Title: A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects With Chronic Kidney Disease on Hemodialysis

AMG 416

Amgen Protocol Number 20140197

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Date: 16 July 2014
Amendment 1 Date 08 March 2017
Amendment 2 Date 20 Sep 2017
Amendment 3 Date 25 May 2018

***Effective July 5, 2012, KAI Pharmaceuticals, Inc. became a wholly owned subsidiary of Amgen Inc. In connection with Amgen's acquisition of KAI, Amgen Inc. will be managing the clinical study described in this protocol on behalf of KAI.**

NCT Number: NCT03283098
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 A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects with Chronic Kidney Disease on Hemodialysis, dated 25 May 2018, 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: A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects with Chronic Kidney Disease on Hemodialysis

Study Phase: Phase I

Indication: Secondary Hyperparathyroidism

Primary Objective:

To characterize the pharmacokinetics of AMG 416 following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis.

Secondary Objectives:

To characterize the safety and tolerability of AMG 416 following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis.

Exploratory Objectives:

[redacted]

Hypotheses: This study will adequately characterize the pharmacokinetics profile of AMG 416 in Chinese subjects with chronic kidney disease receiving hemodialysis.

AMG 416 will be safe and well tolerated after multiple dose administration in Chinese subjects with chronic kidney disease on hemodialysis.

Primary Endpoint:

- Pharmacokinetic parameters of AMG 416 in plasma including maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{last}) over the interdialytic interval following the first and last dose.

Secondary Endpoints:

- Incidence of adverse events
- Vital signs, laboratory safety tests including cCa, and ECGs
- Incidence of anti-AMG 416 antibodies

Exploratory Endpoint(s):

[redacted]

Study Design: This is a multiple-dose, double-blind, randomized, placebo-controlled clinical study conducted in Chinese subjects residing in Mainland China with chronic kidney disease receiving hemodialysis. The treatment duration will be approximately 4 weeks with a post treatment follow-up of 4 weeks. A dose will be given at each scheduled hemodialysis session (Dose administered three times a week for 4 weeks, for a total of 12 doses).

Sample Size: Approximately 32 subjects will be randomized in a 3:1 ratio to receive 5 mg IV of AMG 416 or placebo three times a week (TIW) at the end of each regularly scheduled hemodialysis session for 4 weeks (12 doses).

For PK parameter estimation, 2-sided 90% confidence intervals (CI) for geometric means (GM) of PK measurements can be expressed as (GM/θ, GM.θ) where θ is a measure of precision. Based on AMG 416 study 20120330 (Cohort 3, 5 mg dose), between-subject CV% for AMG 416 AUC_{last} (hr·µg/L) and C_{max} (µg/L) (on original scale) are approximately 50.5% and 52.7%, respectively, following the Day 27 dose. Assuming the same variability for 24 subjects receiving AMG 416 in this study, it is estimated that the precision (θ) of 2-sided 90% CI of geometric mean will be 1.18 and 1.19 for AUC_{last} and C_{max}, respectively.

For safety considerations, with 24 subjects receiving AMG 416, there will be a 21% chance of detecting an adverse event with a true incidence rate of 1% and 98% chance of detecting a more common adverse event with a true incidence rate of 15%.

Summary of Subject Eligibility Criteria:

Male or female subjects ≥ 18 and ≤ 70 years of age at the time of screening, with end stage renal disease receiving hemodialysis with a body mass index between 18 and 35 kg/m^2 that are residents in Mainland China and of Chinese ancestry, inclusive. Corrected calcium (calculated) level is ≥ 2.07 mmol/L (8.3 mg/dL) and iPTH level is between 31.8 – 127.2 pmol/L (300 - 1200 pg/mL), inclusive at enrollment and subject has not received cinacalcet within the 30 days prior to informed consent.

For a full list of eligibility criteria, please refer to Section 4**.**

Investigational Product

Amgen Investigational Product Dosage and Administration:

Investigational product will be administered thrice weekly with each hemodialysis treatment for 4 weeks (12 doses). The dose of investigational product is 5 mg. Each subject will receive AMG 416 or placebo administered by bolus injection into the venous line of the dialysis circuit at the end of each of 12 consecutive hemodialysis treatments, prior to or during rinse-back with each hemodialysis session (ie, 3 times per week). At least 150 mL of rinse back volume should be administered after investigational product injection to ensure investigational product reaches the systemic circulation.

For a complete description see Section 6.3.1.

Procedures:

Screening: After providing written informed consent, subjects enter a screening period of 22 days, during which all screening tests required to establish eligibility will be completed. Subjects who meet the eligibility criteria after completion of all screening, Day -2 and Day 1 predose procedures, will be enrolled in the study. Day -2 assessments will be performed 2 days before investigational product administration.

Screening procedures are summarized in the Schedule of Assessments.

Baseline and Treatment: Subjects will return to the research facility for day -2 assessments. Eligible subjects should be randomized to investigational product in a 3:1 ratio to AMG 416 or placebo, and should then receive the first dose. On Day 1, enrolled subjects will receive the first 5 mg IV dose of AMG 416 given after hemodialysis. Following completion of all study procedures on Day 1, subjects will be released with instructions to return to the research facility at specified time points for dosing, collection of blood samples for PK, PD and completion of safety assessments (including blood samples for antibody analysis) through the end of the study according to the Schedule of Assessments.

IP will be administered at the end of dialysis on Study Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 (12 doses). Dialysis will continue thrice weekly without study drug administration with study visits for data collection on Study Days 29, 34, 41, 55 (EOS). Blood samples for the determination of PK parameters will be collected on Day 1 and 27 at predialysis, and at 10, 30, 60 and 90 min postdose, as well as on Day 2 and 28 between 18 and 30 h after study drug administration, and at predialysis on Days 3, 8, 15, 22, 29, 34, 41, and 55 (EOS) and at 10 min postdose on Days 8, 15 and 22. Subjects will have blood samples drawn for antibody determination prior to dosing on Day 1 and on days 29 and 55. Blood samples for exploratory [redacted] Electrocardiograms (ECG) will be performed at screening, on Day -2, and on days 28 and 55.

The date and time of hemodialysis treatment will be recorded throughout the treatment period. When a visit corresponds to a dialysis day, study procedures should be completed prior to hemodialysis with the exception of dose administration and specified PK sample collection as described in the Schedule of Assessments.

Routine hematology and chemistry safety laboratory tests will be performed periodically. Subjects will be followed for safety throughout the 4-week treatment period and for 4 weeks after the last dose of investigational product. Dosing with investigational product may be suspended, for low predialysis iPTH or cCa, symptomatic hypocalcemia, or other drug-related adverse events.

End of Study

Subjects will be followed through Day 55 (EOS). Subject participation is complete once end-of-study (EOS) procedures are performed. Subjects who test positive for neutralizing antibodies to AMG 416 at the Day 55 EOS visit will be asked to return for additional follow-up testing. This testing should occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month), or testing for a longer period of time, may be requested in the event of safety-related concerns. Subjects who test positive for binding antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 416 antibody response may also be asked to return for additional follow-up testing.

All adverse events (including serious adverse events and deaths) and use of concomitant medication will be collected for the duration of the study up to and including the Day 55 EOS visit. If there is a clinically significant clinical or laboratory abnormality that requires monitoring, subjects will be followed until resolution of the abnormality, or until it is considered stable.

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:

Demographics and safety data will be summarized by treatment groups. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety Analysis Set. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Pharmacokinetic, vital sign, ECG, and clinical laboratory data will be summarized at each time point when samples are collected.

The number and percent of subjects reporting any treatment-emergent adverse events and each adverse event will be tabulated by system organ class and preferred term and will be further classified by relationship to treatment. Subjects who experience clinically-significant changes in clinical laboratory test values, ECGs, or vital signs will be noted.

Individual and mean (SD) plasma concentration-time plots for AMG 416 will be presented. The PK parameters (eg, interdialytic Cmax and AUClast on after the first and last dose on Study Days 1 and 27) will be estimated using noncompartmental methods. Nominal dose and actual sampling time data will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter.

[redacted]

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

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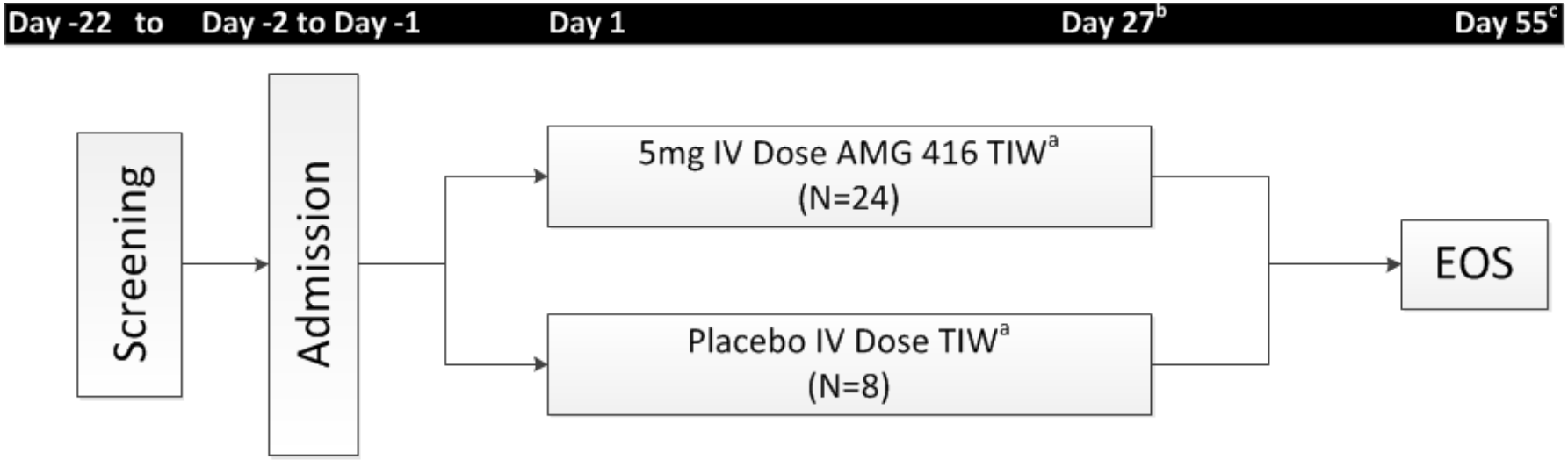
Study Design and Treatment Schema



[a] TIW = Three times a week (12 doses)
[b] Last Dose Administration (Day 27)
[c] EOS = End of Study will occur on Day 55, PK washout and safety followup (Day 28-55)

Study Glossary

Abbreviation or Term	Definition/Explanation
%CV	coefficient of variation
ADA	Anti-drug antibody assay
ADME	Absorption, distribution, metabolism, and excretion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	Active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable sample
BMI	Body Mass Index
CaSR	Calcium sensing receptor
Ca	Calcium
cCa	Total serum albumin corrected calcium concentration
cCa x P	Corrected calcium-phosphorus product
CHD	Coronary heart disease
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral and bone disorder
CI	Confidence Interval
CK	Creatinine kinase
CL	Clearance
C_{max}	Maximum observed concentration
Corrected Total Serum Calcium (for albumin levels < 4.0 g/dL)	Corrected calcium (mg/dL) = Total calcium (mg/dL) + (4 - albumin [g/dL])*0.8.
CRF	Case report form (electronic or paper)
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug-induced liver injury
EDC	Electronic data capture
ECG	Electrocardiogram
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

