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

Amgen Protocol Number (Etelcalcetide) 20140336

EudraCT number 2015-005051-28

Clinical Study Sponsor: Amgen Inc
One Amgen Center Drive
Thousand Oaks, CA 97320-1799

Key Sponsor Contact(s): PPD, Ph.D.
Clinical Pharmacology and Medical Sciences
Tel: PPD
Email: PPD

PPD, M.D, MSc.
Medical Sciences, Medical Director
Tel: PPD
Email: PPD

PPD
Study Manager
Tel: PPD
E-mail: PPD

Date: 18 February 2016

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

Investigator's Agreement

I have read the attached protocol entitled An Open-label, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Etelcalcetide (AMG 416) in Paediatric Subjects Aged 2 to less than 18 Years with Secondary Hyperparathyroidism (sHPT) Receiving Maintenance Haemodialysis dated 18 February 2016 and agree to abide by all provisions set forth therein.

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

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

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

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

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

Study Phase: 1b

Indication: Secondary Hyperparathyroidism

Primary Objective:

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

Secondary Objective:

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

Hypotheses:

Etelcalcetide will be safe and well tolerated after a single IV dose administration in paediatric subjects with sHPT on haemodialysis.

Primary Endpoint:

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

Secondary Endpoint(s):

- Pharmacokinetic parameters (AUC, C_{max}, t_{max}, $t_{1/2}$) of etelcalcetide in plasma
- Pharmacodynamics: concentration of parathyroid hormone (PTH), serum calcium [total calcium, ionized calcium and albumin corrected calcium] over time
- Anti-etelcalcetide antibodies
- Incidence of treatment-emergent adverse events

Study Design:

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

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

Sample Size:

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

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

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

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

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

Summary of Subject Eligibility Criteria:

Subjects in this study will be age 2 to < 18 years diagnosed with CKD and sHPT and receiving maintenance haemodialysis for > 30 days prior to screening. For a full list of eligibility criteria refer to Section 4.1 and Section 4.2.

Investigational Product:

Amgen Investigational Product Dosage and Administration:

Etelcalcetide drug product is a sterile, preservative-free, aqueous solution containing 10 mg etelcalcetide free base, [redacted] mg sodium chloride and [redacted] mg succinic acid, in a single-use 3 mL glass vial. Each vial contains 2 mL of clear, colorless solution with etelcalcetide at a concentration of 5 mg/mL. The solution is ready to administer and has pH between [redacted] and [redacted]. The recommended storage condition for etelcalcetide liquid drug product is between [redacted]°C to [redacted]°C, protect from light. See Section 6.2.1 for complete details.

Procedures:

Screening

Study procedures will only be performed after informed consent has been obtained from the subject's legally acceptable representative.

Subjects will be screened within the period of Day -14 to Day -3 before dosing on Day 1. Screening procedures will include medical history, physical examination, vital signs, body height and weight, 12-lead ECG, safety laboratory testing, study PD endpoint parameters such as serum PTH, serum calcium (total calcium, albumin corrected calcium and ionized calcium) and serum phosphorus.

Treatment Period

Subjects will return to the clinical research unit on Day -2 for vital signs, body weight, 12-lead ECG and safety laboratory testing.

On Day 1 following haemodialysis, subjects will receive a single IV bolus of 0.035 mg/kg of etelcalcetide during the rinse back. Subjects may leave the clinic following the collection of the 4 hour post dose PK sample.

Subjects will return for outpatient visits per the schedule of assessments on Day 3, 5 (or 6, depending on day of study start), 8 and 10.

End of study assessments will be conducted on Day 30 and will include clinical lab testing, physical examination, vital signs, adverse event assessment, body weight, 12-lead ECG, and antibody and PK sampling.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

Statistical Considerations:

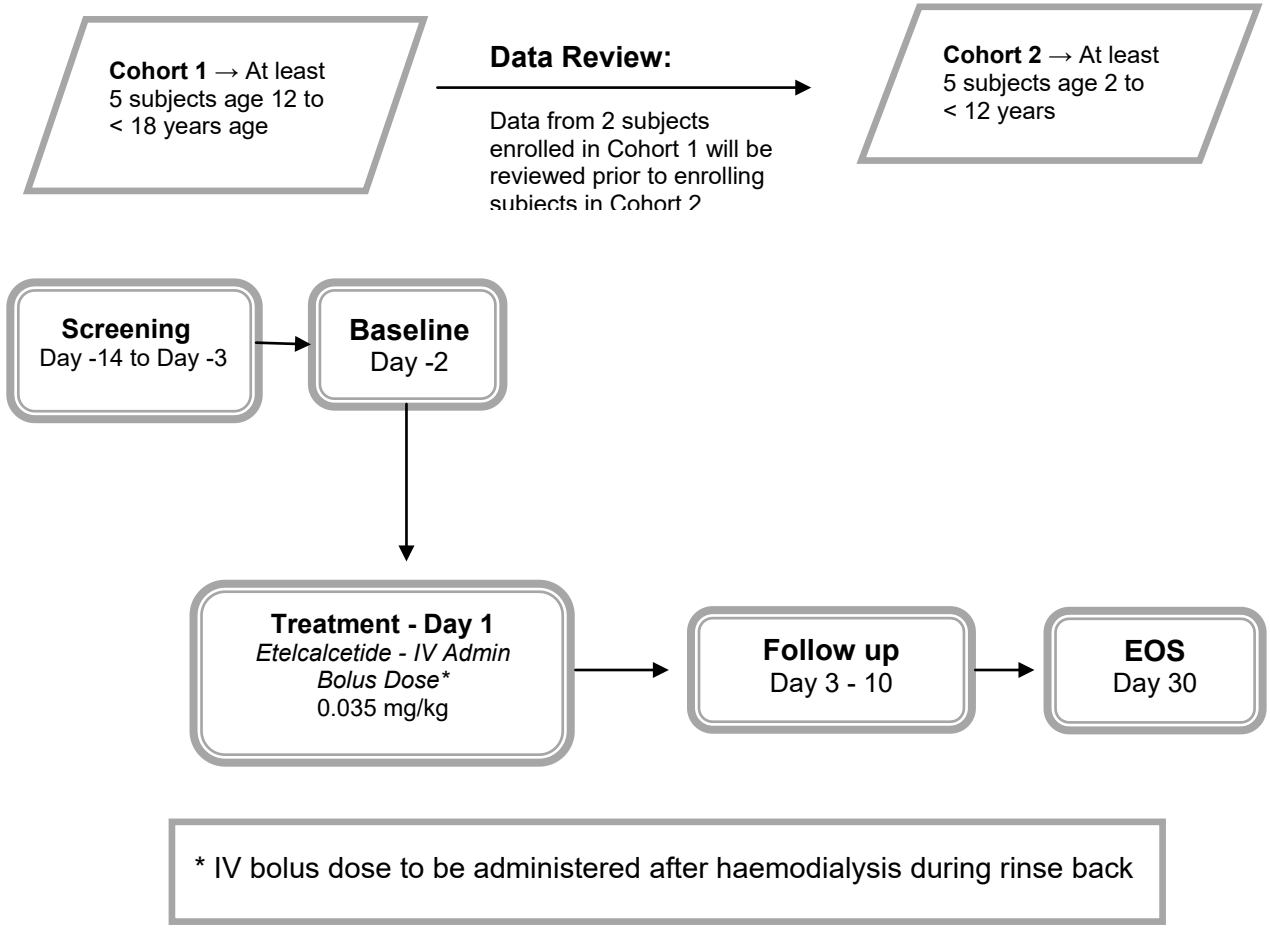
Descriptive statistics will be provided for selected demographics, safety data, PK and PD data for all subjects. Descriptive statistics on continuous measurements will include number of observations, means, medians, first and third quartiles, standard deviations or standard error, and minimum and maximum, while categorical data will be summarized using frequency counts and percentages.

