit (see Pill

Count in Dose Schema in **Table 3)** the investigator or responsible person will determine the level of compliance with the administration of the oral IP.

With:

Oral IP should be taken by the subject with food, at approximately the same time on a daily basis during the 26-week duration of the study treatment period. The oral IP should be taken by the subject at least 12 hours before the PTH **laboratory** assessment.

If ≤ 7 consecutive daily doses of the oral IP were missed, because of reasons unrelated to those described in Section 6, the subject should be instructed to resume dosing at the IVR/IWR assigned dose. The subject must not attempt to make up for any missed doses.

The quantity, start date, stop date, and box number of oral IP are to be recorded on each subject's eCRF. When the oral IP is returned by the subject during a study visit (see Pill Count in Dose Schema in **Figure 1)** the investigator or responsible person will determine the level of compliance with the administration of the oral IP.

Section: 6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Replace:

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results obtained during the prior week.

Subjects will be treated with oral IP daily, for 26 weeks. The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL. The minimum oral IP dose is 25 mg, and the maximum IP dose is 100 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1 unless any of the following criteria are met:

- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- predialysis serum cCa < 8.3 mg/dL during the prior week
- predialysis [redacted] during the prior week

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

With:

Sites and subjects will be blinded to central laboratory serum PTH values. Routine local PTH monitoring during the study should be suspended. IP dose titration will be managed by an IVR/IWR and will be based on predialysis serum PTH and cCa results obtained during the prior **or current** week.

Subjects will be treated with oral IP daily, for 26 weeks. The starting dose of oral IP is 25 mg and will be titrated by the IVR/IWR to target predialysis [redacted] and maintain cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**. The minimum oral IP dose is 25 mg, and the maximum IP dose is 100 mg.

Each subject's predialysis central laboratory serum PTH and cCa result will be evaluated by the IVR/IWR to determine if the dose of IP should be increased. The dose of IP may be increased by the IVR/IWR during weeks 5, 9, 13, and 17 per Table 1 unless any of the following criteria are met:

- the dose of IP was reduced within the prior 3 weeks
- there is an ongoing adverse event, including symptomatic hypocalcemia that precludes a dose increase
- **most recent** predialysis serum cCa < 8.3 mg/dL **(2.07 mmol/L)** during the prior **or current** week
- **most recent** predialysis [redacted] during the prior **or current** week

To maintain the blind, the IVR/IWR will adjust (increase/decrease/suspend) the placebo IP dose in the same subject, if adjustment is required. Any adjustments made by the Investigator independent of the IVR/IWR should follow the same process, with the reason for dose change recoded on the subject eCRF.

Dosing of IP may occur if the cCa results from the central laboratory are not available (as described in Section 6.2.3), but oral IP dose cannot be resumed or increased without an available cCa result from the central laboratory from the prior or current week.

Section: 6.2.3 Suspension and Reduction of Oral and Intravenous Investigational Product

Replace:

Dosing with IP may be suspended by the Investigator or by the IVR/IWR at any time if ANY of the criteria below apply. IP dosing may resume only after ALL criteria contributing to suspension of IP dosing are resolved.

- two consecutive predialysis central laboratory PTH < 100 pg/mL at least 1 week apart (see Section 6.2.3.1)
- cCa is < 7.5 mg/dL (see Section 6.2.3.2
- subject experiences symptomatic hypocalcemia (see Section 6.2.3.3)
- there is any other ongoing adverse event that, in the opinion of the Investigator, necessitates suspension of IP dosing

During a hospitalization or when hemodialysis is provided in a location other than the Investigator's site, both oral and IV IPs should be suspended**.**

The site will immediately enter the information in IVR/IWR and electronic data capture (EDC) system when a dose suspension rule is invoked and the reason for missed or suspended doses recoded on the subject eCRF. Even when dosing with IP is suspended per protocol, all scheduled assessments should be completed.

With:

Dosing with IP may be suspended by the Investigator or by the IVR/IWR at any time if ANY of the criteria below apply. IP dosing may resume only after ALL criteria contributing to suspension of IP dosing are resolved.

- two consecutive predialysis central laboratory PTH < 100 pg/mL **(10.60 pmol/L)** at least 1 week apart (see Section 6.2.3.1)
- cCa is < 7.5 mg/dL **(1.87 mmol/L)** (see Section 6.2.3.2) **measured by either the central or local laboratory**
- subject experiences symptomatic hypocalcemia (see Section 6.2.3.3)
- there is any other ongoing adverse event that, in the opinion of the Investigator, necessitates suspension of IP dosing

Moved from the third paragraph in the section to the second paragraph in the section:

The site will immediately enter the information in IVR/IWR and electronic data capture (EDC) system when a dose suspension rule is invoked and the reason for missed or suspended doses is recorded on the subject eCRF. Even when dosing with IP is suspended per protocol, all scheduled assessments should be completed.

During a hospitalization or when hemodialysis is provided in a location other than the Investigator's site, both oral and IV IPs should be suspended. **When hemodialysis is provided in a location other than the Investigator's site, the visit should not be registered in the IVR/IWR. The reasons for missed doses should be recorded on the subject eCRF.**

Section: 6.2.3.1 Low Predialysis Serum PTH

Replace:

If a subject has 2 consecutive central laboratory predialysis serum PTH results obtained at least 1 week apart that are both < 100 pg/mL then the Investigator will be notified by the IVR/IWR that dosing of both the IV and oral IPs should be suspended.