Abbreviation or Term	Definition/Explanation
Enrollment Date	Same as Study Day 1
EOS	End of Study
eSAE	electronic Serious Adverse Event (form)
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GM	Geometric mean
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HDL-C	high density lipoprotein cholesterol
hERG	human Ether-à-go-go-Related Gene
HepCAb	hepatitis C virus antibodies
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	instructions for Use
INR	international normalized ratio
Interdialytic AUC_{last}	area under the concentration-time curve measured from the time of drug administration to the beginning of the next dialysis session
Interdialytic C_{max}	maximum drug concentration measured between the time of drug administration to the beginning of the next dialysis session
IP	investigational product
IPIM	investigational product instruction manual
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IV	Intravenous
IVR/IWR	Interactive Voice/Web Response System
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

Abbreviation or Term	Definition/Explanation
MedDRA	Medical dictionary for regulatory activities
mL	Milliliter
mM	Millimolar
n	number of subjects or observations
NKF	National Kidney Foundation
P	Phosphorous
PD	Pharmacodynamic(s)
pg	Picograms
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PTH	Parathyroid hormone
qhd	Every hemodialysis day
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc interval	QT interval corrected for heart rate using accepted methodology
RI	renal impairment
RR	respiratory rate
SAE	severe adverse event
SHPT	Secondary hyperparathyroidism
Study Day 1	Defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
TEMP	Temperature
$T_{1/2}$	Terminal elimination phase half life
TBL	Total bilirubin
TIW	Thrice weekly
ULN	Upper limit of normal
URR	Urea reduction ratio
Vit D	Vitamin D

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1. OBJECTIVES

1.1 Primary

To characterize the pharmacokinetics of AMG 416 following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis.

1.2 Secondary

To characterize the safety and tolerability of AMG 416 following thrice weekly intravenous (IV) administration of 5 mg in Chinese subjects with chronic kidney disease receiving hemodialysis.

1.3 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

Secondary hyperparathyroidism occurs commonly among patients with chronic kidney disease (CKD), and it is an integral component of the syndrome of chronic kidney disease-mineral and bone disorder, or CKD-MBD. Persistently elevated levels of intact parathyroid hormone (iPTH) in serum or plasma are the cardinal biochemical feature of SHPT, affecting 40% to 50% of patients receiving dialysis regularly in the US (USRDS 2009). These biochemical changes are associated with abnormalities in bone histology, increased fracture risk, vascular and soft tissue calcifications, calciphylaxis, a variety of patient symptoms (eg, muscle weakness, fatigue, lethargy, bone and joint pain), and increased mortality (USRDS, 2009; Moe, 2001; Diaz- Corte and Cannata-Andia, 2000; Alem et al, 2000; Block and Port, 2000; Bro and Olgaard, 1997; Salusky and Goodman, 1996; Slatopolsky et al, 1980).

Intact parathyroid hormone values not only serve as a useful index of disease severity, but also can be used to monitor evolution of the disorder over time and the response to treatment. The importance of managing SHPT chronically is highlighted in clinical practice guidelines promulgated by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™) and the International Society of Nephrology Kidney Disease Improving Global Outcomes (KDIGO®) (KDIGO, 2009; K/DOQI, 2003).

A retrospective study of Chinese hemodialysis patients during 2006 showed that mineral metabolism control in China remains an unmet medical need (Kong, 2012). Treatment

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

An alternative approach is directed toward enhancing signal transduction through modulation of CaSR in parathyroid tissue, thereby suppressing iPTH. These compounds are called calcimimetic agents, and they include cinacalcet, which is taken daily by mouth, and the investigational medication being evaluated in this study, AMG 416, which is administered intravenously three times per week (TIW) at the end of each hemodialysis treatment. Calcimimetics reduce iPTH secretion from the parathyroid glands and consequently lower serum iPTH levels. Reductions in serum calcium concentrations are also observed and are an expected physiological consequence of iPTH reduction. As such, treatment is initiated with small doses that are subsequently titrated upwards as needed to achieve meaningful reductions in serum iPTH levels only if serum calcium concentrations remain unchanged or decrease only modestly. Intact parathyroid hormone and corrected calcium (cCa) laboratory values are routinely drawn to measure the effectiveness of cinacalcet, and to titrate the dose as appropriate.

Detailed descriptions of the clinical studies of AMG 416 are provided in the Investigator's Brochure.

2.2 Amgen Investigational Product Background

AMG 416 hydrochloride (formerly KAI-4169) is an 8-amino-acid peptide agonist of the calcium-sensing receptor (CaSR) being developed as an intravenous (IV) calcimimetic for the treatment of SHPT. The seven amino acids in the peptide backbone have an unnatural D-configuration which renders the peptide resistant to proteolysis. AMG 416 is administered to patients receiving hemodialysis as a bolus intravenous dose at the end of hemodialysis.

Refer to the Investigator's Brochure for additional information.

2.2.1 Nonclinical Experience

2.2.1.1 Nonclinical Pharmacology

AMG 416 has been shown in pharmacological studies to be a potent and selective allosteric activator of the CaSR, lowering the threshold of receptor activation by calcium,

the natural ligand. As such, it inhibits PTH secretion by the parathyroid tissue. The CaSR was shown in cellular studies to be the molecular target of AMG 416.

Please refer to the Investigator's Brochure for detailed descriptions of the nonclinical pharmacology of AMG 416.

2.2.1.2 Nonclinical Pharmacokinetics, Absorption, Distribution, Metabolism, and Excretion (ADME)

The intravenous administration of AMG 416 to rats and dogs with normal kidney function resulted in a dose-proportional plasma exposure with no evidence of significant accumulation. Renal elimination was the predominant in vivo clearance pathway in rats, with the administered dose excreted as intact AMG 416 or its biotransformed products. Significant biotransformation of AMG 416 occurred in whole blood, predominately via replacement of the L-cysteine moiety of AMG 416; the D-amino acid backbone of the molecule remained intact. A significant portion of administered AMG 416 was covalently bound via disulfide conjugation of the D-amino acid peptide backbone to serum albumin in rat and human plasma. Preliminary in vitro results indicate the covalent binding to serum albumin was reversible. The biotransformation of AMG 416 appeared to be the result of disulfide exchange rather than via conventional metabolism by enzymes such as cytochrome P450. This mechanism is in accord with the disposition of other thiol- or disulfide containing drugs, eg, captopril (Duchin et al, 1984, Narazaki et al, 1997) and E-2072 (Rais et al, 2012). AMG 416 neither inhibited nor induced human hepatic cytochrome P450. AMG 416 was neither a substrate nor an inhibitor of common drug transporters.

Several low molecular weight disulfide biotransformation products formed by conjugation with endogenous thiols have been observed along with the albumin disulfide. Tris(2-carboxyethyl) phosphine (TCEP) is a chemical agent that reduces disulfide bonds. TCEP reduction of plasma obtained from in vitro or in vivo studies resulted in the conversion of AMG 416 and all detected biotransformed products into a single component, M11 (the free thiol of the D-amino acid peptide backbone). Thus, M11 formed upon TCEP treatment of plasma is referred to as "Total M11" and is a measure of all AMG 416 related components with an intact D-amino acid peptide backbone.

Detailed descriptions of the pharmacokinetics (PK), distribution, metabolism, and excretion of AMG 416 in nonclinical species are provided in the Investigator's Brochure.

2.2.1.3 Nonclinical Toxicology

AMG 416 is pharmacologically active in rats and in dogs, and all of the adverse effects observed in both species are related, either directly or indirectly, to the effect of AMG 416 on lowering serum calcium levels. There were no anatomic pathology findings or other effects that suggested off-target toxicity of AMG 416 unrelated to its mechanism of action. Moderate (13 to 17%) prolongation of the QTc interval was observed and related to peak reductions in serum calcium and not plasma drug concentrations. Results of the in vitro human Ether-à-go-go-Related Gene (hERG) assay suggest no direct effect of AMG 416 on the QT interval. The nonclinical data indicates that AMG 416 neither poses a genotoxic risk for humans nor affects fertility and embryo-fetal development.

For a complete list of completed safety studies and additional details about the results, please see the Investigator's Brochure.

2.2.2 Clinical Experience

Etelcalcetide has been studied in three 26-week phase 3 studies, 2 placebo-controlled trials (20120229 and 20120230), and 1 active-controlled trial (20120360). In Study 20120229, 74% of etelcalcetide subjects achieved > 30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP) versus 8.3% of placebo subjects ($p < 0.001$). In Study 20120230, 75.3% of etelcalcetide subjects achieved this endpoint versus 9.6% of placebo subjects ($p < 0.001$). Similarly, the proportion of etelcalcetide subjects who achieved mean predialysis PTH ≤ 300 pg/mL during the EAP was significantly higher in the etelcalcetide group than in the placebo group ($p < 0.001$) in both Studies 20120229 and 20120230. In Study 20120229, 49.6% of subjects in the etelcalcetide group and 5.1% of subjects in the placebo group achieved this endpoint, and 53.3% of subjects in the etelcalcetide group and 4.6% of subjects in the placebo group achieved this endpoint in Study 20120230. The events that occurred with a greater frequency among subjects in the etelcalcetide group compared with subjects in the placebo group (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo) were blood calcium decreased (63.8% etelcalcetide; 10.1% placebo), muscle spasms (11.5% etelcalcetide; 6.6% placebo), diarrhea (10.7% etelcalcetide; 8.6% placebo), nausea (10.7% etelcalcetide; 6.2% placebo), vomiting (8.9% etelcalcetide; 5.1% placebo), headache (7.6% etelcalcetide; 6.0% placebo), and hypocalcemia (7.0% etelcalcetide; 0.2% placebo). An additional phase 3 study (20120360) was performed to compare the therapeutic efficacy of etelcalcetide and cinacalcet for lowering serum PTH

concentrations among subjects with CKD and SHPT receiving maintenance hemodialysis. A higher observed percentage of subjects in the etelcalcetide group (77.9%) had a > 30% reduction from baseline in serum PTH during the EAP compared with the cinacalcet group (63.9%). The estimated treatment difference (cinacalcet - etelcalcetide) was -10.48% (95% confidence interval [CI]: -17.45%, -3.51%). Because the upper bound of the 95% CI is < 12% (the prespecified margin for noninferiority), etelcalcetide is noninferior to cinacalcet in the proportion of subjects with a > 30% reduction from baseline in serum PTH during the EAP. Additionally, etelcalcetide was superior to cinacalcet on the proportion of subjects achieving a > 50% and a > 30% reduction from baseline in mean predialysis serum PTH during the EAP. There was no significant difference in the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment, as measured by a patient-reported outcome instrument. The most common (> 10% in either treatment group) adverse events (etelcalcetide, cinacalcet) were asymptomatic decreased blood calcium (68.9%, 59.8%), nausea (18.3%, 22.6%), vomiting (13.3%, 13.8%), and diarrhea (6.2%, 10.3%). Symptomatic hypocalcemia was reported for 17 subjects (5.0%) in the etelcalcetide group and 8 subjects (2.3%) in the cinacalcet group. Please refer to the Investigator's Brochure for additional information.