No formal statistical testing will be performed.

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

Sponsor: See Protocol Title Page

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
Term:	
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
end of study 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
end of study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
end of study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
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
Abbreviation:	
ANC	absolute neutrophil count
API	Active pharmaceutical agent
ALT	alanine aminotransferase
AUC	area under the curve for plasma etelcalcetide
CaSR	calcium sensing receptor
cCa	albumin-corrected calcium
CKD	chronic kidney disease
C_{max}	maximum plasma etelcalcetide concentration
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
EAP	efficacy assessment phase
ECG	electrocardiogram
EMA	European Medicines Agency

Abbreviation or Term	Definition/Explanation
ESRD	end stage renal disease
EU	European Union
iCa	ionized calcium
ICF	informed consent form
IUD	intrauterine device
LAR	legally authorized representative
IV	intravenous
NAPRTS	North American Pediatric Renal Trials and Collaborative Studies group
PD	pharmacodynamic
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PTH	parathyroid hormone
QTc	corrected QT interval
QTb	Bazett corrected QT interval
sHPT	secondary hyperparathyroidism
$t_{1/2}$	half-life of plasma etelcalcetide
TBIL	total bilirubin
TIW	three times a week
T_{max}	time to Cmax
USRDS	United States Renal Data System

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

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

1.2 Secondary

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

2. BACKGROUND AND RATIONALE

2.1 Disease

Data from the United States Renal Data System (USRDS) reveals that in 2007, there were approximately 1,000 incident and 2,000 prevalent paediatric (0 to 19 years old) patients in the United States with chronic kidney disease (CKD) requiring maintenance dialysis, including haemodialysis and peritoneal dialysis (USRDS, 2009). The mortality rate in children receiving dialysis is 30 to 150 times greater than that of the general paediatric population (USRDS, 2009; McDonald, 2004).

Secondary hyperparathyroidism (sHPT) develops relatively early in the course of CKD as a corrective response to metabolic disturbances resulting from declining kidney function. These disturbances include hypocalcemia, reduced renal synthesis of 1,25-dihydroxy vitamin D, phosphate retention and skeletal resistance to the calcemic action of iPTH (Martinez, 1997). The prevalence and severity of secondary HPT increases as CKD progresses toward end stage and is ubiquitous among patients receiving dialysis therapy. The disordered mineral metabolism that characterizes established secondary HPT is caused not only by renal failure itself but also exacerbated by parathyroid gland hyperplasia and by therapies directed toward treatment of secondary HPT.

Once on dialysis, traditional therapies for secondary HPT (vitamin D [1,25(OH)2D3 and analogs] and phosphate binders) may be inadequate for disease control. While vitamin D derivatives reduce iPTH concentrations, these agents can lead to hyperphosphatemia and relative hypercalcemia due to enhanced gastrointestinal absorption of these divalent ions. Unfortunately, the limitations of traditional therapy for secondary HPT appear to manifest in the paediatric as well as the adult dialysis population. A recent survey conducted among 18 sites belonging to the North American Paediatric Renal Trials and

Collaborative Studies group (NAPRTCS, unpublished data), included data from 320 paediatric haemodialysis and peritoneal dialysis patients, between the ages of 2 to less than 18. The results show that overall, 49% of the paediatric dialysis population has iPTH levels above 300 pg/mL, the upper limit recommended by the National Kidney Foundation NKF K/DOQI guidelines for all paediatric age groups (NKF K/DOQI, 2005). In addition, similar to what is observed in the adult population, this survey revealed inadequate control of other biochemical parameters of secondary HPT in the paediatric dialysis population, including Ca x P. Specifically, 18% of paediatric dialysis patients between the ages of 2 to less than 18 years old display Ca x P above the NK -K/DOQI guidelines (NKF K/DOQI, 2005) recommended target for that age group of < 65 mg^2/dL^2. The prevalence of elevated Ca x P appears to increase with increasing age, as shown by the survey results, where 22% of children between the ages of 6 to less than 12 years old, and 44% of the population from 12 years to less than 18 years old were above the NKF K/DOQI recommended age-group specific target for Ca x P of < 65 and < 55 mg^2/dL^2, respectively. Finally, simultaneous achievement of target concentrations for the 2 biochemical parameters (iPTH and Ca x P) recommended by the NKF K/DOQI (NKF K/DOQI, 2005) guidelines was infrequent across all age groups: 5% for 2 years to less than 6 years old, 16% for 6 years to less than 12 years old, and 9% for 12 years to less than 18 years old.

Failure to achieve NKF K/DOQI biochemical targets for the treatment of secondary HPT is associated with substantial adverse clinical consequence. The clinical outcome most frequently associated with secondary HPT is the development of high-turnover bone disease which results in reduced bone mass and increases the risk of bone deformities and fractures in adults and children with advanced CKD (Cundy, 1985; Spasovski, 2003; Coen, 1996; Sanchez, 2003; Salusky, 1987; Slatopolsky, 1999). In addition, secondary HPT may contribute to growth retardation, which has been linked to uncontrolled SHPT (Chesney, 2006) and also to over-suppression of iPTH with vitamin D in children with CKD, particularly those on dialysis (Kuizon, 1999). It has been suggested that normal growth velocity in this population can be promoted by minimizing renal osteodystrophy through the optimal control of iPTH levels (Waller, 2003), and by treatment with recombinant human growth hormone in an effort to correct disturbances in pulsatile secretion of growth hormone as well as to overcome peripheral growth hormone resistance (Kari, 2005; Tonshoff, 2005). Beyond the classical skeletal complications of secondary HPT, epidemiological data demonstrate that secondary HPT is a risk factor for mortality and cardiovascular morbidity (Moe, 2006; Melamed, 2006). This may be

due to promotion of vascular calcification by disordered mineral metabolism which in turn may lead to increased arterial stiffness and left ventricular hypertrophy (Abdelfatah, 2001; Klassen, 2002). While most available data describing the mortality and cardiovascular morbidity risk associated with secondary HPT are derived from the adult ESRD population, studies have shown that young adults with ESRD and childhood-onset CKD also display a high incidence of cardiovascular complications (Cheung et al, 2000; Oh et al, 2002). Indeed the youngest members of the adult dialysis population (between the ages of 25 and 34 years), many of whom began dialysis as children, have an annual cardiovascular mortality risk that is similar to that of the oldest members of the general population (above 75 years of age) (Foley et al, 1998).