Intact PTH monitoring will continue per the protocol. Once PTH is ≥ 150 pg/mL serum cCa ≥ 8.3 mg/dL, the Investigator will be notified by the IVR/IWR that dosing with the IV and oral IPs may resume at a 2.5 mg lower dose for the IV, and at a 25 mg lower dose for the oral.

If a subject was receiving the 2.5 mg IV dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 2.5 mg dose level when PTH is > 300 pg/mL and the most recent predialysis. serum cCa ≥ 8.3 mg/dL**.**

If a subject was receiving the 25 mg oral dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 25 mg dose level when PTH is > 300 pg/mL, and the most recent predialysis serum cCa ≥ 8.3 mg/dL.

With:

If a subject has 2 consecutive central laboratory predialysis serum PTH results obtained at least 1 week apart that are both < 100 pg/mL **(10.60 pmol/L)**, then the Investigator will be notified by the IVR/IWR that dosing of both the IV and oral IPs should be suspended.

Intact PTH monitoring will continue per the protocol. Once PTH is ≥ 150 pg/mL **(15.90 pmol/L)** and the **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**, the Investigator will be notified by the IVR/IWR that dosing with the IV and oral IPs may resume at a 2.5 mg lower dose for the IV, and at a 25 mg lower dose for the oral.

If a subject was receiving the 2.5 mg IV dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 2.5 mg dose level when PTH is > 300 pg/mL **(31.80 pmol/L)**, and the most recent predialysis **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**.

If a subject was receiving the 25 mg oral dose of IP when dosing was suspended for low PTH, then dosing with IP may be resumed by the IVR/IWR at the 25 mg dose level when PTH is > 300 pg/mL **(31.80 pmol/L),** and the most recent predialysis **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**.

Section: 6.2.3.2 Low Predialysis Serum Corrected Calcium

Replace:

Supplementation with oral calcium and/or increasing the dialysate calcium concentration may be instituted by the Investigator if serum cCa is below the lower limit of the reference range or there is a rapid large reduction in serum calcium, especially in subjects with PTH > 700 pg/mL and markedly elevated serum alkaline phosphatase (ALP) at baseline. Increased calcium supplementation may only be needed on a temporary basis until mineral balance is re-established at the reduced PTH level.

The following guidance is provided for the management of serum cCa below the lower limit of the reference range with any change to therapy based on Investigator clinical judgment. If cCa < 8.3 mg/dL, the following options may be taken by the Investigator:

- May increase oral calcium intake
- May increase dialysate calcium concentration
- May initiate or increase active vitamin D analogues if other therapies are ineffective

If is < 7.5 mg/dL or the subject experiences symptomatic hypocalcemia**:**

- Suspend dosing with IP, and at the next hemodialysis session following notification of the low serum calcium result, draw a confirmatory predialysis serum cCa sample.
- Obtain weekly predialysis serum cCa. Once predialysis serum cCa ≥ 8.3 mg/dL and any hypocalcemic symptoms have resolved the IVR/IWR will provide instructions to resume dosing. For the oral IP, the dose should be reduced by 25 mg or at the minimum dose of 25 mg, whichever is greater. For the IV IP, the dose should be reduced by 5 mg or at the minimum dose of 2.5 mg, whichever is greater. Resume routine laboratory monitoring per Table 2, the Schedule of Assessments. Refer to Section 7.2 for central laboratory samples to be submitted.

With:

Supplementation with oral calcium and/or increasing the dialysate calcium concentration may be instituted by the Investigator if serum cCa is below the lower limit of the reference range or there is a rapid large reduction in serum calcium, especially in subjects with PTH > 700 pg/mL **(74.20 pmol/L)** and markedly elevated serum alkaline phosphatase (ALP) at baseline. Increased calcium supplementation may only be needed on a temporary basis until mineral balance is re-established at the reduced PTH level.

The following guidance is provided for the management of serum cCa below the lower limit of the reference range with any change to therapy based on Investigator clinical judgment. If **the** cCa **measured by either the central or local laboratory is** < 8.3 mg/dL **(2.07 mmol/L)**, the following options may be taken by the Investigator:

- May increase oral calcium intake
- May increase dialysate calcium concentration
- May initiate or increase active vitamin D analogues if other therapies are ineffective

If **the** cCa **measured by either the central or local laboratory** is < 7.5 mg/dL **(1.87 mmol/L)** or the subject experiences symptomatic hypocalcemia, in addition to the above actions, do the following:

- Suspend dosing with IP, and at the next hemodialysis session following notification of the low serum calcium result, draw a confirmatory predialysis serum cCa sample **and send to the central laboratory**.
- Obtain weekly predialysis **central laboratory** serum cCa. Once predialysis serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)** and any hypocalcemic symptoms have resolved the IVR/IWR will provide instructions to resume dosing. For the oral IP, the dose should be reduced by 25 mg or at the minimum dose of 25 mg, whichever is greater. For the IV IP, the dose should be reduced by 5 mg or at

the minimum dose of 2.5 mg, whichever is greater. Resume routine laboratory monitoring per Table 2, the Schedule of Assessments. Refer to Section 7.2 for central laboratory samples to be submitted.

An unscheduled collection of cCa from the central laboratory can be done at any time for safety. A cCa collected and measured by the local laboratory can only be done for the management of safety concerns. If the cCa measured by the local laboratory is < 7.5 mg/dL (1.87 mmol/L), IP must be suspended and can only be resumed once the cCa measured by the central laboratory is ≥ 8.3 mg/dL (2.07 mmol/L) (see Section 6.2.5).