2.2.2.1 Clinical Pharmacokinetics

After both single and repeat IV bolus administration in end stage renal disease (ESRD) patients, plasma AMG 416 exhibited a multiple exponential decay, characterized by rapid initial distribution followed by a prolonged log-linear elimination phase (Studies 20130139 and 20120330, respectively). Exposure (as assessed by mean C_{max} and AUC parameters) increased in a dose-related fashion.

In Study 20120330, AMG 416 was given at a dose of 5 or 10 mg three times a week (TIW) for 4 weeks (12 doses given IV at the end of dialysis to Cohorts 3 and 4). Repeated TIW dosing of AMG 416 was associated with modest accumulation as measured by plasma AMG 416 C_{max} and AUC_{last} ratios, mean C_{max} and AUC_{last} after twelve 5 mg doses were approximately 2-fold higher (C_{max}), and approximately 3-fold higher (AUC_{last}), relative to corresponding values on Study Day 1.

Population PK analysis was conducted using the PK data from patients receiving hemodialysis. A three-compartment PK model with non-specific linear elimination and linear dialysis elimination from the central compartment was deemed appropriate to describe the PK of AMG 416 after single and multiple IV administrations in subjects with

SHPT receiving hemodialysis. Within the dose range of 2.5 to 60 mg, no evidence of nonlinear elimination or time-dependent PK was observed. Dose-proportional increases in systemic exposures were observed.

Within the range of values evaluated, demographic factors (body weight, age, sex, race), liver function biomarkers (aspartate aminotransferase, alanine aminotransferase, serum albumin, total bilirubin), as well as baseline alkaline phosphatase, iPTH, cCa, phosphorus, serum creatinine, smoking status, and calcium supplements had no discernible impact on AMG 416 PK parameters. Consequently, further dose adjustments on the basis of these covariates are not warranted in subjects with SHPT receiving hemodialysis.

Ono Pharmaceuticals (ONO) conducted a comparative ethnic sensitivity study of the PK of AMG 416 in healthy Japanese and non-Asian subjects by comparing results at the matching dose levels (2 mg and 5 mg) from Amgen's Study 20130107 (n=12 non-Asian subjects) and Study ONO-5163-01 (n=12 Japanese subjects). ONO also conducted a comparative ethnic sensitivity study of the PK of AMG 416 in Japanese and non-Asian subjects receiving hemodialysis by comparing results from Amgen's Study 20130139 (n=11) and the ongoing Study ONO-5163-02 (n=12) at the matching dose levels (5 mg, 10 mg, and 20 mg). While these data are preliminary and do not represent full efficacy and safety comparisons, preliminary analysis of the data in healthy subjects and subjects with SHPT suggests that there are no significant differences in AMG 416 PK parameters between Japanese and non-Asian subjects.

Metabolism, Distribution and Excretion

AMG 416 does not undergo conventional metabolism (see section 2.2.1.2). The PK, biotransformation, and excretion, and elimination by hemodialysis of [^{14}C] AMG 416 is currently being assessed in human hemodialysis subjects in study 20130147.

2.3 Risk Assessment

Safety reporting for all subjects in open-label and blinded studies completed as of 10 November 2017 and the investigators brochure have identified the following risks:
Important identified risks:

- Hypocalcemia
- Worsening heart failure
- QT prolongation secondary to hypocalcemia

Important potential risks:

- Ventricular arrhythmias
- Infusion and hypersensitivity reactions
- Convulsions (seizures)
- Adynamic bone
- Co-administration of cinacalcet (HCl) and etelcalcetide

The important identified risk is hypocalcemia, which will be mitigated in the protocol by close monitoring, and treatment as required. Coadministration of cinacalcet and AMG 416 is contraindicated until further studies inform the safety of simultaneous administration of these agents. The likelihood of these risks occurring with the planned dose for this study is expected to be low. In this study, cinacalcet will be prohibited from 30 days prior to informed consent and throughout the study.

Please refer to the Investigator's Brochure, Section 7 for additional information for the investigator.

2.4 Rationale

The purpose of the current study is to characterize the PK, safety and tolerability of AMG 416 in Chinese subjects with chronic kidney disease receiving hemodialysis. This study will use a placebo-controlled dose of 5 mg AMG 416 administered IV at the end of dialysis thrice weekly for 4 weeks. Within the dose range of 2.5 to 60 mg, no evidence of nonlinear PK was observed. This design is similar to multiple dose Study 20120330 Cohort 3, conducted in non-Asian hemodialysis subjects (n = 12 at the 5 mg dose).

The 5 mg dose level, given thrice weekly for 4 weeks, was selected because it is the starting dose in the AMG 416 dose titration that is used in pivotal Phase 3 clinical trials, where dose may be adjusted every 4 weeks based on serum predialysis iPTH and cCa levels obtained in the prior week. The 5 mg dose was safe and well-tolerated in phase 2 studies and demonstrated a clinically meaningful effect on iPTH with approximately 50% of subjects achieving > 30% reduction in iPTH from baseline after approximately 4 weeks of dosing.

2.5 Clinical Hypotheses

This study will adequately characterize the PK profile of AMG 416 in Chinese subjects with chronic kidney disease receiving hemodialysis.

AMG 416 will be safe and well tolerated after multiple dose administration in Chinese subjects with chronic kidney disease receiving hemodialysis.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multiple dose, double-blind, randomized, placebo-controlled clinical study. Chinese subjects residing in Mainland China with chronic kidney disease receiving hemodialysis will be randomized in a 3:1 ratio to receive 5 mg IV of AMG 416 or placebo thrice weekly (TIW) for approximately 4 weeks, with a subsequent follow up period of approximately 4 weeks.

Subjects will participate in the study as outpatients on scheduled study Day 1 through Day 55 (EOS) while receiving hemodialysis three times a week. All subjects, regardless of treatment assignment, will receive standard of care with calcium supplements, active vitamin D sterols, and phosphate binders, as prescribed by each individual Investigator. 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

This study will be conducted in Chinese subjects with chronic kidney disease receiving hemodialysis at multiple clinical sites in Mainland China.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 32 subjects are expected to participate in this study. Approximately 24 subjects are expected to receive AMG 416, and approximately 8 are expected to receive placebo. Refer to Section 10.2 for the rationale for the number of required subjects.

3.4 Replacement of Subjects

Randomized subjects who miss AMG 416 or matching placebo doses may be replaced at the discretion of Amgen in consultation with the investigator or their designee. Subjects who drop out of the study may be replaced at the discretion of Amgen in consultation with the investigator or their designee.

Replacement subjects will receive the identical treatment as the assigned treatment for the subject to be replaced. All data from the replaced subjects will be captured and kept in the clinical trial database and identified as such.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The estimated duration of study participation for each subject is approximately 77 days. This includes a 22-day screening period preceding a 55-day treatment and follow-up period. Subject participation may be adjusted based on treatment-emergent data. All adjustments or modifications to the schedule will be agreed upon by the investigator in consultation with Amgen. The institutional review board (IRB) will be informed via written correspondence and the informed consent form (ICF) will be updated accordingly.

3.5.2 End of Study

The end of the entire study for all subjects occurs at the primary completion time point.

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.

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 procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1	Subject has provided informed consent prior to initiation of any study-specific activities/procedures
4.1.2	Resident in Mainland China and of Chinese ancestry
4.1.3	Male or female subject ≥ 18 and ≤ 70 years of age at the time of screening, with end stage renal disease receiving hemodialysis
4.1.4	Body mass index is between 18 and 35 kg/m2, inclusive
4.1.5	Subject must be receiving hemodialysis 3 times weekly for at least 3 months through a functioning permanent dialysis access prior to Day -2 and have adequate hemodialysis with a delivered Kt/V ≥ 1.2 or urea reduction ratio (URR) ≥ 65% within 4 weeks to screening or at screening. The subject's routine hemodialysis session must be of 3-4.5 hours in duration, inclusive
4.1.6	Subject has stable dialysis prescription and this prescription is not anticipated to significantly change during the course of the study

4.2 Exclusion Criteria

4.2.1 Corrected calcium (calculated) level is < 2.07 mmol/L (8.3 mg/dL), and/or intact PTH level is outside the range of 31.8 – 127.2 pmol/L (300 - 1200 pg/mL) at screening and Day -2 (Day -2 assessments are only required if screening visit performed greater than 7 days prior to Day 1)

4.2.2 Chemistry and all other laboratory tests are not within clinically acceptable range to the investigator and sponsor at screening

4.2.3 Female subjects who are pregnant lactating/breastfeeding, or who plan to conceive, or breastfeed while on study through 3 months after receiving the dose of study drug

4.2.4 Female subject of reproductive potential not willing to use a(n) acceptable method(s) of effective birth control during treatment with AMG 416, and for an additional 3 months after the end of treatment with AMG 416. Female subjects who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal ligation, or who are postmenopausal are not required to use contraception. Postmenopausal is defined as:

- Age > 55 years with cessation of menses for 12 months or more
- Age < 55 but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 years, but currently amenorrheic, AND with postmenopausal gonadrotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (<5.3 pmol/L or 5 ng/dL) or according to the definition of “postmenopausal range” for the laboratory involved
- Underwent a bilateral oophorectomy

4.2.5 Females of reproductive potential with a positive pregnancy test, unless medical follow-up confirms the subject is not pregnant

4.2.6 Positive for human immunodeficiency virus (HIV) at screening or known diagnosis of acquired immune deficiency syndrome (AIDS)

4.2.7 Positive Hepatitis B Surface Antigen (HepBsAg) at screening (indicative of chronic Hepatitis B)

4.2.8 Positive for Hepatitis C virus Ribonucleic acid (RNA) by Polymerase Chain Reaction (PCR) at screening (indicative of active Hepatitis C – screening is generally done by Hepatitis C Antibody (HepCAb), followed by Hepatitis C virus RNA by PCR if HepCAb is positive)

4.2.9 Previous administration of AMG 416

4.2.10 Subject has received cinacalcet within the 30 days prior to informed consent (treatment with cinacalcet is prohibited during the study)

4.2.11 Subject has known sensitivity to any of the products or components to be administered during dosing

4.2.12 Use of concomitant medication other than that used in the management of end stage renal disease and its expected comorbidities that could in the opinion of the investigator or Amgen medical monitor interfere with the safety of subjects or interpretation of study results

4.2.13 Use of any herbal medicine, vitamins, and supplements consumed by the subject within 30 days prior to the dose of investigational product and continued use, if appropriate, 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.

4.2.14 Positive result for alcohol at Day -2, known alcohol or illicit drug abuse within 12 months of screening, unwilling or unable to refrain from alcohol consumption 24 hours in advance of each study visit, unwilling or unable to limit alcohol consumption to up to 2 drinks per day for the duration of the study during (1 drink being equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits).