It is currently estimated that 60% to 80% of the paediatric dialysis population receives treatment for secondary HPT with vitamin D (USRDS, 2009; NAPRTCS, 2006). The burden of complications of secondary HPT in the paediatric dialysis population and limitations of current therapy underscore the need for better treatments for secondary HPT in these patients, with a goal of simultaneously improving serum iPTH, calcium, phosphorus, and Ca x P concentration.

2.2 Amgen Investigational Product Background

Etelcalcetide (AMG 416, formerly KAI 4169) is a synthetic peptide with a molecular weight of 1048 Da, comprised of 7 D-amino-acid backbone and one L-cysteine. It is an allosteric activator of the calcium sensing receptor (CaSR) intended for the treatment of secondary HPT in CKD patients receiving haemodialysis. Etelcalcetide is the only calcimimetic formulated for IV administration and is administered TIW (three times a week) as a bolus dose at the end of the haemodialysis treatment during rinse back such that no additional invasive injection is needed. In the context of expected clinical use, dose levels of etelcalcetide are adjusted individually based on PTH and serum calcium levels.

Refer to the Etelcalcetide Investigator's Brochure for additional information.

2.2.1 Clinical Experience

In total, more than 1700 adult subjects from 14 clinical studies have received etelcalcetide. Etelcalcetide has been studied in two phase 3 placebo-controlled studies (Studies 20120229 and 20120230) in adult populations. In Study 20120229, 74.0% of etelcalcetide treated subjects achieved the primary endpoint of at least 30% reduction from baseline in mean PTH during Efficacy Assessment Phase (EAP) versus 8.3% of placebo subjects ($p < 0.001$). In Study 20120230, 75.3% of etelcalcetide treated

subjects achieved this endpoint versus 9.6% of placebo subjects ($p < 0.001$). Consistent with the primary endpoint, all secondary endpoints (proportion of subjects with predialysis mean PTH ≤ 300 pg/mL during the EAP, percent change from baseline in predialysis PTH, cCa, cCaXP, and P during the EAP) evaluated in Studies 20120229 and 20120230 achieved statistical significance after adjusting for multiplicity. The primary and secondary endpoints collectively demonstrated the efficacy of etelcalcetide. Refer to the Etelcalcetide Investigator's Brochure for additional information.

In a head-to-head phase 3 study with cinacalcet (Study 20120360), etelcalcetide was demonstrated to be non-inferior to cinacalcet for achievement of > 30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP). Etelcalcetide was also superior to cinacalcet for this endpoint (68.2% AMG 416 versus 57.7% cinacalcet, $p = 0.004$). A greater proportion of subjects randomized to the etelcalcetide group achieved > 50% reduction from baseline in mean PTH during the EAP compared with subjects in the cinacalcet group (52.4% etelcalcetide versus 40.2% cinacalcet; $p = 0.001$).

Etelcalcetide was generally well-tolerated. Most of the risks characterized for etelcalcetide are related to its mechanism of action as a calcimimetic and are consistent with the known safety profile of cinacalcet. The most important risk of etelcalcetide is hypocalcemia and associated events that may occur secondary to reductions in serum calcium.

2.2.2 Clinical Pharmacokinetics

In the adult population, the pharmacokinetics of etelcalcetide are linear and does not change over time following single (5 to 60 mg) and multiple IV doses (2.5 to 20 mg) in CKD patients with secondary HPT requiring haemodialysis. Etelcalcetide exhibited tri-exponential decay following IV administration. Following three times a week IV dosing at the end of each 3 to 4 hour haemodialysis session in adult CKD patients, etelcalcetide plasma levels reached near steady-state after 4 weeks of dosing with an observed accumulation ratio of 2- to 3-fold, and the effective half-life was 3 to 5 days when dosed three times a week following hemodialysis. Etelcalcetide is rapidly cleared in patients with normal renal function, while haemodialysis is the predominant elimination pathway in CKD patients requiring haemodialysis.

Etelcalcetide is not metabolized by CYP450 enzymes. Etelcalcetide is predominately bound to plasma albumin by reversible covalent binding. In adult CKD patients requiring haemodialysis, etelcalcetide was predominantly eliminated by haemodialysis.

2.3 Paediatric Risk Assessment

The purpose of this study is to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamics of a single dose IV administration of etelcalcetide in paediatric subjects receiving haemodialysis. A dose of 0.035 mg/kg etelcalcetide will be given IV in paediatric subjects aged 2 to less than 18 years old. This weight based dose corresponds to a 2.5 mg dose for a 70 kg individual which is half of the 5 mg starting dose given to adult subjects. The 2.5 mg dose was the lowest dose studied in adult subjects on haemodialysis.

Amgen anticipates minimal risk with no prospect of direct benefit to the paediatric subject after a single dose. The study is likely to yield generalizable knowledge about safety, PK and PD characteristics of etelcalcetide in paediatric subjects with sHPT receiving maintenance haemodialysis. Although no previous studies have been conducted in paediatric patients, a favorable risk-benefit profile of etelcalcetide was demonstrated during a clinical development program in the adult population where more than 1700 subjects received at least one dose of the drug with approximately 499 patients having received etelcalcetide for > 12 months. In clinical studies, administration of etelcalcetide resulted in statistically significant and clinically relevant reductions in PTH, including in difficult to manage subgroups of patients, such as those with baseline PTH > 1000 pg/mL. Reductions in serum calcium and serum phosphorus secondary to PTH reduction were also observed, consistent with the pharmacologic action of a calcimimetic. The most important risk of etelcalcetide is hypocalcemia and associated events that can occur secondary to reductions in serum calcium (such as QTc prolongation, ventricular arrhythmia and convulsions).

Please refer to the Etelcalcetide Investigator's Brochure, section 7 for a description of known and additional potential risks based on experience with etelcalcetide in the adult population.

2.4 Rationale

This study is being carried out to fulfill Amgen's commitment to the etelcalcetide Paediatric Investigation Plan (PIP) agreed with the European Medicines Agency (EMA) Paediatric Committee (PDCO) in accordance with the Paediatric Regulation (Regulation (EC) No 1901/2006) in the EU (EMEA-001554-PIP01-13, decision dated 01 Oct 2014). This phase 1 study is intended to investigate the safety, tolerability, PK and PD characteristics of etelcalcetide after a single dose administration in paediatric population that may represent a safe starting dose for this titratable drug. The dose of 0.035 mg/kg

selected for this study corresponds to a 2.5 mg dose for a 70 kg individual which is half of the 5 mg starting dose given to adult subjects. The 2.5 mg dose was the lowest dose studied in adult subjects on haemodialysis.