Section: 6.2.3.3 Symptomatic Hypocalcemia

Replace

If dosing with IP is suspended for symptomatic hypocalcemia, dosing may resume at a lower dose once symptomatic hypocalcemia has resolved when the central laboratory cCa ≥ 8.3 mg/dL**,** and once the Investigator has notified the IVR/IWR.

With:

If dosing with IP is suspended for symptomatic hypocalcemia, dosing may resume at a lower dose once symptomatic hypocalcemia has resolved when the central laboratory cCa ≥ 8.3 mg/dL **(2.07 mmol/L)**, and once the Investigator has notified the IVR/IWR.

Section: 6.2.3.4 Adverse Event

Replace:

If the adverse event was deemed to be IP related by the Investigator but not related to PTH < 100 pg/mL**,** cCa < 7.5 mg/dL or symptomatic hypocalcemia, dosing with IP may resume once the adverse event has resolved or stabilized with the dose reduced.

With

If the adverse event was deemed to be IP related by the Investigator but not related to PTH < 100 pg/mL **(10.60 pmol/L)**, cCa < 7.5 mg/dL **(1.87 mmol/L)** or symptomatic hypocalcemia, dosing with IP may resume once the adverse event has resolved or stabilized **and the central laboratory serum cCa is ≥ 8.3 mg/dL (2.07 mmol/L)** with the dose reduced.

Section: 6.2.4 Resumption of Investigational Product After Repeated Missed Doses

Replace:

If more than 14 consecutive days of IP are missed (eg, extended hospitalization for an adverse event unrelated to IP, vacation), a central laboratory cCa must be obtained prior to restarting IP. Only after the cCa is ≥ 8.3 mg/dL should dosing with IP resume.

With:

If more than 14 consecutive days of IP are missed (eg, extended hospitalization for an adverse event unrelated to IP, vacation), a central laboratory cCa must be obtained prior to restarting IP. Only after the **central laboratory** cCa is ≥ 8.3 mg/dL **(2.07 mmol/L)** should dosing with IP resume.

Section: **6.2.5 cCa performed at the local laboratory**

New section added:

A cCa can only be collected and measured by the local laboratory for the management of safety concerns and/or suspension of IP. All cCa results measured by the local laboratory will be recorded on the eCRF. If the cCa is < 7.5 mg/dL (1.87 mmol/L) or the subject experiences symptomatic hypocalcemia, refer to Section 6.2.3.2 for further management. The IP can only be resumed once the cCa measured by the central laboratory is ≥ 8.3 mg/dL (2.07 mmol/L).

A local laboratory cCa and central laboratory cCa, must not be collected at the same time.

If the local laboratory cCa is < 7.5 mg/dL (1.87 mmol/L), suspend IP by registering a suspension in IVR/IWR with the reason of adverse event related to IP or symptomatic hypocalcemia depending on the clinical assessment.

Section: 6.4 Hepatotoxicity Stopping and Rechallenge Rules

Replace:

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, 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).

With:

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, 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).**Note: If the central laboratory is unable to perform the analysis of the hepatic laboratory tests (as discussed with Amgen during screening) then those tests should be measured by the local laboratory.**

Section: 6.4.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Replace:

IP should be discontinued permanently by the Investigator 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 x ULN or International Normalized Ratio (INR) > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

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

  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"

With:

IP should be discontinued permanently by the Investigator 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 x ULN or International Normalized Ratio (INR) > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

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

- **AND no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or TBL values include, but are not limited to:**
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"

Section: 6.5.6.1 Management of Elevated Serum Corrected Calcium or Symptomatic Hypercalcemia

Replace:

If a subject has 2 consecutive central laboratory cCa > 10.6 mg/dL, then doses of active vitamin D sterol, oral calcium intake, and/or dialysate calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L), unless otherwise permitted by Amgen.

If a subject has a central laboratory cCa > 11.0 mg/dL, or develops symptomatic hypercalcemia, then any active vitamin D sterol and oral calcium intake (including calcium-based phosphate binders) may be reduced or discontinued, and dialysate

calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L).

With:

If a subject has 2 consecutive central laboratory cCa > 10.6 mg/dL **(2.64 mmol/L)**, then doses of active vitamin D sterol, oral calcium intake, and/or dialysate calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L), unless otherwise permitted by Amgen.

If a subject has a central laboratory cCa > 11.0 mg/dL **(2.74 mmol/L)** or develops symptomatic hypercalcemia. then any active vitamin D sterol and oral calcium intake (including calcium-based phosphate binders) may be reduced or discontinued, and dialysate calcium concentration may be reduced based on Investigator clinical judgment; however, dialysate calcium concentration must remain ≥ 2.5 mEq/L (1.25 mmol/L).

Section: 6.5.6.2 Management of Serum Phosphorous

Replace:

- If 2 consecutive local predialysis serum P values are > 5.5 mg/dL and not amenable to modification via dietary counseling, then the dose of phosphate binder may be increased.
- If 2 consecutive local predialysis serum P values are < 3.0 mg/dL, then the dose of phosphate binder may be decreased.

With:

- If 2 consecutive local predialysis serum P values are > 5.5 mg/dL **(1.78 mmol/L)** and not amenable to modification via dietary counseling, then the dose of phosphate binder may be increased.
- If 2 consecutive local predialysis serum P values are < 3.0 mg/dL **(0.97 mmol/L)**, then the dose of phosphate binder may be decreased.

Section: 7 STUDY PROCEDURES

Replace:

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Dosing schema is provided in **Table 3**

With:

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits **unless discussed with Amgen**.