4.2.15 Receiving or has received any investigational drug (or is currently using an investigational device) within the 30 days before receiving study drug, or at least 10 times the respective elimination half-life (whichever is longer)

4.2.16 Subject has lost 500 mL or more of blood or plasma within 8 weeks of study drug administration or during the study period

4.2.17 Anticipated or scheduled to have major surgical procedures during the study period such as kidney transplant or parathyroidectomy

4.2.18 Subject has an active infection at screening or Day -2, or a history of any illness that, in the opinion of the Investigator, might confound the results of the study or pose additional risk to the subject

4.2.19 History of malignancy within 5 years before Day -2 (except non-melanoma skin cancers, or cervical carcinoma in situ)

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

4.2.21 Subject has current or history of cardiovascular conditions such as uncontrolled hypertension, symptomatic ventricular dysrhythmias, Torsades de Pointes, angina pectoris congestive heart failure (New York Heart Association Classification III or IV), myocardial infarction, coronary angioplasty, or coronary arterial bypass grafting within the past 6 months prior to screening

4.2.22 Subject is receiving treatment for a seizure disorder or has a history of a seizure within the last 12 months prior to screening

4.2.23 Subject has had major surgery (excluding hemodialysis access repair) within the last 8 weeks prior to screening

4.2.24 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

4.2.25 History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written IRB approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific procedures. All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a unique subject identification number assigned manually before any study-related activities/procedures are performed. 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 Amgen. A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment case report form (CRF).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization.

This number will not necessarily be the same as the randomization number assigned for the study. [redacted]

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

5.1 Randomization/Treatment Assignment

Subjects will be randomized by IVR/IWR in a 3:1 ratio to either TIW IV etelcalcetide or placebo in a double-blind manner prior to the Day 1 activities. The randomization number will be provided to the unblinded pharmacist by accessing the IVR/IWR and then the unblinded pharmacist will obtain the appropriate IP/Placebo box. Details for this

procedure will be provided in the IVR/IWR manual. In the event subjects are randomized, but are withdrawn before receiving study medication, a replacement subject may be enrolled in the subject's place and assigned to receive the identical treatment as the replaced subject.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

5.2 Site Personnel Access to Individual Treatment Assignments

An unblinded pharmacist at the research facility (and/or their qualified designee) will have access to subjects' treatment assignment and will be responsible for preparing the appropriate treatment based on the randomized treatment provided by the IVR/IWR. Access to the randomization list or unblinded safety records will be limited to the unblinded pharmacist and/or their qualified designee. A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject or may potentially impact the safety of subjects currently enrolled or subjects enrolled in the future.

Unblinding at the research facility for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen study manager before unblinding any subject's treatment assignment, but must do so within 24 hours after the event.

6. TREATMENT PROCEDURES

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

The Amgen Investigational Product and placebo used in this study are AMG 416, also known as KAI-4169, and placebo. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of AMG 416 and placebo.

6.2 Investigational Product

Investigational product will be administered at the research facility by a qualified staff member. A physician, trained healthcare provider or qualified designee must be available at the time of administration of investigational product.

6.3 Amgen Investigational Product AMG 416

AMG 416 will be manufactured and packaged by Amgen Inc. or its designee, and distributed using Amgen clinical investigational product distribution procedures. The

active pharmaceutical ingredient (API) in AMG 416 is an eight-amino acid synthetic peptide prepared as a hydrochloride salt.

The AMG 416 investigational drug is supplied as a sterile, preservative-free, aqueous solution containing 10 mg AMG 416 API, [redacted] mg sodium chloride and [redacted] mg succinic acid, in a single-use 3 mL glass vial. The drug product vial contains 2 mL of clear, colorless solution with AMG 416 concentration of 5 mg/mL. The solution is ready to administer and has pH between [redacted] and [redacted]. The recommended storage condition for AMG 416 liquid drug product is between [redacted]°C to [redacted]°C.

Placebo will be presented in identical containers and stored/packaged in the same manner as AMG 416. Placebo is supplied as a sterile, preservative-free, aqueous solution containing [redacted] mg sodium chloride and [redacted] mg succinic acid, in a single-use 3 mL glass vial. The placebo vial contains 2 mL of clear, colorless solution. The solution is ready to administer and has pH between [redacted] and [redacted]. The recommended storage condition for the placebo drug product is [redacted]°C to [redacted]°C. Additional details regarding AMG 416 and placebo are provided in the IPIM.

6.3.1 Dosage, Administration, and Schedule

Each subject will receive twelve intravenous doses of 5 mg AMG 416 or placebo administered by bolus injection into the venous line of the dialysis circuit at the end of each of the 12 consecutive hemodialysis treatments, just prior to or during rinse-back with each hemodialysis session (ie, one dose per hemodialysis session, see Section 7.2).

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

After investigational product (IP) administration has been completed by a qualified healthcare professional, subjects will be observed for at least 30 minutes.

The date, time, package lot number, and quantity administered will be recorded on the individual subject's Investigational Product Administration CRF prior to database lock.

The effects of overdose of AMG 416 are not known. All overdose occurrences must be documented and corresponding adverse events must be recorded on the appropriate CRF and in the source documents.

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

Subjects will be treated with investigational product thrice weekly for 4 weeks. The dose of investigational product is 5 mg. Dosing will be stopped or modified by the investigator and Amgen Medical Monitor if suspected adverse drug reactions, changes in vital signs, physical examination, or clinical laboratory results are observed and these changes pose a significant health risk. Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point in time at the discretion of the sponsor.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

6.4.1 Criteria for Permanent Withholding of AMG 416 due to Potential Hepatotoxicity

AMG 416 should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- 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

- TBL > 2 X the 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 TBL values include, but are not limited to:
  - Hepatobiliary tract disease (obstructive gall bladder or bile duct disease)

- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Non-alcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolosis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on subject population and/or severity of the hepatotoxicity or event) if AMG 416 and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.5 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 6.9. Concomitant therapies are to be collected from informed consent through the EOS. Collect therapy name, indication, dose, unit, frequency and route, start date, and stop date.

Details of all concomitant medications will be recorded in the subject's source documents and on the CRF.

6.6 Alcohol Restrictions

Subjects should not consume any alcohol within 24 hours prior to each visit (including screening).

Subjects will be required to limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 drinks per day for the duration of the study. (1 drink being equivalent to 12 ounces (approximately 355 mL) of regular beer, 8 to 9 ounces

(approximately 237 to 266 mL) of malt liquor, 5 ounces (approximately 148 mL) of wine, or 1.5 ounces (approximately 44 mL) of 80 proof distilled spirits).

6.7 Medical Devices

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

Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

6.8 Product Complaints

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

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

6.9 Excluded Treatments and/or Procedures During Study Period

Treatment with cinacalcet is prohibited during the study through the last study visit (ie, Day 55 (EOS)). Treatment during the study with other medications known to be associated with hypocalcemia is strongly discouraged. Cinacalcet must not have been taken for at least 30 days prior to informed consent.

Subjects should not have a planned kidney transplant during this study.

Subject should not be allowed to donate blood and/or plasma during this study.

6.10 Hemodialysis Treatment Procedures and Concomitant Medications

Subjects should be on maintenance hemodialysis treatment with a prescription for dialysis 3 times per week. Dialysis duration and membrane may be modified in order to maintain adequate hemodialysis treatment (eg, Kt/V ≥ 1.2 or URR > 65%). If there is a change to the hemodialysis prescription the sponsor should be notified. In the event of a significant permanent change to the hemodialysis prescription, the subject may be

withdrawn from treatment with investigational product as deemed necessary by the sponsor.

Intermittent additional hemodialysis treatment (eg, for ultrafiltration) or changes in hemodialysis schedule (eg, missed/rescheduled treatments or shifts in schedule) are not considered significant changes in hemodialysis treatment prescription.

Subjects must have a prescribed dialysate calcium concentration ≥ 2.25 mEq/L stable for at least 4 weeks prior to screening laboratories, and the dialysate calcium concentration must be maintained ≥ 2.25 mEq/L throughout the study.

Medications used to treat hemodialysis-related symptoms or comorbid conditions should be reported as concomitant medications whenever administered to the subject.

Medications administered at each dialysis session (eg, heparin, diphenhydramine) should be reported on the CRF with a frequency of every hemodialysis (qhd) unless a change in dose or frequency occurs. The following medications used in the delivery of hemodialysis should not be reported on the CRF as concomitant medication:

- local anesthetic for cannulation
- saline prime for the dialysis circuit
- saline or hypertonic saline for management of intradialytic hypotension
- oxygen

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

Table 1a. Schedule of Non-laboratory Assessments

	Study Visit (Day)																			
Assessment	Screening	-2	1 (HD)	2	3 (HD)	6 (HD)	8 (HD)	10 (HD)	13 (HD)	15 (HD)	17 (HD)	20 (HD)	22 (HD)	24 (HD)	27 (HD)	28	29/ET[a,h] (HD)	34 (HD)	41 (HD)	55 (HD)
Informed consent	X																			
Eligibility	X																			
Medical and surgical history	X																			
Demographics[i]	X																			
Prior medications	X	X																		
Body Height[b]	X																			
Body Weight[b]	X	X	X														X			X
Physical exam[b]	X		X							X							X			X
Hemodialysis symptoms[c]	X																			
Investigational product administration[d]			X		X	X	X	X	X	X	X	X	X	X	X					
Vital Signs (BP, HR, RR, TEMP)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram[f]	X	X														X				X
Adverse Event Monitoring[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes displayed on the next page

ET = early termination; HD = hemodialysis.

[a] If a treated subject withdraws before completion of dosing, the investigator will make every effort to perform Day 29 assessments as close to 2 days after the last dose of investigational product as possible.

[b] A physical examination will be performed at screening. Abbreviated physical examinations will be performed on day 1 (unless day 1 occurred more than 2 weeks after screening physical examination), Days 15, 29 and 55. Height will be captured once at screening. Weight will be recorded before dialysis.

[c] Common symptoms associated with hemodialysis will be captured at screening. Any worsening of hemodialysis symptoms will be reported as an adverse event.

[d] Investigational product will be administered by intravenous (IV) injection over approximately 30 seconds into the venous line with dialysis rinse back at the end of the dialysis session.

[e] Subjects will remain seated for at least 10 minutes prior to measurement of predialysis heart rate and blood pressure. Vital signs will include blood pressure, heart rate, respiratory rate, and oral or ear temperature. Vital signs will be obtained pre-dialysis treatments on scheduled dialysis days, and at ET and on Day 55 (EOS).

[f] Subjects will remain supine for at least 5 minutes prior to recording 12-lead electrocardiogram (ECG). Screening 12-lead ECG will be recorded prior to hemodialysis. The Day -2 12-lead ECG will be recorded within 4 hours after hemodialysis rinse back. After the last dose of investigational product on Day 27, 12-lead ECGs will be recorded between 18 and 30 hours (recorded on day 28) post-dose.

[g] Adverse events will be monitored and recorded from the dose of investigational product (AMG 416) or placebo. Serious adverse events will be monitored and recorded from the time of informed consent through Day 55.

[h] After Day 28, hemodialysis will continue on study days 29, 31, 34, 36, 38, 41, 43, 45, 48, 50, 52 and 55; data collection and study procedures will only occur on hemodialysis days 29, 34, 41, and 55(EOS).

[i] Demographic information collected at screening includes sex, age, race, and ethnicity.