2.5 Clinical Hypotheses

Etelcalcetide will be safe and well tolerated after a single IV dose administration in paediatric subjects with sHPT on maintenance haemodialysis.

3. EXPERIMENTAL PLAN

3.1 Study Design

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

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

Subjects will be enrolled at approximately 15 sites. Recruitment will be competitive across sites.

3.3 Number of Subjects

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

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

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

3.4 Replacement of Subjects

Subjects who are withdrawn from the study may be replaced at the discretion of the investigator in consultation with Amgen.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The estimated study duration is 6 weeks, which includes up to a 14 day screening period and 30 days on study.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis. Subjects with clinically significant adverse events at the end of study will be followed until resolution of the adverse event or until it is considered clinically stable.

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).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained from the subject's legally acceptable representative (LAR) (see Section 11.1).

In addition to written informed consent from a legally acceptable representative, the assent of the child must also be obtained as appropriate to the age of the subject and/or based on local regulations.

4.1 Inclusion Criteria

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

102 Male or female subjects (aged 2 to less than 18 years) diagnosed with CKD and sHPT and receiving maintenance haemodialysis or haemodiafiltration for > 30 days prior to screening.

103 Subject must be on a dialysate calcium concentration of ≥ 2.5 mEq/L (1.25 mmol/L) for at least 1 month prior to enrollment and throughout the duration of the study.

104 Screening and Baseline serum PTH level > 200 pg/mL (21 pmol/L).

105 Subject must weigh ≥ 7 kg at Baseline (Day -2).

106 Screening and Baseline serum corrected calcium from the local laboratory ≥ 9 mg/dL (2.25 mmol/L).

107 Subjects on anti-convulsant medication must be on a stable dose for 3 months.

108 Free of any disease or condition other than those diseases or conditions related to their renal disease that, in the opinion of the investigator, would impact the subject's safety or the integrity of the study data.

4.2 Exclusion Criteria

201 Currently receiving or has received any investigational drug (or is currently using an investigational device) within the 30 days or 5 half-lives (whichever is longer), prior to receiving the first dose of etelcalcetide. Other investigational procedures while participating in this study are excluded.

202 Subject previously has entered this study or previously exposed to etelcalcetide.

203 All herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of etelcalcetide, and continuing use if applicable, will be reviewed by the Principal Investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation.

204 Use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer) prior to receiving the first dose of etelcalcetide that are not established therapies for subjects with renal disease or other conditions secondary to renal disease will be reviewed by the Principal Investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation. Paracetamol (up to 2 g per day) for analgesia will be allowed.

205 Malignancy except non-melanoma skin cancers,within the last 5 years.

206 History of hypersensitivity or allergic reaction to any of the excipients listed in Section 6.2.1.

207 Subject received cinacalcet therapy within less than 30 days prior to etelcalcetide dosing.

208 A new onset of seizure or worsening of a pre-existing seizure disorder within 2 months prior to etelcalcetide administration.

209 Subject's screening 12-lead ECG suggests unstable arrhythmia or other cardiac abnormality that could place the subject at increased risk, based upon the Investigator's opinion.

210 History of prolongation of the QT interval (eg, congenital long QT interval, second or third degree heart block or other conditions which prolong the QT interval) or history of ventricular arrhythmias.

211 Concurrent or within 28 days prior to enrollment use of medications that prolong QT interval (eg, sotalol, amiodarone, erythromycin, or clarithromycin). Please refer to the complete QT prolongation medication list at http://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf

212 Subjects with a corrected QT Interval (QTc) > 500 ms during screening, using Bazett's formula.

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

214 Subject has a screening ALT or AST from the local lab ≥ 1.5 times the upper limit of normal (ULN).

215 Female subjects of childbearing potential who are unwilling to practice true sexual abstinence or use an acceptable method(s) of effective birth control during treatment through 3 months after receiving the etelcalcetide. Female subjects are considered of childbearing potential following menarche. Female subjects who have reached puberty must receive pregnancy prevention (sexual) counseling and be advised of the risk to the fetus if they become pregnant during treatment and for an additional 3 months after receiving the study drug. Acceptable methods of effective birth control include True sexual abstinence (The reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.); Hormonal (Combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route); Intrauterine device (IUD); Intrauterine hormonal-releasing system (IUS); Two barrier methods (one by each partner) and the female partner must use spermicide with the barrier method [the male must use a condom (latex or other synthetic material) and the female may select either a diaphragm, 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.

216 Post-menarchal subject who is pregnant or breastfeeding, or is planning to become pregnant or breastfeed during treatment and for an additional 3 months after etelcalcetide administration. Female subjects with a positive pregnancy test at screening.

217 Subject likely to not be 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.

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). The subject's legally acceptable representatives (LAR) must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

Adverse Events are to be collected for a subject once they have received the dose of investigational product (IP). A subject is considered enrolled once they have met all eligibility criteria based on screening and Day -2 (Baseline Visit) assessments.

Provided all eligibility criteria have been met, subjects will be asked to return to the research facility for admission on Day -2 (Baseline Visit) where additional assessments will be performed to confirm that the subject remains eligible for the study. If subject

eligibility is confirmed, the subject will be assigned to Cohort 1 or Cohort 2 based on the subject's age at screening:

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

Cumulative data from 2 subjects enrolled in Cohort 1 will be reviewed prior to enrolling subjects in Cohort 2 (see section 6.2.1).

The investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment CRF.

Each subject who enters into the screening period for the study (defined as when the LAR signs the informed consent) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. 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. Subjects may be rescreened at the discretion of the investigator in consultation with the Amgen Medical Monitor.

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.

6. TREATMENT PROCEDURES

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

The Amgen Investigational Product(s) used in this study include: Etelcalcetide.

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

6.2 Investigational Product

All investigational product(s) will be administered at the research facility by a qualified staff member.

A physician must be available at the time of administration of Investigational Product.

6.2.1 Amgen Investigational Product Etelcalcetide (AMG 416)

Etelcalcetide drug product will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The active

pharmaceutical ingredient (API) is an eight-amino acid synthetic peptide prepared as a hydrochloride salt.

Etelcalcetide drug product will be presented as a sterile, preservative-free, aqueous solution containing 10 mg etelcalcetide free base, CC mg sodium chloride and CC mg 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 CCI and CCI. The recommended storage condition for etelcalcetide liquid drug product is between C°C to C°C, protect from light.

6.2.1.1 Dosage, Administration, and Schedule

Prior to administration of study drug, a pharmacist, pharmacy technician, or other appropriately qualified staff member, other than the staff member who prepared the dose, will check the dosing preparation to ensure the correct investigational product has been used, the dose level is correct and the investigational product is within expiration date. An Amgen monitor may also be present to ensure study drug is prepared according to the protocol.