Dosing schema is provided in **Figure 1**

Section 7.1 Schedule of Assessments

Replace:

Table 2. Schedule of Assessments and Dosing Schema

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
IV investigational product administration		**Three times per week at the end of the hemodialysis session starting from day 1**																
Dose titration[b]						X				X				X				X
Informed Consent	X																	
Inclusion/Exclusion	X																	
Medical History	X																	
Demographics	X																	
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X																	
Assessment of Kt/V or URR[j]	X																	
Randomization[c]		X																
Dispensation of oral IP bottle		X				X				X				X				X
Pill count				X		X		X		X		X		X		X		X
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior to dialysis																		
ECG[f]	X																	
Serum pregnancy test[g]	X	X											X					
Hematology	X																	
Chemistry	X																	
Albumin, Ca		X	X		X		X		X		X		X		X		X	
Phosphorus		X			X				X				X				X	
PTH	X	X	X		X		X		X		X		X		X		X	
PK[h]					X								X					
25(OH)D		X																
[redacted]																		
ADA		X											X					

Footnotes defined on the next page

Table 2. Schedule of Assessments and Dosing Schema

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
After dialysis																		
Pulse and blood pressure[i]		X																
Height		X																
Weight		X																
PK (10-30 minutes postdose)[h]					X								X					

25(OH)D = 25-hydroxy vitamin D; ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted]; ECG = electrocardiogram; IP = investigational product; IV = intravenous; Kt/V = measure of dialysis adequacy; PTH = parathyroid hormone, PK = pharmacokinetic; TIW = three times per week; URR = urea reduction ratio

[a] Baseline assessments will be performed on the first day of dosing with IP (day 1). Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] The dose of IP may be increased or decreased at any time. The dose of either active IP will be titrated to target predialysis [redacted] but maintaining cCa ≥ 8.3 mg/dL. Doses of investigational product will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before dose adjustment.

[c] The first dose of IP should occur within 1 day after randomization.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Subjects should remain supine or sitting for at least 10 minutes prior to recording the screening ECG, and be supine during the ECG. The screening predialysis ECG is a single recording.

[g] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[h] PK assessments can be done at any hemodialysis session during the treatment week.

[i] Subjects must be in a supine position in a rested and calm state for at least 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

[j] Perform Kt/V or URR assessment at screening unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

With:

Table 2. Schedule of Assessments

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
IV investigational product administration		**Three times per week at the end of the hemodialysis session starting from day 1**																
Dose titration[b]						X				X				X				X
Informed Consent	X																	
Inclusion/Exclusion	X																	
Medical History	X																	
Demographics	X																	
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X																	
Assessment of Kt/V or URR[L]	X																	
Randomization[c]		X																
Dispensation of oral IP bottle		X				X				X				X				X
Pill count				X		X		X		X		X		X		X		X
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior to dialysis																		
ECG[f]	X																	
Serum pregnancy test[g]	X	X											X					
Hematology	X																	
Chemistry	X																	
Albumin, Ca[i j]		X	X		X		X		X		X		X		X		X	
Phosphorus		X			X				X				X				X	
PTH	X	X	X		X		X		X		X		X		X		X	
PK[h]					X								X					
25(OH)D		X																
[redacted]																		
ADA		X											X					

Footnotes defined on the next page

Table 2. Schedule of Assessments

		Treatment Period[a]																
Study Week	**Screening**	**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Study Day	**Day -56 to -1**	**Day 1**	**8-14**	**15-21**	**22-28**	**29-35**	**36-42**	**43-49**	**50-56**	**57-63**	**64-70**	**71-77**	**78-84**	**85-91**	**92-98**	**99-105**	**106-112**	**113-119**
After dialysis																		
Pulse and blood pressure[ik]		X																
Height		X																
Weight		X																
PK (10-30 minutes postdose)[h]					X								X					

25(OH)D = 25-hydroxy vitamin D; ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted];
ECG = electrocardiogram; IP = investigational product; **HIV = Human immunodeficiency virus,** IV = intravenous; Kt/V = measure of dialysis adequacy;
PTH = parathyroid hormone, PK = pharmacokinetic; TIW = three times per week; URR = urea reduction ratio

[a] Baseline assessments will be performed on the first day of dosing with IP (day 1). Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] The dose of IP may be increased or decreased at any time. The dose of either active IP will be titrated to target predialysis [redacted] but maintaining cCa ≥ 8.3 mg/dL **(2.07 mmol/L).** Doses of investigational product will be managed by IVR/IWR and will be based on regular measurements of serum PTH and cCa levels obtained the week before dose adjustment.

[c] The first dose of IP should occur within 1 day after randomization.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol87mmol/L)**, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Subjects should remain supine or sitting for at least 10 minutes prior to recording the screening ECG, and be supine during the ECG. The screening predialysis ECG is a single recording.

[g] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[h] PK assessments can be done at any hemodialysis session during the treatment week. **Note: Per Section 7.4.2 this will not be drawn in subjects with a known history of HIV.**

[i] **To be measured by the central laboratory**

[j] **Chemistry will also include albumin and calcium**

[k] Subjects must be in a supine position in a rested and calm state for at least 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

[L] Perform Kt/V or URR assessment at screening unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

Replace:

Table 3. Schedule of Assessments

				Treatment Period[a]							Follow-up		
Study Week (Study Day)	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[b]**	**30 days after last dose ± 3 days**	**Early Term**	**Dose Suspension**
IV investigational product administration				**Three times per week at the end of the hemodialysis session ending at week 26**									
Dose titration[c]													
Informed Consent													
Inclusion/ Exclusion													
Medical History													
Demographics													
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination											X	X	
Randomization													
Dispensation of oral IP bottle				X				X					
Pill count		X		X		X		X	X			X	
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]	X	X	X	X	X	X	X	X	X				
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status[f]									X			X	
Prior to dialysis													
ECG[g]										X		X	
Serum pregnancy test[h]							X				X	X	
Hematology											X	X	
Chemistry											X	X	
Albumin, Ca	X		X		X		X		X	X			X[d]
Phosphorus			X				X		X	X			
PTH	X		X		X		X		X	X	X	X	
PK[i]									X		X		
25(OH)D													
ADA											X	X	
After dialysis													
Pulse and blood pressure[j]										X		X	
Height													
Weight										X		X	
PK (10-30 min post dose)[i]													

Footnotes defined on the next page

ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted]; ECG = electrocardiogram; IP = investigational product; IV = intravenous; PTH = parathyroid hormone, PK = pharmacokinetic; TIW = three times per week

[a] Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] Week 27 assessments should be performed on the day of the first hemodialysis treatment after the last dose of IP.

[c] The dose of IP may be decreased at any time.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Vital status will only be appropriately ascertained by sites for subjects who early terminated the study.

[g] Subjects should remain supine or sitting for at least 10 minutes prior and be supine during the ECG. The predialysis ECG is a single recording.

[h] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[I] PK assessments can be done at any hemodialysis session during the treatment week.

[j] Subjects must be in a supine position in a rested and calm state 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

With:

Table 3 Schedule of Assessments Continued

				Treatment Period[a]							Follow-up		
Study Week (Study Day)	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[b]**	**30 days after last dose ± 3 days**	**Early Term**	**Dose Suspension**
IV investigational product administration				**Three times per week at the end of the hemodialysis session ending at week 26**									
Dose titration[c]													
Informed Consent													
Inclusion/ Exclusion													
Medical History													
Demographics													
Prior & Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination											X	X	
Randomization													
Dispensation of oral IP bottle				X				X					
Pill count		X		X		X		X	X			X	
TIW Admin of IV IP (by site staff at the end of hemodialysis)[d]	X	X	X	X	X	X	X	X	X				
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status[f]									X			X	
Prior to dialysis													
ECG[g]										X		X	
Serum pregnancy test[h]							X				X	X	
Hematology											X	X	
Chemistry											X	X	
Albumin, Ca[i,j]	X		X		X		X		X	X			X[d]
Phosphorus			X				X		X	X			
PTH	X		X		X		X		X	X	X	X	
PK[k]									**X**		X		
25(OH)D													
[redacted]													
ADA											X	X	
After dialysis													
Pulse and blood pressure[L]										X		X	
Height													
Weight										X		X	
PK (10-30 min post dose)[ik]									**X**				

Footnotes defined on the next page

ADA = antidrug antibody; [redacted]; cCa = correct calcium; Ca =calcium; [redacted]; ECG = electrocardiogram; IP = investigational product; IV = intravenous; PTH = parathyroid hormone, PK = pharmacokinetic; TIW = three times per week

[a] Assessments during the Treatment Period should be performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.

[b] Week 27 assessments should be performed on the day of the first hemodialysis treatment after the last dose of IP.

[c] The dose of IP may be decreased at any time.

[d] When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol87mmol/L),** a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended. Dose suspension samples do not need to be collected if a routine, local chemistry or albumin/calcium/P sample is obtained on the same day.

[e] After informed consent and before first dose of IP, only serious adverse events are to be reported. Subjects will be followed for both adverse events and serious adverse events for 30 days after the last dose of IP.

[f] Vital status will only be appropriately ascertained by sites for subjects who early terminated the study.

[g] Subjects should remain supine or sitting for at least 10 minutes prior and be supine during the ECG. The predialysis ECG is a single recording.

[h] Additional pregnancy tests may be performed at the discretion of the investigator or per local regulatory requirements.

[i] **o be measured by the central laboratory.**

[j] **Chemistry will also include albumin and calcium**

[k] PK assessments can be done at any hemodialysis session during the treatment week.

[L] Subjects must be in a supine position in a rested and calm state 5 minutes prior to all measurements of pulse rate and blood pressure. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

Section: 7.2.2 Re-screening

Replace:

Screening assessments may be repeated up to 2 times during the 8-week screening period. Subjects who do not meet eligibility requirements during the screening period will be permitted to be re-screened once. Screen failures more than 8 weeks after informed consent form completion require re-consent and repeat of all screening assessments. If a subject fails to meet eligibility criteria after re-screening within 8 weeks, that subject may not re-screen again and will be considered ineligible for the study.

With:

Screening assessments may be repeated up to 2 times during the 8-week screening period. Subjects who do not meet eligibility requirements during the screening period will be permitted to be re-screened once **as described in Section 5.**

Section: 7.2.3 Treatment

Replace:

Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL), screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) and country (China versus non-China). The date of the first dose of IP is defined as day 1.

With:

Randomization will be stratified by screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(< 95.40 pmol/L, ≥ 95.40 pmol/L), screening central laboratory serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) (≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non-China). The date of the first dose of IP is defined as day 1.

Section: 7.3.2 Medical History

Replace:

Detailed medical history including parathyroidectomy will be obtained at screening. Specific details on cardiovascular history will also be collected

With:

Detailed medical history including parathyroidectomy **and known human immunodeficiency syndrome (HIV) Status (yes/no)** will be obtained at screening. Specific details on cardiovascular history will also be collected.

Section: 7.4 Laboratory Assessments

Replace:

When dosing with IP is suspended for cCa < 7.5 mg/dL, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended.