Table 1b. Schedule of Laboratory Assessments

		Study Visit (Day)																			
Time	Assessment	Screening	-2	1 (HD)	2	3 (HD)	6 (HD)	8 (HD)	10 (HD)	13 (HD)	15 (HD)	17 (HD)	20 (HD)	22 (HD)	24 (HD)	27 (HD)	28	29/ ET[a] (HD)	34 (HD)	41 (HD)	55 (HD)
Laboratory Assessments																					
Pre HD	Hematology, PT, aPTT[c]	X		X							X							X			X
	Clinical Chemistry	X		X							X							X			X
	Albumin[d]	X	X[b]	X		X		X			X			X		X		X	X	X	X
	Phosphorus	X	X[b]			X		X			X			X		X			X	X	X
	Calcium (cCa)[d]	X	X[b]	X				X			X			X		X		X	X	X	X
	Serum or Urine Pregnancy (females only)	X	X[b]																X		
	Serum FSH[g] (female only)	X																			
	Breath Alcohol Screen	X	X																		
	HIV, Hep C Ab, HBsAg	X																			
	iPTH	X	X[b]	X				X			X			X		X			X	X	X
	25(OH) vitamin D	X																			
	Kt/V or URR[e]	X																			
	Anti-drug antibodies[f]			X														X			X

Footnotes displayed on the next page

HD = hemodialysis; ET = early termination; cCa = albumin-corrected calcium; SDA = Study drug administration ; Kt/V = measure of dialysis adequacy; URR = urea reduction ratio

[a] If a treated subject withdraws from study before completion of dosing, the investigator will make every effort to obtain day 29 samples as close to 2 days after the last dose of investigational product as possible.

[b] If screening albumin, phosphorus, cCa, pregnancy, and iPTH tests occur within 7 days prior to start of IP, then Day -2 lab tests can be waived

[c] Blood sample for PT and aPTT will be drawn prior to heparin administration for dialysis. Day 1 hematology and coagulation tests will be performed only if day 1 occurs more than 2 weeks after the screening hematology and coagulation tests.

[d] Serum samples for albumin and calcium for screening and routine monitoring of predialysis cCa. When albumin is less than 4.0 g/dL, the calcium level will be corrected according to the formula: cCa (mg/dL) = total Ca (mg/dL) + (4 – albumin (g/dL))*0.8. Corrected calcium results will inform dosing/dose withholding at the next hemodialysis treatment.

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

[f] Serum samples for anti-drug antibodies will be collected predialysis on days 1, 29, and 55. Any subjects with positive titers for antibodies to AMG 416 may be asked to return to the clinical research unit to provide additional serum samples.

[g] Luteinizing hormone and estradiol levels may additionally be collected if deemed necessary for confirmation of postmenopausal status as described in exclusion criteria section 4.2.4

Table 1c. Schedule of Pharmacokinetic Assessments

Time	Assessment	Study Visit (Day)																			
		Screening	-2	1 (HD)	2	3 (HD)	6 (HD)	8 (HD)	10 (HD)	13 (HD)	15 (HD)	17 (HD)	20 (HD)	22 (HD)	24 (HD)	27 (HD)	28	29/ ET[a] (HD)	34 (HD)	41 (HD)	55 (HD)
Central Laboratory																					
Pre HD	PK			X		X		X			X			X		X		X	X	X	X
SDA + 10 min	PK			X				X			X			X		X					
SDA + 30 min	PK			X												X					
SDA + 60 min	PK			X												X					
SDA + 90 min	PK			X												X					
SDA + 18 to 30 hr	PK				X												X				

HD = hemodialysis; ET = early termination; SDA = Study drug administration.

7.2 General Study Procedures

Study tests and procedures will be performed only after written informed consent is obtained. All screening procedures must be completed within 22 days before investigational product administration (Day 1). Eligible subjects will be admitted to the clinical research facility on Day -2 at which time continued eligibility will be reconfirmed and baseline safety assessments will be performed. Subjects will be administered AMG 416 or placebo on Day 1 after completion of baseline assessments.

In the event that multiple post dose procedures are required to be conducted at the same nominal time point, the following order of precedence will be used to ensure certain post dose safety assessments will not be disturbed by blood draws: (1) electrocardiogram (ECG) recording; (2) vital signs assessment; (3) PK blood sampling; (4) clinical laboratory tests; and (5) physical examination and physical measurements. Electrocardiograms and vital signs may be conducted up to 15 and 10 minutes, respectively, prior to the nominal time so that PK samples will be collected as close to the nominal time point as possible. The remaining postdose procedures/assessments may be conducted up to 30 minutes after the nominal time.

Every effort should be made to conduct study procedures as scheduled. Acceptable windows for the timing of PK are as follows:

- Plus or minus 2 mins for the 10 min sample
- Plus or minus 5 mins for the 30 min sample
- Plus or minus 10 mins for the 60 min sample
- Plus or minus 15 mins for the 90 min sample
- Plus or minus 4 hours for the 18-30 hour post dose samples

7.2.1 Screening

Screening assessments will be completed after the informed consent form is signed, but prior to initiating treatment with investigational product, in a 22 day screening period.

Screening assessments must be performed within these 22 days prior to the first dose of investigational product. All inclusion and exclusion central laboratory requirements must be met during the 3 weeks prior to randomization. Screening assessments may be repeated up to 2 times during the 3-week screening period, utilizing the same informed consent signature. A new informed consent form must be signed if it has been more than 22 days since the previous signature. Subjects may re-sign a new informed consent form two additional times.

After informed consent is obtained the following procedures will be completed during the screening period according to the Schedule of Assessments:

- Non Laboratory Assessments:
    - Confirmation of informed consent
    - Eligibility
    - Demographics (sex, age, race, ethnicity)
    - Medical and surgical history
    - Prior (from 4 weeks prior to informed consent) and concomitant medication
    - Body weight (before dialysis if on a dialysis day)
    - Height
    - Physical examination
    - Hemodialysis symptoms
    - Vital signs (BP,HR,RR, TEMP)
    - 12 lead ECG recording
    - Serious adverse event monitoring
    - B ultrasound to exclude ovarian cancer (Optional at PI's discretion)
- Laboratory assessments (all pre-hemodialysis samples)
    - Clinical hematology
    - Clinical chemistry
    - PT, aPTT
    - Albumin, Phosphorus, Calcium (cCa)
    - Serum or urine pregnancy test (women of child-bearing potential only; within 7 days prior to first study drug administration)
    - Serum FSH (females only)
    - Breath alcohol screen
    - HIV, Hepatitis C Antibody, Hepatitis B surface antigen
    - iPTH
    - 25(OH) vitamin D
    - Kt/V or URR

Subjects who meet the eligibility criteria after completion of all screening, Day -2 procedures will be considered enrolled in the study.

If screening albumin, phosphorus, cCa, pregnancy, and iPTH tests occur within 7 days prior to start of IP, then Day -2 lab tests can be waived.

Day -2 assessments will be performed 2 days before investigational product administration. Day -2 assessments will include recording the date and time of the last hemodialysis treatment before investigational product administration.

Evaluations obtained as part of routine medical care may be performed prior to informed consent and may be used in place of the study specific evaluations, provided they are performed within 22 days prior to Day 1 and meet the time windows described above.

7.2.2 Day -2

Two days before dosing (day -2) the following baseline procedures will be performed and confirmed to meet eligibility requirement :

- Non Laboratory Assessments:
    - Medication use over 4 weeks prior to informed consent
    - Vital signs (BP, HR, RR, TEMP)
    - Body weight
    - 12 lead electrocardiogram
    - Serious adverse event monitoring
    - Concomitant medications
- Laboratory assessments:
    - Albumin, Phosphorus, Calcium (cCa)
    - Serum or urine pregnancy test (women of child-bearing potential only)
    - Breath alcohol screen
    - iPTH

Eligible subjects will be randomized prior to dosing to receive either AMG 416 or placebo in a 3:1 ratio.

7.2.3 Treatment (Day 1-27) and Follow up Periods (Day 28-55)

On day 1 the following predose activities will be conducted:

- Non Laboratory Assessments:
    - Body weight (before dialysis)
    - Physical examination
    - Vital signs (BP,HR,RR, TEMP)
    - Adverse event monitoring
    - Concomitant medications
- Laboratory assessments and predose collections (pre-hemodialysis samples):
    - Hematology, PT, aPTT
    - Clinical chemistry

- Calcium (cCa)
- iPTH
- Albumin
- Anti-Drug Antibodies
- Pre-hemodialysis PK sample

- IP Administration, Dialysis and Pharmacokinetic Schedule

IP will be administered at the end of dialysis on Study Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 (12 doses). Investigational product will be administered by bolus injection into the venous line of the dialysis circuit at the end of hemodialysis treatment, prior to or during rinse-back with each hemodialysis session (ie, 3 times per week). At least 150 mL of rinse back volume should be administered after investigational product injection to ensure investigational product reaches the systemic circulation. If rinse-back is completed and investigational product was not administered, then investigational product may be administered intravenously followed by at least 10 mL saline flush volume. The end of hemodialysis treatment is defined as when the prescribed hemodialysis treatment time is completed (ie, remaining time on dialysis (RTD) is zero) or when the arterial flow is stopped (eg, arterial line is clamped or disconnected to discontinue treatment), whichever occurs first. If a regularly scheduled hemodialysis session is missed and subsequently rescheduled, investigational product will not be administered at the rescheduled hemodialysis session. For example, a subject on a Mon/Wed/Fri schedule who misses a Wed session will be dosed on Mon and Fri; if a make-up session is added on Thu and the subject maintains the regularly scheduled session on Fri, the subject will only be dosed on Mon and Fri and not on Thu. If an additional hemodialysis treatment is needed intermittently (eg, fourth treatment during a week for ultrafiltration) then an additional dose of investigational product will not be administered during the extra dialysis session. Additional details will be provided in IPIM. Investigational product must only be administered intravenously; it must not be administered via any other route. Investigational product must not be administered concurrently with any other intravenous medications. If there is a significant permanent change to the hemodialysis prescription, then the sponsor will be notified and subject may be withdrawn from treatment with investigational product.

Blood samples for the determination of PK parameters will be collected on Day 1 and 27 at predialysis, and at 10, 30, 60 and 90 min postdose and on Day 2 and 28 between

18 and 30 h after study drug administration, and at predialysis on Days 3, 8, 15, 22, 29, 34, 41, and 55 and at 10 min postdose on Days 8, 15 and 22.

The date and time of hemodialysis treatment will be recorded throughout the treatment period. When a visit corresponds to a dialysis day, study procedures should be completed prior to hemodialysis.

Following completion of all study procedures on Day 1, subjects will be discharged with instructions to return to the research facility at specified time points for dosing, collection of blood samples for PK, PD and completion of safety assessments (including blood samples for antibody analysis) through the end of the study according to the schedule of assessments.

- Other Predialysis Assessments after Day 1:
    - Body Weight (before dialysis) on Days 29 and 55
    - Physical exam on Days 15, 29 and 55
    - Vital signs (BP,HR,RR, TEMP) – all visits
    - 12 lead Electrocardiograms (ECG) on Day 28 and Day 55 (EOS)
    - Adverse event monitoring (including serious adverse events and deaths) – all visits
    - Concomitant medications – all visits
    - Pregnancy test on Day 34
    - Hematology, PT, aPTT on Days 15, 29 and 55
    - Clinical Chemistry on Days 15, 29 and 55
    - Albumin on Days 3, 8,15, 22, 27, 29, 34, 41, 55
    - Phosphorus on Days 3, 8, 15, 22, 27, 34, 41, 55
    - Calcium (cCa) on Days 8, 15, 22, 27, 29, 34, 41, 55
    - iPTH on Days 8, 15, 22, 27, 34, 41, and 55
    - Anti-Drug Antibodies on Day 29 and 55

Subjects will be followed for safety throughout the 4-week treatment period and for 4 weeks after the last dose of investigational product to Day 55 (EOS). Dosing with investigational product may be suspended, for low predialysis iPTH or cCa, symptomatic hypocalcemia, or other drug-related adverse events.