Etelcalcetide will be administered at the research facility by a qualified staff member, under the supervision of a licensed physician. The date, time, administered volume, concentration (as applicable) and lot number of the investigational product will be recorded in the subject records and on the individual subject's electronic case report form (CRF).

A single dose of etelcalcetide is to be administered by IV bolus administration at 0.035 mg/kg given into the venous line of the dialysis circuit at the end of haemodialysis session. Etelcalcetide will be administered during rinse back to ensure the investigational product reaches the systemic circulation.

Overdosage of etelcalcetide may lead to hypocalcemia with or without clinical symptoms and may require treatment (see Warnings and Precautions, Etelcalcetide Investigator's Brochure). No cases of overdose were reported in two pivotal double-blind placebo-controlled Phase 3 clinical trials.

While etelcalcetide is dialyzable, haemodialysis has not been studied as a treatment for overdosage.

6.2.1.2 Safety Monitoring and Data Review

The investigator will be responsible for routine monitoring of subject safety during the study and any follow-up period necessary for events requiring continued monitoring

beyond end of study. The Amgen Medical Monitor and Amgen Global Safety Officer (GSO) or designee will review each subject's cumulative safety data through end of study on an ongoing basis.

Additionally, after end of study visits have been completed for 2 subjects enrolled in Cohort 1, cumulative study data will be reviewed by a team composed of the Investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designee and additional members as needed (eg, Amgen Clinical Research Study Manager (CRSM), Biostatistician, PK Scientist, etc.). The voting members include the Principal Investigator or designee, Amgen Medical Monitor, and Amgen Global Safety Officer or designee. All available study data, including demographics, IP administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory and PK results will be reviewed. Data review will not require that all queries be resolved or source verified. Cohort 2 will open for enrollment when the dose has been found to be reasonably tolerated based on available study data for at least 2 subjects enrolled in Cohort 1 and upon unanimous decision by the review committee. Based on emerging safety and PK data, the review committee may make other decisions (eg,. lower the dose level, enroll additional subjects in Cohort 1, etc.). All decisions will be documented in meeting minutes.

6.2.2 Cohort Stopping Rules

Dosing within the cohort will be stopped if suspected treatment-related AEs or changes in vital signs, ECGs or clinical laboratory results are observed and pose a significant health risk to the subject. In addition, dosing within the cohort will be stopped for any occurrence of the following:

- suspected treatment-related Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Grade 2 adverse events in 2 or more subjects; or
- 2 separate, suspected treatment-related CTCAE v4.0 Grade 2 adverse events in a single subject;

or

- suspected treatment-related CTCAE v4.0 Grade 3 or greater adverse event in a single subject or
- suspected treatment-related serious adverse event (SAE) in a single subject

The review team will be convened, and the event and all relevant safety data will be reviewed for evidence of relationship to treatment and clinical or medical significance.

Dosing of additional subjects in the cohort may only be resumed upon unanimous vote by the Investigator(s), Amgen Medical Monitor, and Amgen GSO.

The review of safety data and dosing decisions will be documented in meeting minutes. Amgen will issue a written notification of the dosing decision to the Investigator(s).

6.3 Criteria for Additional Safety Assessment due to Potential Hepatotoxicity

Subjects should be followed according to the recommendations in Appendix B (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- 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

- TBIL > 2x upper limit of normal (ULN) or INR > 1.5

AND

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

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

An attempt should be made not to change the subjects' treatment during the course of the study as long as, in the judgment of the investigator, the subjects' safety is not jeopardized. All use of concomitant medications and supplements will be recorded on the applicable CRF. Concomitant therapies are to be collected from informed consent through the end of safety follow-up period. Collect therapy name, indication, dose, unit, frequency, route, and start date and stop date.

In cases of symptomatic hypocalcemia or if the serum calcium level is less than 7.5 mg/dL (1.875 mmol/L), oral or IV calcium will be administered as necessary.

All herbal supplements, vitamins, and nutritional supplements taken within the last 30 days prior to dosing on Day 1 (and continued use, if appropriate) must be reviewed and approved by the Principal Investigator and Amgen Medical Monitor.

6.5 Other Treatment Procedures - Haemodialysis

Haemodialysis information - including date(s), mode of dialysis, start and stop times - and the dialysate (amount of calcium and potassium) must be captured in the subject's chart and reported on the appropriate case report form.

6.6 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 investigational product.

Any product complaint(s) associated with etelcalcetide supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.7 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Treatment with cinacalcet is prohibited within 30 days prior to receiving etelcalcetide and for the duration of the study. Use of any medications that prolong QT interval (eg, sotalol, amiodarone, erythromycin, or clarithromycin) within 28 days prior to receiving

etelcalcetide and for the duration of the study is prohibited. Please refer to the complete QT prolongation medication list at http://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf. These excluded therapies and procedures will not be allowed during the study unless necessitated in order to maintain subject safety.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

	Screening	Baseline		Treatment		Follow up				EOS
Study Day	**-14 to -3**	**-2**		**1**		**3**	**5[a]**	**8**	**10**	**30**
Study Time			**0**	**10 min**	**4 hour**					
General and Safety Assessments										
Informed consent	X									
Medical history	X									
Weight (kg)	X	X								X
Height (cm)	X									
Vital signs (BP, HR, Temp)	X	X								X
Physical examination	X									X
12-lead ECG	X	X								X
Serious adverse events	X----------									----------X
Adverse Events				X----------						----------X
Concomitant medications	X----------									----------X
Dosing										
Etelcalcetide administration[b]			X							
Laboratory Assessments										
Clinical chemistry	X									X
Hematology	X									X
Ionized Ca, Serum albumin, Serum cCa[c, d]	X	X			X	X		X	X	X
Serum PTH[c]	X	X			X	X		X	X	X
Serum pregnancy test (females of child bearing potential only)[e]	X									
Pharmacokinetic and Other Blood Samples										
Etelcalcetide PK plasma collection[c, f]				X	X	X[f]	X	X	X	X
Antibody sample collection[g]		X								X

Footnotes defined on next page of table

cCa = albumin-corrected calcium; EOS = End of Study; iCa = ionized calcium; HD = haemodialysis; IV = intravenous

[a.] Subjects will continue to receive HD per their regular schedule (Day -2, 1, 3, 5 [or Day 6 depending on the day of the week the study begins], 8 and 10).
[b.] On Day 1, etelcalcetide will be administered as an IV bolus dose after HD during rinse back.
[c.] All procedures (except those scheduled on Day 1 at time 0, 10 min and 4 hour and Day 3 post-HD) will be performed prior to HD on the respective study day.
[d.] Serum samples for albumin and calcium for screening and routine monitoring of pre-HD cCa. When albumin is less than 4.0 mg/dL, the calcium level will be corrected according to the formula: cCa (mg/dL) = total Ca (mg/dL) + (4 – albumin (g/dL))*0.8.
[e.] Pregnancy tests will be performed in female subjects of child-bearing potential within 7 days prior to start of investigational product.
[f.] PK plasma collection pre-HD and post-HD on Day 3
[g.] Subjects with positive titers for antibodies to etelcalcetide at EOS may be asked to return to the clinical research unit to provide additional serum samples.