With:

When dosing with IP is suspended for cCa < 7.5 mg/dL **(1.87 mmol/L)**, a predialysis serum sample for albumin and calcium should be submitted to the central laboratory on the day dosing is suspended.

Table 4. Analytes Table

Replace:

Chemistry	Hematology	Other
Sodium	Hemoglobin	Antibodies[a]
Potassium	Hematocrit	Pregnancy test
Chloride	Platelets	Intact PTH
Bicarbonate	WBC	25-hydroxyvitamin D
Total protein	RBC	[redacted]
Albumin		
Calcium		Urea[b]
Corrected calcium (calculated)		
Magnesium		
Phosphorus		
Glucose		
Total bilirubin		
Direct bilirubin		
ALP		
LDH		
AST (SGOT)		
ALT (SGPT)		

Footnotes defined on next page

ALP = serum alkaline phosphatase; ALT = alanine aminotransaminase; AST = aspartate transaminase; [redacted]; LDH = lactate dehydrogenase; PTH = parathyroid hormone; RBC = red blood cells; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; WBC = white blood cells

[a] These assays may be performed at a specialty laboratory.

[b] Urea measurement to be performed locally for Kt/V or URR assessment at screening, unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

When albumin is < 4.0 g/dL, the calcium level will be corrected according to the following formula:

$$cCa\ (mg/dL) = total\ Ca\ (mg/dL) + (4 - albumin\ [g/dL]) \times 0.8.$$

With:

Chemistry	Hematology[c]	Other
Sodium	Hemoglobin	Antibodies[a]
Potassium	Hematocrit	Pregnancy test
Chloride	Platelets	Intact PTH
Bicarbonate	WBC	25-hydroxyvitamin D
Total protein	RBC	[redacted]
Albumin		
Calcium		Urea[b]
Corrected calcium (calculated)		
Magnesium		
Phosphorus		
Glucose		
Total bilirubin[c]		
Direct bilirubin[c]		
ALP		
LDH		
AST (SGOT)[c]		
ALT (SGPT)[c]		

ALP = serum alkaline phosphatase; ALT = alanine aminotransaminase; AST = aspartate transaminase; [redacted] LDH = lactate dehydrogenase; PTH = parathyroid hormone; RBC = red blood cells; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; WBC = white blood cells

[a] These assays may be performed at a specialty laboratory.

[b] Urea measurement to be performed locally for Kt/V or URR assessment at screening, unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

[c] **If the central laboratory result is not available, local laboratory values may be used to determine eligibility, but Amgen must be contacted prior to randomization.**

When albumin is < 4.0 g/dL **(40g/L)**, the calcium level will be corrected according to the following formula:

$$cCa\ (mg/dL) = total\ Ca\ (mg/dL) + (4 - albumin\ [g/dL]) \times 0.8.$$

Section: 7.4.2 Pharmacokinetic Sampling

Replace:

Blood samples will be collected and assayed for etelcalcetide serum concentration. The PK samples will be analyzed only for those subjects assigned to etelcalcetide. PK assessments can be done at any hemodialysis session during the treatment week.

Predialysis samples will be collected at weeks 4, 12, 26, and at the 30-day Safety Follow-up visit. Post-dialysis (10 to 30 minutes post-dose) blood samples will be collected at weeks 4, and 12.

With:

Blood samples will be collected and assayed for etelcalcetide serum concentration. The PK samples will be analyzed only for those subjects assigned to etelcalcetide. PK **Subjects with a known history of HIV will not have labs drawn for PK sampling.**

Predialysis samples will be collected at weeks 4, 12, 26, and at the 30-day Safety Follow-up visit. Post-dialysis (10 to 30 minutes post-dose) blood samples will be collected at weeks 4, 12, **and 26**.

Section: 7.5 Antibody Testing Procedures

Add:

Subjects with a known history of HIV will not have labs drawn for antibody testing.

Section: 8.3.1 Reasons for Removal From Treatment

Replace:

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

- Protocol Specified Criteria
  - safety concern (eg, because of an adverse event, failure to follow contraception, breast feeding, and/or protocol requirements)
  - subject requires a significant permanent change in hemodialysis prescription to maintain adequate hemodialysis
  - subject receives a kidney transplant
  - subject undergoes a parathyroidectomy
  - Subject request
  - Death

- Lost to follow-up
- Decision by Sponsor (other than subject request, safety concern, lost to follow-up)

With:

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

- Protocol Specified Criteria
  - subject requires a significant permanent change in hemodialysis prescription to maintain adequate hemodialysis
  - subject receives a kidney transplant
  - subject undergoes a parathyroidectomy
- **Ineligibility determined**
- **Protocol deviation**
- **Noncompliance**
- Subject request
- **Adverse event**
- Death
- Lost to follow-up
- Decision by Sponsor (other than subject request, safety concern, lost to follow-up)

Section: 9.1.1 Adverse Events

Replace:

For the purpose of this study asymptomatic reductions in serum cCa below 7.5 mg/dL or asymptomatic reductions in serum cCa between 7.5 mg/dL and < 8.3 mg/dL**,** that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as “blood calcium decreased.” Symptomatic reductions in serum cCa < 8.3 mg/dL should be reported as “hypocalcemia”, and the associated signs and symptoms should also be captured.

With:

For the purpose of this study **any** asymptomatic reductions in serum cCa below 7.5 mg/dL **(1.87 mmol/L) measured by either the central laboratory or the local laboratory** or asymptomatic reductions in serum cCa between 7.5 mg/dL **(1.87 mmol/L)** and < 8.3 mg/dL **(2.07 mmol/L), measured by either the central laboratory or the local laboratory,** that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as “blood calcium decreased.”