Subjects who test positive for antibodies to AMG 416 at the EOS visit will be asked to return for additional follow-up testing (see section 7.4)

If there is a clinically significant clinical or laboratory abnormality that requires monitoring, subjects will be followed until resolution of the abnormality or until it is considered stable.

Subject participation is complete once Day 55 end-of-study (EOS) procedures are performed.

For a full list of study procedures, including the timing of each procedure, please refer to the Schedule of Assessments.

7.3 Description of Study Procedures

7.3.1 Informed Consent

Before any study-related screening or baseline procedure can be completed, a subject must sign and date the IRB-approved ICF.

7.3.2 Demographics

Demographic data, including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on pharmacokinetics of the protocol required therapy.

7.3.3 Subject Residency

There is no in-house residency period. Subjects will be admitted to the research facility on each scheduled day and they will remain until all assessments are completed.

7.3.4 Medical History

A complete medical history will be obtained at screening by the investigator or qualified designee. Medical history will include information on the subject's current health, surgical history, and use of tobacco, alcohol, and prescription and non-prescription medication(s). Relevant medical history findings will be recorded in the subject's source and on the appropriate pages of the CRF.

7.3.5 Physical Examination

Physical examinations will be performed by the investigator or designated physician at time points specified in the Schedule of Assessments. A complete physical examination (excluding genital and rectal examination) will be performed at screening. Abbreviated physical examinations will be performed on Day 1 (unless Day 1 occurred more than 2 weeks after screening physical examination), Days 15, 29 and 55.

The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal findings found during screening or Day 1 will be

reported on the medical history page of the CRF. Abnormal findings found after the subject has received study medication will be reported on the Event CRF.

7.3.6 Height

Height measurement in centimeters and without shoes will be performed at screening.

7.3.7 Weight and Body Mass Index

Weight (in kg and without shoes) will be obtained at screening, 2 days prior to dosing (Day -2), Day 1, Day 29 and Day 55 (EOS). On a hemodialysis day, weight will be recorded before dialysis.

Body mass index will be calculated for eligibility at screening using the screening height and weight measurements according to the following formula:

BMI (kg/m2) = weight (kg)/[height (cm)/100]^2

7.3.8 Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate and oral or ear temperature will be recorded by the investigator or qualified designee at screening, Day -2, and time points specified in the Schedule of Assessments (Table 1).

Subjects must be seated position for at least 10 minutes prior to vital signs measurements. Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding CRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn.

7.3.9 12-Lead Electrocardiograms

The 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.

The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals.

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

7.3.10 Clinical Chemistry, Hematology

Blood samples for clinical chemistry and hematology will be collected at screening, the day -2, and the time points specified in the Schedule of Assessments.

The tests listed below in Table 2, will be conducted on samples collected and analyzed by standard laboratory procedures.

Table 2. Chemistry, Hematology

Chemistry	Hematology	Other Labs
Sodium Potassium Chloride Total protein Albumin Glucose (Random) Blood urea nitrogen Creatinine Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Calcium Adjusted Calcium Creatinine phosphokinase Phosphorus Thyroid-stimulating hormone (TSH)[a]	Red blood cells Hemoglobin Hematocrit Mean corpuscular volume Platelets White blood cells Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Antidrug Antibodies Hep B surface antigen Hep C antibody HIV Pregnancy Intact PTH (iPTH) 25-hydroxyvitamin D PK PT aPTT FSH[b] Luteinizing hormone[b] Estradiol[b] Syphilis[c] Urea/BUN[d]

[a] Only required at screening for subjects who have a history of hyper- or hypothyroidism and do not have available TSH results within 6 months prior to screening
[b] Females only, and only collected if deemed necessary for confirmation of postmenopausal status as described in exclusion criteria section 4.2.4
[c] Only collected at screening when investigator consider it is necessary
[d] Urea/BUN measurement to be performed locally for Kt/V or URR assessment at screening, unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

All clinical chemistry and hematology tests must be reviewed, signed, and dated by the Investigator or qualified designee, and all abnormal values must have clinical significance assessed. Additional safety laboratory assessments may be performed, if clinically indicated.

7.3.11 Follicle Stimulating Hormone Test (Females Only)

To confirm postmenopausal status for eligibility, a blood sample for the determination of serum FSH will be collected at screening and analyzed by standard laboratory procedures. To be eligible for this study, FSH results must be within or above the laboratory's reference range for postmenopausal. Serum FSH is required for subjects as described in exclusion criteria section 4.2.4 (age < 55 years and spontaneous menses within the past 1 years, but currently amenorrheic).

7.3.12 Human Immunodeficiency Virus Antibodies, Hepatitis B Surface Antigen, and Hepatitis C Antibodies

Human immunodeficiency virus 1 and 2 antibodies, HBsAg, and HepCAb titers will be assessed at screening. Serology tests must be negative in order for a subject to be eligible for the study.

7.3.13 25-hydroxy Vitamin D

The 25-hydroxy vitamin D will be obtained at screening as a part of the clinical chemistry sample. Subjects with a 25-hydroxyvitamin D level < 20 ng/mL can be repeated at the Investigator's discretion. Amgen will not provide or reimburse for vitamin D supplements.

7.3.14 Alcohol Screen

A breath screen for alcohol will be performed at screening and 2 days prior to dosing (Day -2), respectively. Subjects with a positive screen for alcohol at screening will be allowed to retest at Day -2. Subjects with a positive screen for alcohol at Day -2 will be excluded from participation in the study.

7.3.15 Intact Parathyroid Hormone

Blood samples for the determination of intact parathyroid hormone (iPTH) will be collected at the following time points: Screening , Day -2, and time points specified in the Schedule of Assessments (Table 1).

7.3.16 AMG 416 Plasma Concentrations

Blood samples for the determination of AMG 416 concentrations will be collected at the time points specified in the Schedule of Assessments (Table 1c).

7.3.17 Adverse Event Reporting

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the CRF for the duration of the study as specified in Section 9.1 and Section 9.2 of this protocol. Determination of the severity of all adverse events will be consistent with CTCAE Version 4.0 (Appendix A) unless specified otherwise.

7.3.18 Concomitant Medications

Subjects will be assessed for concomitant medication(s) usage at each visit. Any concomitant medication use reported throughout the study will be recorded in the source documents and CRF.

7.3.19 Blood Volume

Subjects enrolled in this study will agree to provide whole blood for safety, serology, PK, and other assessments during participation in this study. The approximate volumes collected for each sample, and the approximate total blood volume are presented in Table 3.

Table 3. Estimated Blood Volume Collection

Test	Average Volume (mL) per Collection	Number of Collections	Total Volume (mL)
Clinical chemistry (including FSH, when applicable)	6	5	30
Hematology	5	5	25
Serology (HIV, HBsAg, and HepCAb)	15	1	15
iPTH	5	10	50
AMG 416 plasma concentration	3	23	69
Antibody sampling	3	3	9
TOTAL			198

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.

7.4 Antibody Testing Procedures

Blood samples will be collected from all subjects for the measurement of anti-AMG 416 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-AMG 416 antibodies during the study.

Subjects who test positive for neutralizing antibodies to AMG 416 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should occur approximately every 12 weeks (± 4 weeks) starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one year (± 4 weeks) from the day of dosing. More frequent testing (eg, every month), or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 416.

Subjects who test positive for binding antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 416 antibody response may also be asked to return for additional follow-up testing.

7.5 Sample Storage and Destruction

Any blood, serum, plasma 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, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the dose response and/or prediction of response to AMG 416 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 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, serum or plasma 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) 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 does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, 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, noncompliance, requirement for alternative therapy, pregnancy)
- decision by sponsor (other than subject request, safety concern, lost to follow-up, missed doses and/or hemodialysis treatments)
- death
- lost to follow-up
- protocol specific criteria
    - subject requires a significant permanent change in hemodialysis prescription to maintain adequate hemodialysis (see section 6.10)
    - subject receives a kidney transplant
    - subject undergoes a parathyroidectomy

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

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 Definition of Serious Adverse Events

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

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

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

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could

include allergic bronchospasm, convulsions, blood dyscrasias, 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 Reporting of 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 from the dose of investigational product (AMG 416) through the Day 55 EOS are reported using the applicable CRF (eg, 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 [and/or toxicity per protocol]
- assessment of relatedness to AMG 416 or other therapies,
- action taken

The adverse event grading scale used will be the CTCAE version 4. The grading scale used in this study is described in Appendix A. The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

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 any study mandated activity (eg, protocol-required procedure (including any screening procedure[s]). 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, and/or 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 as a single event with the worst 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 the last dose of investigational product or Day 55 End of Study, whichever is later are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours of 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.

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 eSAE Contingency Report Form. For EDC studies where the first notification of a serious adverse event is reported to Amgen via the eSAE 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 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 serious adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

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

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

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

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

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

9.3 Changes in Serum Calcium and Symptomatic Hypocalcemia

Investigators should assess subjects for the onset of signs and symptoms associated with low serum calcium (see Section 6.3.1.1) at each visit. When observed,

"hypocalcemia" should be reported as the adverse event, and the associated signs and symptoms will also be captured.

Any serum calcium (corrected) (cCa) ≥ 7.5 and < 8.3 mg/dL can be reported as low blood calcium; however, low a calcium result does not need to be reported as an adverse event if no action is taken, and the value is not deemed clinically significant by the investigator. If the cCa is < 8.3 mg/dL and there are symptoms of hypocalcemia then the event is to be reported as hypocalcemia and considered a serious adverse event. The associated signs and symptoms should also be captured.

Also, any cCa level < 7.5 mg/dL is to be reported as a serious adverse event of low blood calcium if there are no associated signs and symptoms, but it is to be reported as hypocalcemia if there are associated symptoms. The associated signs and symptoms should also be captured.

9.4 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking AMG 416, 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 the last dose of AMG 416 through 3 months after the last dose of study drug (for female subjects and female partners of male subjects).

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet Appendix C. The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking AMG 416, report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of AMG 416 through 3 months after the last dose of study drug.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

The primary endpoint of this study is:

- PK parameters of AMG 416 in plasma including maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{last}) over the interdialytic interval following the first and last dose

10.1.1.2 Secondary Endpoints

The secondary endpoints of this study are:

- Incidence of adverse events
- Vital signs, laboratory safety tests including cCa, and ECGs
- Incidence of anti-AMG 416 antibodies

10.1.1.3 Exploratory Endpoints

[redacted]

10.1.2 Analysis Sets

10.1.2.1 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who received at least one dose of investigational product.

10.1.2.2 PK Concentration Analysis Set

The PK Concentration Analysis Set will contain all subjects who received at least one dose of AMG 416 and have at least one PK sample collected.

10.1.2.3 PK Parameter Analysis Set

The PK Parameter Analysis Set will contain all subjects who received at least one dose of AMG 416 and for whom at least one PK parameter can be adequately estimated.

10.1.2.4 Covariates and Subgroups

No covariate adjusted or subgroup analyses are planned.

10.2 Sample Size Considerations

Approximately 32 subjects will be randomized in a 3:1 ratio to receive 5 mg IV of AMG 416 or placebo three times a week (TIW) at the end of each regularly scheduled hemodialysis session for 4 weeks (12 doses).