7.2 General Study Procedures

During the study, every effort should be made to perform the study procedures as indicated in the Schedule of Assessments (Table 1, Section 7.1). Study visits should coincide with the subject's haemodialysis (HD) schedule. Unless otherwise noted all procedures should be performed prior to HD (pre-HD). Depending on the day of the week that each subject begins the study (Day 1), Day 5 assessments may be performed on Day 6 to align with the subject's HD schedule.

Throughout the study, the permitted time windows for scheduled assessments will be as follows:

- ± 15 minutes for events on Day 1
- ± 30 minutes for Day 3 through 10
- +1 day for Day 5
- + 3 days for Day 30 (EOS)

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

Key assessments are described in the subsections below.

7.2.1 Informed Consent

Before any study-specific procedure, the appropriate written informed consent must be obtained from the subject's legally acceptable representative.

7.2.2 Screening

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 1) (Section 7.1).

- Confirmation that the Informed Consent Form and Assent form (as applicable) have been signed
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety
- Physical Examination as per standard of care (including medical/surgical history)
- Height and Weight
- Vital signs (eg, blood pressure, heart rate, temperature) (pre-HD)
- 12-Lead ECG (pre-HD)
- Laboratory assessments (pre-HD)
- Serious Adverse Event reporting
- Documentation of concomitant medications

If a subject is rescreened, a new informed consent form must be signed unless it has been **< 30 days** since the previous ICF signature was obtained.

7.2.3 Baseline

Two days before dosing (Day -2) eligible subjects will return to the research center for testing to confirm final eligibility and to establish baseline assessments prior to dosing.

The following procedures will be completed at baseline and at time points designated in the Schedule of Assessments (Table 1) (Section 7.1).

- Weight
- Vital signs (eg, blood pressure, heart rate, temperature) (pre-HD)
- 12-Lead ECG (pre-HD)
- Laboratory assessments (pre-HD)
- Anti-etelcalcetide antibody collection (pre-HD)
- Serious Adverse Event reporting
- Documentation of concomitant medications

After the investigator has confirmed eligibility based on screening and Day -2 assessments, the subject will be enrolled to Cohort 1 or Cohort 2 based on the subject's age.

7.2.4 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 1). On Day 1 etelcalcetide is to be administered after the completion of all required pre-dose assessments and after HD, during rinse back. Subjects will remain in the clinical research unit for observation until the 4 hour PK sample is collected.

- Etelcalcetide administration
- PK (10 min and 4 hour post dose)
- Laboratory assessments (pre-HD)
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

7.2.5 Safety Follow-up Visit(s)

Safety follow up visits will occur on Day 3, 5 or 6 (depending on study start day), 8 and 10. The following procedures will be completed at the safety follow-up visits according to the Schedule of Assessments (Table 1).

- PK assessments (pre-HD and post-HD on Day 3; pre-HD on Day 5 or 6, Day 8 & Day 10)
- Laboratory Assessments (pre-HD)
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

7.2.6 End of Study Visit

The end of study visit will occur on Day 30. The following procedures will be completed at the safety follow-up visits according to the Schedule of Assessments (Table 1).

- Physical Examination as per standard of care
- Weight
- Vital signs (eg, blood pressure, heart rate, temperature) (pre-HD)
- 12-Lead ECG (pre-HD)
- PK assessments (pre-HD)
- Laboratory Assessments (pre-HD)
- Anti-etelcalcetide antibody collection (pre-HD)
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

7.2.7 Medical History

The investigator or qualified designee will obtain a complete medical history at screening and within 14 days prior to enrollment of a study subject. Medical history will include the subject's history of chronic kidney disease and secondary hyperparathyroidism. Relevant medical history findings will be recorded in the subject's source document and on the appropriate CRF. Any unresolved medical history will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A).

7.2.8 Vital Signs

Vital signs, including systolic/diastolic blood pressure, heart rate, and temperature will be recorded by the investigator or qualified designee at the time points specified in the Schedule of Assessments (Table 1). All measurements will be obtained prior to hemodialysis.

Subjects must be in a supine position for at least 5 minutes prior to vital signs measurements. Abnormal measurements may be repeated (upon investigator discretion) and must be reported on the CRF. When vital signs and blood sample

collection occur at the same time, vital signs should be performed before blood samples are drawn. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study.

Record all measurements on the vital signs CRF.

7.2.9 Physical Examination

A physical examination will be performed by the investigator or designated physician at the time points specified in the Schedule of Assessments.

Abnormal findings found during screening will be reported on the medical history page of the CRF. Any abnormal findings or worsening findings found after the subject has received etelcalcetide will be reported on the Event CRF.

7.2.10 Electrocardiograms

Subject must be in supine position in a rested and calm state for at least 5 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. All measurements will be obtained prior to hemodialysis.

A single 12-lead ECG will be performed at timepoints designated in the Schedule of Assessments (Table 1). Data will be reported on the CRF. The ECG must include the following measurements: Heart Rate, QRS, QTc, and PR intervals.

The PI 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.

7.2.11 Clinical Laboratory Safety Assessments

Blood sampling (not to exceed 5.6 mL) for safety laboratory testing will be conducted at time points designated in the Schedule of Assessments. Results will be reported on the CRF. Table 2 below outlines the panel of analytes required for safety laboratory testing.

Table 2. List of Analytes

Chemistry	Hematology
Sodium	Hemoglobin
Potassium	Hematocrit
Chloride	Mean corpuscular volume
Bicarbonate (HCO3)	Platelets
Total protein	White blood cell differentials
Albumin	• Total neutrophils
Calcium[a]	• Eosinophils
PTH	• Basophils
Magnesium	• Lymphocytes
Phosphorus	
Blood urea nitrogen (BUN)	
Creatinine	
Uric Acid	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase	
Alanine aminotransferase (ALT) (SGPT)	
Aspartate aminotransferase (AST) (SGOT)	

[a]To include total calcium, albumin-corrected calcium, and ionized calcium

7.2.12 Pharmacodynamic Measurements

Measurements of serum calcium (total calcium, albumin corrected calcium and ionized calcium) and PTH determinations will be collected at time points designated in the Schedule of Assessments (Table 1).

The calcium level determinations described in this section are derived from the samples drawn as part of the Clinical Laboratory Safety Assessments described in Section 7.2.11. Results will be reported in the CRF. Approximate blood draw volumes are shown in Table 3.

7.2.13 Pharmacokinetic Measurements

Blood samples (0.15 mL) for the determination of etelcalcetide PK parameters will be collected at time points designated in the Schedule of Assessments. Study site staff will complete a shipping log that will include subject identification information and the time and date of collection of each sample. Detailed instructions on sample collection, storage and shipment to the central laboratory are provided in a separate Sample Collection Notebook.