Symptomatic reductions in serum cCa < 8.3 mg/dL **(2.07 mmol/L) measured by either the central laboratory or the local laboratory** should be reported as "hypocalcemia", and the associated signs and symptoms should also be captured.

Section: 9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Replace:

The adverse event grading scale used will be the following:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations or prolongation of current hospitalization possible
- Maximal/Life-threatening: Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or prolongation of current hospitalization or hospice care probable

With:

- Mild: **Aware of sign or symptom, but easily tolerated**
- Moderate: **Discomfort enough to cause interference with usual activity**
- Severe: **Incapacitating with inability to work or do usual activity**

Section: 9.2.3 Changes in Serum Calcium and Symptomatic Hypocalcemia

Replace:

Serum cCa levels will be analyzed by the central laboratory throughout the study, and these results will be incorporated in the clinical database. Per Section 6.2.3.2 dosing with IP will be suspended if a predialysis serum cCa < 7.5 mg/dL value is observed. A repeat serum cCa will be obtained prior to hemodialysis at the next hemodialysis session, to allow verification of the low serum cCa level. Serum cCa will continue to be monitored per protocol if IP dosing is suspended for low serum cCa. Dosing may subsequently resume when serum cCa ≥ 8.3 mg/dL and any hypocalcemic symptoms have resolved with the dose (1) reduced by 5 mg, or at the minimum dose of 2.5 mg, whichever is greater for IV IP, or (2) reduced by 25 mg, or at the minimum dose of 25 mg, whichever is greater for oral IP.

Investigators should assess subjects for the onset of signs and symptoms associated with low serum calcium (see Section 6.2.3.3) at each visit. Asymptomatic reductions in serum cCa below 7.5 mg/dL or asymptomatic reductions in serum cCa between 7.5 mg/dL **(**and < 8.3 mg/dL that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as “blood calcium decreased.”

With

Serum cCa levels will be analyzed by the central laboratory throughout the study, and these results will be incorporated in the clinical database. **The cCa measured by the local laboratory and collected for the management of safety concerns will also be incorporated in the clinical database.** Per Section 6.2.3.2 dosing with IP will be suspended if a predialysis serum cCa < 7.5 mg/dL **(1.87 mmol/L)** value **from either the central or local laboratory** is observed. A repeat **central laboratory** serum cCa will be obtained prior to hemodialysis at the next hemodialysis session, to allow verification of the low serum cCa level. **Central laboratory** serum cCa will continue to be monitored per protocol if IP dosing is suspended for low serum cCa. **Dosing** may subsequently resume when **central laboratory** serum cCa ≥ 8.3 mg/dL **(2.07 mmol/L)** and any hypocalcemic symptoms have resolved with the dose (1) reduced by 5 mg, or at the minimum dose of 2.5 mg, whichever is greater for IV IP, or (2) reduced by 25 mg, or at the minimum dose of 25 mg, whichever is greater for oral IP.

Investigators should assess subjects for the onset of signs and symptoms associated with low serum calcium (see Section 6.2.3.3) at each visit. **Any** asymptomatic reductions in serum cCa below 7.5 mg/dL **(1.87 mmol/L) from either the central or local laboratory** or asymptomatic reductions in serum cCa between 7.5 mg/dL **(1.87 mmol/L)** and < 8.3 mg/dL **(2.07 mmol/L) from either the central or local laboratory** that the investigator deems clinically significant (eg, required medical management) should be reported on the eCRF as “blood calcium decreased.”

Section: 10.1.1.3 Other Secondary Endpoints

Replace:

- Percent change from baseline in mean predialysis serum cCa during the EAP

With:

- Percent change from baseline in mean predialysis **central laboratory** serum cCa during the EAP
- Achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

Section: 10.1.1.4 Safety Endpoints

Replace:

- Incidence of cCa < 8.3 mg/dL at any time during the study
- Incidence of cCa < 8.0 mg/dL at any time during the study
- Incidence of cCa < 7.5 mg/dL at any time during the study

With:

- Incidence of cCa < 8.3 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 8.0 mg/dL **measured by the central laboratory** at any time during the study
- Incidence of cCa < 7.5 mg/dL **measured by the central laboratory** at any time during the study

Section: 10.1.1.5 Exploratory Endpoints

Replace:

Section: 10.1.2.3 cCa Completer Analysis Set

Replace:

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

With:

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

Section: 10.1.2.5 Per Protocol Analysis Set

Replace:

The Per Protocol Analysis Set (PPAS) is defined as all randomized subjects who have no major protocol violations and have at least one post-dose PTH value and had at least 16 weeks exposure of IP. Subjects in the PPAS will be analyzed according to randomized treatment assignment. PPAS will be used in the sensitivity analysis of the primary endpoint. Removed according to ICH E9R1.

With:

The Per Protocol Analysis Set (PPAS) is defined as all randomized subjects who have no major protocol violations and have at least one post-dose PTH value and had at least 16 weeks exposure of IP. Subjects in the PPAS will be analyzed according to randomized treatment assignment.

Section: 10.1.3 Covariates and Subgroups

Replace:

All analyses of primary and key secondary endpoints will be adjusted for the effect of the stratification factors of screening PTH level (< 900 pg/mL, ≥ 900 pg/mL), screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL)**,** and country (China versus non-China).