For PK parameter estimation, 2-sided 90% confidence intervals (CI) for geometric means (GM) of PK measurements can be expressed as (GM/θ, GM.θ) where θ is a measure of precision. Based on AMG 416 study 20120330 (Cohort 3, 5 mg dose), between-subject CV% for AMG 416 AUC_{last} (hr· µg/L) and C_{max} (µg/L) (on original scale) are approximately 50.5% and 52.7%, respectively, following the Day 27 dose. Assuming the same variability for 24 subjects receiving AMG 416 in this study, it is estimated that the precision (θ) of 2-sided 90% CI of geometric mean will be 1.18 and 1.19 for AUC_{last} and C_{max}, respectively.

For safety considerations, with 24 subjects receiving AMG 416, there will be a 21% chance of detecting an adverse event with a true incidence rate of 1% and 98% chance of detecting a more common adverse event with a true incidence rate of 15%.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Treatment groups will be blinded to the investigator (other than unblinded pharmacist), subjects, and the Amgen study team (other than unblinded role, eg, unblinded CRA). Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded at the time of primary analysis snapshot except as specified in Section 5.2 and Section 9.2.2.

The staff associated with tracking, assaying, and analyzing the PK, PD, and anti-AMG 416 antibody samples and data will not be blinded. Designated statistician(s) may be unblinded for performing PK/PD analyses to inform future study designs with AMG 416.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject, or may impact the safety of subjects currently enrolled, or subjects in subsequent cohorts. If deemed necessary, unblinding will be performed according to Amgen standard practices.

10.4 Planned Analyses

10.4.1 Interim Analyses

No formal interim analysis is planned

10.4.2 Primary Analysis

The primary analysis for this study will occur when all subjects have completed all planned study procedures up to and including the EOS visit, as outlined in the Schedule of Assessments, and any follow up of a clinically significant clinical or laboratory abnormality and following data base lock.

10.5 Planned Methods of Analysis

10.5.1 General Approach/Considerations

Demographics and safety data will be summarized by treatment groups. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety Analysis Set. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

10.5.2 Pharmacokinetic Endpoints

Plasma concentrations of AMG 416 will be determined using a validated assay. Individual and mean plasma concentration-time plots for AMG 416 will be presented. The PK parameters (ie, C_{max}, AUC_{last}) will be estimated using noncompartmental methods. Nominal dose and actual sampling time data will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter.

The PK analysis set will be used in the analyses for the primary endpoint.

10.5.3 Adverse Events

Subject incidence of all treatment-emergent adverse events, will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product and treatment-emergent hypocalcemia (depending on number of subject incidences) will be provided.

10.5.4 Vital Signs

Vital signs will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital sign data over time and/or changes from baseline over time by period may be provided.

10.5.5 Electrocardiograms

The ECG measurements from this clinical study are to be performed per standard of care for routine safety monitoring, rather than for purposes of assessment of potential

QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned. These data would not be expected to be useful for meta-analysis with data from other trials. Subject level listing will be provided for these measurements.

10.5.6 Clinical Laboratory Tests

Subject level data for all lab tests will be provided and reviewed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings. Additionally serum albumin, iPTH, cCa and phosphorus measurements will be summarized by treatment group for all scheduled visits. Change and percent change from baseline may also be summarized for all post-baseline scheduled visits by treatment group, as applicable.

10.5.6.1 Anti-drug Antibodies

The incidence and percentage of subjects who develop anti-AMG 416 antibodies (binding) at any time will be tabulated.

10.5.7 Exploratory Endpoints

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF 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 ICF is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative

after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any 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.

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF 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 for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB 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/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB 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 ICFs) 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 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 must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB 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 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, 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, ICFs, and subject identification list
- study files containing the protocol with all amendments, Investigator's Brochure, copies of pre study documentation, and all correspondence to and from the IRB and Amgen
- investigational product-related correspondence including proof of receipts, investigational product accountability record(s), return of investigational product for destruction form(s), and final investigational product reconciliation statement, as applicable
- non-investigational product 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 Amgen clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical

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

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

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

Data capture for this study is planned to be electronic:

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

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

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, 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

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

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

12.6 Publication Policy

To coordinate dissemination of data from this study, the investigator will solicit input and assistance from Amgen staff as appropriate.

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.
- 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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version, version 4 (CTCAE V 4) is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4.1 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.

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 6.4.1 and Appendix A or who experience AST or ALT elevations > 3 × 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 > 2 × 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 with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 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 nonprescription 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 Electronic Adverse Event Contingency Report Form

AMGEN Study # 20140197 AMG 416	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<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	Is 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? [illegible] (AMG416) No/ Yes/	Relationship (cont.) [illegible] Prefilled Autoinjector/ Pen/AI/Pen) Device No/ Yes/	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg. biopsy
				☐Yes ☐No					
				☐Yes ☐No					
				☐Yes ☐No					

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN
Study # 20140197
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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
Evolocumab (AMG 145)	☐ blinded ☒ open label						
1.0 mL Prefilled Autoinjector/Pen (AIPen) Device	☐ blinded ☒ open label						

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✓ YES✓	Continuing NO✓ YES✓	Dose	Route	Freq	Treatment Med NO✓ 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	Test / Unit										
Day Month Year											

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

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AMGEN
Study # 20140197
AMG 416

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 -	Title	Date
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.		

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Appendix C. Sample Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SUBJECT OR TYPE IN A FAX

1. Case Administrative Information

Protocol/Study Number: 20140197

Study Design: ☐ Interventions ☐ Observations (If Observations: ☐ 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: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

Appendix D. Sample Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

Amendment 3

Protocol Title: A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects with Chronic Kidney Disease on Hemodialysis

AMG 416

Amgen Protocol Number 20140197

Amendment 3 Date: 25 May 2018

Rationale:

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

- Updated Study Contacts information
- Administrative and formatting changes were made throughout the protocol
- Updated the introduction of the drug product including Clinical Experience and Risk Assessment to reflect the most up to date information
- Clarify that the assessment of Kt/V or URR can be performed at screening
- Corrected the process of subject Identification Number assignment
- Updated the time window of Day -2 12-lead ECG from 15 minutes after Hemodialysis rinse back to within 4 hours after Hemodialysis rinse back
- Corrected AE collection time requirement in the table footnote
- Moved Anti-drug antibodies test from Day -2 to Day 1 Pre HD
- Added statement explaining that if screening albumin, phosphorus, cCa, pregnancy, iPTH tests occur within 7 days prior to start of IP, then Day -2 lab tests can be waived
- Added acceptable windows for the timing of PK
- Added clarification that evaluations obtained as part of routine medical care may be performed prior to informed consent and may be used in place of the study specific evaluations, provided they are performed within 22 days prior to Day 1 and meet the time windows described in the protocol schedule
- Moved anti-drug antibody lab schedule from Day -2 to Day 1
- Removed the informed consent process of primary care physician in order to meet China situation. No primary care physician in China.
- Corrected the description of FSH test in section 7.3.11
- Corrected the CRF language from local language to English

Description of Changes :

Section: Global

Change:

correcting typographical and formatting errors

Section: Header Date

Replace:

Date : 20 September 2017

With:

Date : **25 May 2018**

Section: Title page

Delete:

~~EudraCT Number: 2012-002805-23~~

~~US IND number 109,773~~

Section: Title page

Replace:

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With:

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Section: Title page

Add:

Amendment 3 Date 25 May 2018

Section: Investigator's Agreement

Replace:

dated 08 Mar 2017

With:

dated **25 May 2018**

Section: Protocol Synopsis

Replace:

Baseline and Treatment: Two days before dosing (Day -2) baseline procedures will be performed. Eligible subjects should be randomized to investigational product in a 3:1 ratio to AMG 416 or placebo, and should then receive the first dose. On the morning of Day 1, enrolled subjects will receive the first 5 mg IV dose of AMG 416 given after hemodialysis. Following completion of all study procedures on Day 1, subjects will be released with instructions to return to the research facility at specified time points for dosing, collection of blood samples for PK, PD and completion of safety assessments (including blood samples for antibody analysis) through the end of the study according to the Schedule of Assessments.

IP will be administered at the end of dialysis on Study Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 (12 doses). Dialysis will continue thrice weekly without study drug administration with study visits for data collection on Study Days 29, 34, 41, 55 (EOS). Blood samples for the determination of PK parameters will be collected on Day 1 and 27 at predialysis, and at 10, 30, 60 and 90 min postdose, as well as on Day 2 and 28 between 18 and 30 h after study drug administration, and at predialysis on Days 3, 8, 15, 22, 27 (last dose), 29, 34, 41, and 55 (EOS) and at 10 min postdose on Days 8, 15 and 22. Subjects will have blood samples drawn for antibody determination on Day -2 and on days 29 and 55. Blood samples for exploratory [redacted] Electrocardiograms (ECG) will be performed at screening, on Day -2, and on days 28 and 55.

With:

Baseline and Treatment: **Subjects will return to the research facility for day -2 assessments.** Eligible subjects should be randomized to investigational product in a 3:1 ratio to AMG 416 or placebo, and should then receive the first dose. **On Day 1**, enrolled subjects will receive the first 5 mg IV dose of AMG 416 given after hemodialysis. Following completion of all study procedures on Day 1, subjects will be released with instructions to return to the research facility at specified time points for dosing, collection of blood samples for PK, PD and completion of safety assessments (including blood samples for antibody analysis) through the end of the study according to the Schedule of Assessments.

IP will be administered at the end of dialysis on Study Days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, 24, 27 (12 doses). Dialysis will continue thrice weekly without study drug administration with study visits for data collection on Study Days 29, 34, 41, 55 (EOS). Blood samples for the determination of PK parameters will be collected on Day 1 and 27 at predialysis, and at 10, 30, 60 and 90 min postdose, as well as on Day 2 and 28 between 18 and 30 h after study drug administration, and at predialysis on **Days 3, 8, 15, 22 , 29, 34, 41, and 55 (EOS)** and at 10 min postdose on Days 8, 15 and 22. Subjects will have blood samples drawn for antibody determination **prior to dosing on Day 1** and on days 29 and 55. Blood samples for exploratory

[redacted] Electrocardiograms (ECG) will be performed at screening, on Day -2, and on days 28 and 55.

Section: 2.2.2 Clinical Experience

Replace:

Five clinical studies have been completed to date. The first 2 clinical trials (phase 1a and phase 1b) evaluated the safety, tolerability, PK and pharmacodynamics (PD) of single doses in healthy male subjects and in hemodialysis subjects with SHPT, respectively. Most adverse events were mild or moderate in severity. The incidence of nausea, vomiting, and diarrhea was similar in subjects given AMG 416 or placebo. The administration of AMG 416 produced dose-dependent reductions in PTH in both healthy male subjects and in hemodialysis subjects with SHPT. Antibodies to AMG 416 were not detected following single dose exposures.