7.2.14 Anticipated Blood Collection Volumes

It is anticipated that subjects enrolled in this study with weights greater than 12 kg will be asked to donate approximately 28.8 mL of blood over the course of the study period (see Table 3 for estimated volumes). At screening approximately 5.6 mL of blood will be drawn for safety laboratory assessments (including Baseline PD endpoints). Females of child bearing potential will have an additional blood sample (0.5 mL) obtained for serum pregnancy testing at screening. On Day -2 (Baseline) approximately 3.6 mL of blood will be drawn for antibody (0.45 mL) and safety lab/PD endpoints (3.1 mL). On Day 1 and at each safety follow up visit (Day 3, 5 (or 6), 8 and 10), approximately 0.15 to 3.3 mL will be drawn. Approximately 6.2 mL of blood will be drawn for antibody (0.45 mL), PK (0.15 mL) and safety laboratory assessments (5.6 mL) at the end of study visit.

Subjects that weigh 7 to 12 kg will be asked to donate smaller amounts of blood, approximately 16.7 mL. At screening approximately 2.8 mL of blood will be drawn for safety laboratory assessments (including Baseline PD endpoints). Female subjects weighing 12 kg or less are not anticipated to be of child bearing potential and therefore will not require a serum pregnancy test. On Day -2 (Baseline) approximately 2.3 mL of blood will be drawn for antibody (0.45 mL) and safety lab/PD endpoints (1.8 mL). On Day 1 and at each safety follow up visit (Day 3, 5 (or 6), 8 and 10), approximately 0.15 to 2.1 mL will be drawn. Approximately 3.4 mL of blood will be drawn for antibody (0.45 mL) safety laboratory assessments (2.8 mL) at the end of study visit.

Specified blood volumes are approximate and may vary, however, per individual, the study-related blood loss (including any losses in the maneuver) will not exceed 3% of the total blood volume during a period of four weeks and will not exceed 1% at any single time per regulatory guidance on paediatric clinical trials.

Table 3. Approximate Blood Draw Volume

Sample	Volume (mL) Subject Weight > 12 kg	Volume (mL) Subject Weight 7-12 kg	No of Samples All Subjects	Total Volume (mL) Subject Weight > 12 kg	Total Volume (mL) Subject Weight 7 – 12 kg
Safety Lab Tests (including Calcium, PTH)	5.6	2.8	2	11.2	5.6
cCA, albumin, PTH	3.1	1.8	5	15.5	9
PK	0.15	0.15	8	1.2	1.2
Antibody	0.45	0.45	2	0.9	0.9
Total				**28.8**	**16.7**

7.3 Antibody Testing Procedures

Blood sample(s) for Antibody testing are to be collected at Baseline (Day -2) and at EOS (Schedule of Assessments, Table 1) for the measurement of anti-etelcalcetide binding antibodies. 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.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-etelcalcetide antibody response may also be asked to return for additional follow-up testing.

Refer to the Schedule of Assessments (Table 1), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.4 Sample Storage and Destruction

Any blood PK or antibody sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject's LAR, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the secondary hyperparathyroidism due to chronic kidney disease, the dose response and/or prediction of response to etelcalcetide, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

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 (LAR)) can decline to continue receiving investigational product 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 investigational product or other protocol required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Table 1) 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 (or a LAR) does not wish to receive further protocol-required therapies or procedures, and the subject (or a LAR) 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, publically 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 investigational product 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 investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.2.1 Reasons for Removal From Treatment

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

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

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease has increased in severity, frequency, and/or duration more than expected by the investigator's assessment. 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.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 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, drug induced liver injury (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 - Adverse Events

9.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of study 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,
- Assessment of relatedness to etelcalcetide,
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational product. 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 investigational product?

The investigator must assess whether the adverse event is possibly related to other protocol-required therapies. 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 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. If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after etelcalcetide administration 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 electronic data capture (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 (eSAE) 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 eSerious 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.

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

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

9.2.2.1 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 end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. 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.

9.2.2.2 Reporting of Reductions in Serum Calcium

Asymptomatic reductions in calcium below 7.5 mg/dL or asymptomatic reductions in serum corrected calcium between 7.5 and < 8.3 mg/dL that required medical management or that the investigator deemed clinically significant should be reported as adverse events of "blood calcium decreased". Symptomatic reductions in serum corrected calcium < 8.3 mg/dL should be reported as adverse events of "hypocalcemia", 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 etelcalcetide, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after etelcalcetide administration through 3 months after etelcalcetide administration.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking etelcalcetide, 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 etelcalcetide administration through 3 months after etelcalcetide administration.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

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

10.1.1.2 Secondary Endpoints

- Pharmacokinetic parameters (AUC, C_{max}, t_{max}, $t_{1/2}$) of etelcalcetide in plasma
- Pharmacodynamics: concentration of parathyroid hormone (PTH), serum calcium [total calcium, ionized calcium and albumin corrected calcium] over time
- Anti-etelcalcetide antibodies
- Incidence of treatment-emergent adverse events

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive a dose of etelcalcetide.

10.2 Sample Size Considerations

The sample size is based on practical consideration. No formal sample size calculations have been performed.

10.3 Planned Analysis

10.3.1 Primary Analysis

The objective of the primary analysis is to assess safety, tolerability, PK, and PD of a single dose of etelcalcetide in this patient population. The primary analysis will be performed upon achieving the Primary Completion milestone described in section 3.5.2.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety data, PK and PD data for all subjects by cohort where appropriate. Descriptive statistics on continuous measurements will include number of observations, means, medians, first and third quartiles, standard deviations or standard error, minimum and maximum, while categorical data will be summarized using frequency counts and percentages.

No formal statistical testing will be performed.

10.4.2 Primary Endpoints

10.4.2.1 Common Treatment-emergent Adverse Events

All reported adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Determination of the severity of all adverse events (AE) will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless specified otherwise.

Common adverse events include those with occurrence in 2 or more subjects. Subject incidence of all common treatment-emergent adverse events will be tabulated by system organ class and preferred term.

10.4.2.2 Clinical Laboratory Tests, ECG and Vital Signs

Summaries of key laboratory [albumin corrected calcium (cCalcium), phosphorus, potassium, parathyroid hormone (PTH)], ECG and vital sign data over time and changes from baseline over time will also be provided at each time point when samples are collected. Subject Incidence of low calcium (<7.5 mg/dL, <8.0 mg/dL and <8.3 mg/dL) post-baseline will be provided.

10.4.3 Secondary Endpoint(s)

10.4.3.1 Pharmacokinetic Endpoints

Etelcalcetide concentration-time data in plasma will be used to determine the PK parameters using non-compartmental methods. Plasma etelcalcetide concentrations below the lower limit of quantifications will be set to zero for the estimation of the pharmacokinetic parameters for each subject and for the calculation of the summary statistic for each time point. Actual dosing and sampling time will be used for all calculations. The reasons for excluding any sample from the analyses will be provided.