With:

All analyses of primary and key secondary endpoints will be adjusted for the effect of the stratification factors of screening PTH level (< 900 pg/mL, ≥ 900 pg/mL) **(95.40 pmol/L, ≥ 95.40 pmol/L)**, screening serum cCa (≥ 9.0 mg/dL, < 9.0 mg/dL) **(≥ 2.25 mmol/L, < 2.25 mmol/L) measured by the central laboratory**, and country (China versus non China).

Section 10.5.1 General Considerations

Replace:

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

With:

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

Section: 10.5.2 Primary Efficacy Endpoint

Replace:

The following 2 sensitivity analyses for the primary analysis on FAS will be conducted:

- PCAS: Only subjects with PTH data during the EAP are included.
- For subjects without PTH data during the EAP, the mean of the last 2 predialysis PTH values obtained after day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. A similar imputation approach as the primary analysis will be applied to subjects without a post-baseline PTH value.

In addition, a sensitivity analysis using PPAS will also be conducted using the non-inferiority null imputation method.

With:

The following sensitivity **analysis** for the primary analysis on FAS will be conducted:

- For subjects without PTH data during the EAP, the mean of the last 2 predialysis PTH values obtained after day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. A similar imputation approach as the primary analysis will be applied to subjects without a post-baseline PTH value.

In addition, **supplementary analyses will be performed for primary endpoint using PCAS and PPAS.**

Section: 10.5.3.1 Other Secondary Efficacy Endpoints

Replace:

The following secondary endpoints will be formally tested if both key secondary endpoints are statistically significant. To control the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used:

- percent change from baseline in mean predialysis serum cCa during the EAP
- achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

A repeated measures mixed effects model will be used to compare the percent change from baseline in serum cCa levels during the EAP and will include the randomization

stratification factors. The difference between treatment groups will be presented with 95% CI. The analysis will be performed on the FAS and sensitivity analysis will be performed using the cCa completer analysis set.

With:

The following secondary endpoints will be formally tested if both key secondary endpoints are statistically significant. To control the family-wise error rate, the Hochberg procedure of adjustment for multiple comparisons will be used:

- percent change from baseline in mean predialysis **central laboratory** serum cCa during the EAP
- achievement of mean predialysis serum P ≤ 4.5 mg/dL during the EAP

A repeated measures mixed effects model will be used to compare the percent change from baseline in serum cCa levels during the EAP, and will include the randomization stratification factors. The difference between treatment groups will be presented with 95% CI. The analysis will be performed on the FAS and **supplementary** analysis will be performed using the cCa completer analysis set.

Section: 10.5.4 Safety Endpoints

Replace:

Proportion of subjects (with 95% confidence interval) with the following will be presented by treatment group:

- cCa < 8.3 mg/dL
- cCa < 8.0 mg/dL
- Ca < 7.5 mg/dL treatment-emergent symptomatic hypocalcemia adverse event during the study.

With:

Proportion of subjects (with 95% confidence interval) with the following will be presented by treatment group:

- cCa < 8.3 mg/dL **measured by the central laboratory**
- cCa < 8.0 mg/dL **measured by the central laboratory**
- cCa < 7.5 mg/dL **measured by the central laboratory**
- treatment-emergent symptomatic hypocalcemia adverse event during the study **will be presented by treatment group.**

Section: 12.2 Study Monitoring and Data Collection

Remove:

- 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.

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Replace:

Grade	Amgen Standard Adverse Event Grading Scale
1	MILD: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
2	MODERATE: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required
3	SEVERE: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations or prolongation of current hospitalization possible
4	MAXIMAL/LIFE-THREATENING: Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or prolongation of current hospitalization or hospice care probable.

With:

The Amgen Standard Grading Scale as show below:

Grade	**Definition**
MILD	**Aware of sign or symptom, but easily tolerated**
MODERATE	**Discomfort enough to cause interference with usual activity**
SEVERE[a]	**Incapacitating with inability to work or do usual activity**

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Additional Clinical Assessments and Observation

Replace:

- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(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

Add:

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic. **Note: Bilirubin (total and direct), ALT, and AST should be measured by the local laboratory if the central laboratory is unable to perform the analysis.**

- 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 **plasma or** 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

Amendment 2

Protocol Title: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism

Amgen Protocol Number (Etelcalcetide) 20150238

Amendment 2 Date: 16 February 2018

Rationale:

The rationale for the major changes in the study design is provided below:

- An assessment of Kt/V or URR at screening has been added to the Schedule of Assessments to facilitate enrollment.
- Protocol language has been added indicating that Kt/V or URR is to be processed at the site's local laboratory and urea has been added to the analyte table for local Kt/V or URR assessment at screening, if necessary.

Other changes to the protocol:

- Exclusion criterion number 211 has been amended for specificity and consistency with exclusion criteria format.
- The location of the study sites has been updated to accurately reflect sites of subject enrollment.
- The description of the drug product has been updated to correctly reflect the form of etelcalcetide as a free base and to correct the pH of the drug solution.
- Clarification language has been added to indicate that both sites and subjects are to be blinded to PTH values.
- Clarification language has been added to indicate that "initial" IP dosing must start with a Monday through Friday hemodialysis treatment.
- Administrative and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: A Multicenter, Multiple-dose, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide (AMG 416) in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism

Amgen Protocol Number 20150238 (Etelcalcetide [AMG 416])

Amendment Date: 07 February 2017

Rationale:

The protocol is being amended for the following key reasons:

- Units for PTH and cCa corrected.
- Eligibility requirements clarified.
- Concomitant medication collection clarified.
- Make minor corrections and clarifications throughout, including administrative, typographical, and formatting changes.
- Remove all references to fibroblast growth factor 23 (FGF-23)