Individual and mean (SE) plasma concentration-time data for etelcalcetide will be presented graphically. PK parameters will be summarized for all subjects using descriptive statistics.

10.4.3.2 Pharmacodynamic Endpoints

For concentrations of serum PTH and serum calcium (total calcium, albumin corrected calcium, and ionized calcium) over time, individual and mean (SE) of the absolute value and change from baseline at each post-baseline time point will be plotted and descriptive statistics will be tabulated.

10.4.3.3 Antibody

A table summarizing the evaluation of antibody formation to etelcalcetide will be provided.

10.4.3.4 Treatment-emergent Adverse Events

In addition to the common treatment-emergent adverse events analyzed in the primary endpoints, all treatment emergent adverse events will be included as secondary endpoints. Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term. Tables of all treatment-related adverse events, fatal adverse events, serious adverse events, treatment emergent adverse events of interest will also be provided.

10.4.4 Additional Analyses

10.4.4.1 Subject Accountability

The number of subjects who receive etelcalcetide and complete the study will be summarized. In addition, significant known protocol deviations will be noted for individual subjects.

Age, race, sex, height, weight and selected baseline characteristics will be summarized for all the subjects receiving etelcalcetide using descriptive statistics.

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed

of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject's 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's 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.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

The investigator is responsible for obtaining annual IRB approval and renewal for IRBs and IECs 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:

- 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 demographics page, in addition to the unique subject identification number, include the age at the 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 strict 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 named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

Subjects may be eligible for continued treatment with Amgen investigational product 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 investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed CRF, 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
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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

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

Amgen (or designee) will perform self-evident corrections (SECs) to obvious data errors in the clinical trial database. SECs will be documented in the Standard Self Evident Corrections document and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date but different visits eg, week 4 and early termination) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically 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, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), 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. Authors should meet conditions 1, 2, and 3.
- 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 corporate 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

Abdelfatah A, Motte G, Ducloux D, Chalopin J. Determinants of mean arterial pressure and pulse pressure in chronic haemodialysis patients. *J Hum Hypertens*. 2001;15(11):775-779.

Chesney RW, Brewer E, Moxey-Mims M, Watkins S, et al. Report of an NIH task force on research priorities in chronic kidney disease in children. *Pediatr Nephrol.* 2006;21:14-25.

Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic haemodialysis patients. *Kidney Int*. 2000;58(1):353-62.

Coen G, Mazzaferro S, Ballanti P, et al. Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. *Nephrol Dial Transplant*. 1996;11:813-819.

Cundy T, Hand DJ, Oliver DO, et al. Who gets renal bone disease before beginning dialysis? *Br Med J (Clin Res Ed)*. 1985;290:271-275.

Etelcalcetide Investigator's Brochure. Thousand Oaks, CA: Amgen Inc. 05 Oct 2015

EMEA-001554-PIP01-13, decision dated 01 Oct 2014

Foley R, Parfrey P, Sarnak M. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32(5 Suppl 3):112-119.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2006. http://www.icmje.org/

Kari JA, Rees L. Growth hormone for children with chronic renal failure and on dialysis. *Pediatr Nephrol*. 2005;20:618–621.

Klassen S, Edmund G, et al. Association between pulse pressure and mortality in patients undergoing maintenance haemodialysis. *JAMA*. 2002;287:1548-1555.

Kuizon BD, Salusky IB. Growth retardation in children with chronic renal failure. *J Bone Miner Res*. 1999;14:1680–1690.

Martinez I, Saracho R, Montenegro J, et al. The importance of dietary calcium and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis.* 1997;29:496-502.

McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. *NEJM*. 2004;350(26):2654-2662.

Melamed M, Eustace J, et al. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: A longitudinal study. *Kidney Int*. 2006;70:351-357.

Moe S, Drüeke T, et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006;69:1945-1953.

NKF K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease *Am J of Kidney Disease* 2005;46, 4.

North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), 2006 Annual Report, In: https://web.emmes.com/study/ped/annlrept/annlrept.html

Oh J, Wunsch R, Turzer M, et al. Advanced Coronary and Carotid Arteriopathy in Young Adults With Childhood-Onset Chronic Renal Failure *Circulation*. 2002;106:100-105.

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of Official Journal of the European Union 12 December 2006. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Sanchez CP. Secondary hyperparathyroidism in children with chronic renal failure: pathogenesis and treatment. *Paediatr Drugs*. 2003;5(11):763-776.

Salusky IB, Fine RN, Kangarloo H, et al. "High-dose" calcitriol for control of renal osteodystrophy in children on CAPD. *Kidney Int*. 1987;32(1):89-95.

Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. *Kidney Int Suppl*. 1999;73:S14-S19.

Spasovski GB, Bervoets AR, Behets GJ, et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. *Nephrol Dial Transplant*. 2003;18:1159-1166.

Tonshoff B, Kiepe D, Ciarmatori S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. *Pediatr Nephrol*. 2005;20:279–289.

US Renal Data System. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, Maryland, 2009.

Waller S, Ledermann S, Trompeter R, van't Hoff W, Ridout D, Rees L. Catch-up growth with normal parathyroid hormone levels in chronic renal failure. *Pediatr Nephrol*. 2003;18(12):1236-1241.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The common Terminology Criteria for Adverse Evens Version 4.0 is available at the following link:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, 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 9.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.3 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 investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

- Obtain serum acetaminophen (paracetamol) levels
- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Serious Adverse Event Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Definitions:

- Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.
- Serious Adverse Event – An adverse event that meets serious criteria
- Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.
- Serious Suspected Adverse Reaction – An SAR that meets serious criteria

What types of events to report on this form:

Type of Event	Clinical Trials
Adverse Event that is *not serious*	No
Serious Adverse Event (regardless of relationship)	Yes

Type of Event	Observational Studies
Suspected Adverse Reaction (SAR)	Yes
Serious Suspected Adverse Reaction	Yes
Serious Adverse Events that are not suspected to be related	ONLY if instructed by protocol or by local Amgen office or CRA

1. Site Information

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. Adverse Event

   Provide the date the Investigator became aware of this Information

   Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalizion. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. ***For observational studies, remember that SARs are, by definition, related to the drug under study.*** **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device,**

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field for serious events.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP/drug under study or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**
If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
Initial Start Date – Enter date the product was first administered, regardless of dose.
Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**
Indicate if there are any medications.
Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
Co-suspect – Indicate if the medication is co-suspect in the event
Continuing – Indicate if the subject is still taking the medication
Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**
Indicate if there are any relevant laboratory values.
For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**
Indicate if there are any tests, including any diagnostics or procedures.
For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20140336 Etelcalcetide	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 death. 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	Event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						Etelcalcetide		<Pick>		<Pick>		<Pick>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐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 # 20140336
Etelcalcetide

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 #
Etelcalcetide	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐ blinded ☐ open label							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:

Date (Day Month Year)	Test											
	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

AMGEN Study # 20140336 Etelcalcetide	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

Page 3 of 3

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

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

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

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