The AMG 416 phase 2 clinical program included a 4-week, double-blind, randomized, placebo-controlled study (Study 20120330 also known as KAI-4169-003) and a 12-week, open-label, dose-titration study (Study 20120331 also known as KAI-4169-005); both were conducted in hemodialysis subjects with SHPT, and the results are summarized in the Investigator's Brochure. Treatment with AMG 416 appeared to be generally safe and well-tolerated. The incidences of nausea, vomiting, or diarrhea were low and similar in subjects receiving AMG 416 or placebo. Serum iPTH levels decreased by 36.7% and 76.9%, respectively, from baseline values at the end of treatment among subjects given 5 or 10 mg doses of AMG 416. The reductions were significantly different in both dosage cohorts compared with placebo ($p < 0.01$ for both). Reductions in iPTH ≥ 30% from baseline occurred in 53.9% of subjects treated with 5 mg and in 76.2% of those treated with 10 mg of AMG 416, compared with 15.4% ($p = 0.10$) and 9.5% ($p < 0.0001$) of those given placebo. Dose-dependent reductions in serum calcium also were observed. There were no treatment-emergent (developing) antibody responses detected against AMG 416 following up to 4 weeks of dosing in hemodialysis subjects with SHPT. Pre-existing antibodies against AMG 416 were detected in 1 subject not previously exposed to AMG 416.

In a 12-week, single-arm, open-label, dose titration phase 2 study among hemodialysis subjects with SHPT, 5 mg was given thrice weekly during hemodialysis with subsequent dose increases to 10 mg after 4 weeks of treatment, and up to 15 mg or 20 mg after 8 weeks of treatment based upon serial measurements of iPTH and cCa the week before dose titration. Doses were reduced for low iPTH or low cCa. Thirty-seven subjects were enrolled in the study and 5 discontinued the study early. Three treatment-emergent serious adverse events were reported, but none were considered to be related to study drug. The final dose of AMG 416 ranged from 2.5 mg to 20 mg after 12 weeks. The mean reduction in iPTH at the end of the 12-week treatment period was 53%; furthermore, 82% of the subjects achieved a reduction in iPTH ≥ 30% at 12 weeks. The decreases in serum cCa were well tolerated, but 35% of subjects had 1 or more values of serum cCa < 8.0 mg/dL, and 2 subjects (5%) had 1 or more values of cCa< 7.5 mg/dL during treatment.

Four subjects (9%) reported symptomatic hypocalcemia as an adverse event. The incidences of treatment-emergent diarrhea (14%) and nausea (5%) were relatively low. The AMG 416 phase 3 program is designed to demonstrate the safety and efficacy of AMG 416 for the treatment of SHPT in CKD patients on hemodialysis. It is comprised of two 26-week, randomized, double-blind, placebo-controlled pivotal studies (Study 20120229 and Study 20120230) in CKD patients on hemodialysis with SHPT

(iPTH > 400 pg/mL) and one 26-week randomized, active-controlled, double-blind, double-dummy, dose-titration study (Study 20120360) in CKD patients on hemodialysis with SHPT (iPTH > 500 pg/mL). Safety will be evaluated in Studies 20120229, 20120230, and 20120360, and long-term safety of AMG 416 will be evaluated in 2 single-arm, open-label extension studies (Study 20120231 and Study 20120213). The objectives of these studies are to evaluate the efficacy of AMG 416 compared with placebo in the treatment of SHPT in CKD subjects receiving hemodialysis as assessed by the change from baseline in serum iPTH, cCa, cCa x P and phosphorus. Investigational product will be administered thrice weekly at the end of hemodialysis and the dose will be titrated to achieve iPTH levels ≤ 300 pg/mL while maintaining serum calcium levels within an acceptable range. Please refer to the Investigator's Brochure for additional information.

With:

Etelcalcetide has been studied in three 26-week phase 3 studies, 2 placebo-controlled trials (20120229 and 20120230), and 1 active-controlled trial (20120360). In Study 20120229, 74% of etelcalcetide subjects achieved > 30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP) versus 8.3% of placebo subjects (p < 0.001). In Study 20120230, 75.3% of etelcalcetide subjects achieved this endpoint versus 9.6% of placebo subjects (p < 0.001). Similarly, the proportion of etelcalcetide subjects who achieved mean predialysis PTH ≤ 300 pg/mL during the EAP was significantly higher in the etelcalcetide group than in the placebo group (p < 0.001) in both Studies 20120229 and 20120230. In Study 20120229, 49.6% of subjects in the etelcalcetide group and 5.1% of subjects in the placebo group achieved this endpoint, and 53.3% of subjects in the etelcalcetide group and 4.6% of subjects in the placebo group achieved this endpoint in Study 20120230. The events that occurred with a greater frequency among subjects in the etelcalcetide group compared with subjects in the placebo group (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo) were blood calcium decreased (63.8% etelcalcetide; 10.1% placebo), muscle spasms (11.5% etelcalcetide; 6.6% placebo), diarrhea (10.7% etelcalcetide; 8.6% placebo), nausea (10.7% etelcalcetide; 6.2% placebo), vomiting (8.9% etelcalcetide; 5.1% placebo), headache (7.6% etelcalcetide; 6.0% placebo), and hypocalcemia (7.0% etelcalcetide; 0.2% placebo). An additional phase 3 study (20120360) was performed to compare the therapeutic efficacy of etelcalcetide and cinacalcet for lowering serum PTH concentrations among subjects with CKD and SHPT receiving maintenance hemodialysis. A higher observed percentage of subjects in the etelcalcetide group (77.9%) had a > 30% reduction from baseline in serum PTH during the EAP compared with the cinacalcet group (63.9%). The estimated treatment difference (cinacalcet - etelcalcetide) was -10.48% (95% confidence interval [CI]: -17.45%, -3.51%). Because the upper bound of the 95% CI is < 12% (the prespecified margin for noninferiority), etelcalcetide is noninferior to cinacalcet in the proportion of subjects with a > 30% reduction from baseline in serum PTH during the EAP. Additionally, etelcalcetide was superior to cinacalcet on the proportion of subjects achieving a > 50% and a > 30% reduction from baseline in mean predialysis serum PTH during the EAP. There was no significant difference in the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment, as measured by a patient-reported outcome instrument. The most common (> 10% in either treatment group) adverse events (etelcalcetide, cinacalcet) were asymptomatic decreased blood calcium (68.9%, 59.8%), nausea (18.3%, 22.6%), vomiting (13.3%, 13.8%), and diarrhea (6.2%, 10.3%). Symptomatic

hypocalcemia was reported for 17 subjects (5.0%) in the etelcalcetide group and 8 subjects (2.3%) in the cinacalcet group. Please refer to the Investigator's Brochure for additional information.

Section: 2.2.2.1 Clinical Pharmacokinetics

Replace:

Preliminary population PK analysis was conducted using the PK data from patients receiving hemodialysis. The dataset consisted of 1775 plasma samples from 143 subjects, with 96 subjects receiving IV doses ranging from 2.5 mg to 60 mg of AMG 416.

With:

Population PK analysis was conducted using the PK data from patients receiving hemodialysis. ~~**The dataset consisted of 1775 plasma samples from 143 subjects, with 96 subjects receiving IV doses ranging from 2.5 mg to 60 mg of AMG 416.**~~

Section: 2.2.2.1 Clinical Pharmacokinetics

Delete:

~~**The estimated non-specific linear clearance (CL) and the hemodialysis CL were 0.564 L/h and 22.2 L/h, respectively. The distribution volumes of the central and the two peripheral compartments were 37.6, 105, and 482 L, respectively. Inter-individual variability in AMG 416 distribution and elimination were relatively moderate to high, with coefficient of variation in key PK parameters ranging from approximately 50% to 100%**~~

Section: 2.3 Risk Assessment

Replace:

Safety reporting for all subjects in open-label and blinded studies completed as of May 1st 2014 and the investigators brochure have identified the following risks: The important identified risk is hypocalcemia, which will be mitigated in the protocol by close monitoring, and treatment as required. Other important potential risks include 1) injection and hypersensitivity reactions, 2) ventricular arrhythmias, 3) hypophosphatemia, 4) convulsions, 5) adynamic bone, 6) worsening heart failure, and 7) coadministration of cinalcalcet. Coadministration of cinacalcet and AMG 416 is contraindicated until further studies inform the safety of simultaneous administration of these agents. The likelihood of these risks occurring with the planned dose as planned for this study is expected to be low. In this study, cinacalcet will be prohibited from 30 days prior to informed consent and throughout the study.

Please refer to the Investigator's Brochure, Section 7 for a complete description of potential risks related to AMG 416.

With:

Safety reporting for all subjects in open-label and blinded studies completed as of 10 November 2017and the investigators brochure have identified the following risks:

Important identified risks:

- **Hypocalcemia**
- **Worsening heart failure**
- **QT prolongation secondary to hypocalcemia**

Important potential risks:

- **Ventricular arrhythmias**
- **Infusion and hypersensitivity reactions**
- **Convulsions (seizures)**
- **Adynamic bone**
- **Co-administration of cinacalcet (HCl) and etelcalcetide**

The important identified risk is hypocalcemia, which will be mitigated in the protocol by close monitoring, and treatment as required. Coadministration of cinacalcet and AMG 416 is contraindicated until further studies inform the safety of simultaneous administration of these agents. The likelihood of these risks occurring with the planned dose for this study is expected to be low. In this study, cinacalcet will be prohibited from 30 days prior to informed consent and throughout the study.

Please refer to the Investigator's Brochure, Section 7 for additional information for the investigator.

Section: 3.1 Study Design

Replace:

Subjects will participate in the study as outpatients on scheduled study Day -2 through Day 55 (EOS) while receiving hemodialysis three times a week.

With:

Subjects will participate in the study as outpatients on scheduled study **Day 1** through Day 55 (EOS) while receiving hemodialysis three times a week.

Section: 3.1 Study Design

Delete:

The overall study design is described by a study schema at the end of the ~~**8 March 2017**~~ protocol synopsis section.

Section: 4.1.5 Inclusion Criteria

Add:

Subject must be receiving hemodialysis 3 times weekly for at least 3 months through a functioning permanent dialysis access prior to Day -2 and have adequate hemodialysis with a delivered Kt/V ≥ 1.2 or urea reduction ratio (URR) ≥ 65% within 4 weeks to screening **or at screening**. The subject's routine hemodialysis session must be of 3-4. 5 hours in duration, inclusive

Section: 4.2.1 Exclusion Criteria

Add:

Corrected calcium (calculated) level is < 2.07 mmol/L (8.3 mg/dL), and/or intact PTH level is outside the range of 31.8 – 127.2 pmol/L (300 - 1200 pg/mL) **at screening and Day -2 (Day -2 assessments are only required if screening visit performed greater than 7 days prior to Day 1)**

Section 5 Subject Enrollment

Replace:

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a unique subject identification number assigned by IVR/WR before any study-related activities/procedures are performed.

With:

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the ICF) will receive a unique subject identification number **assigned manually** before any study-related activities/procedures are performed.

Section: 5.1 Randomization/Treatment Assignment

Replace:

Subjects will be randomized by IVR/IWR in a 3:1 ratio to either TIW IV etelcalcetide or placebo in a double-blind manner prior to the first dose of IP. Treatment groups will be blinded to the investigator (other than unblinded pharmacist), subjects, and the Amgen study team.

With:

Subjects will be randomized by IVR/IWR in a 3:1 ratio to either TIW IV etelcalcetide or placebo in a double-blind manner prior to the **Day 1 activities**.

Section: 7.1 Schedule of Assessments
Table 1a Schedule of Non-Laboratory Assessments-Footnotes

Replace:

[e] Subjects will remain seated for at least 10 minutes prior to measurement of predialysis pulse rate and blood pressure. Vital signs will include blood pressure, heart rate, respiratory rate, and oral or ear temperature. Vital signs will be obtained pre-dialysis treatments on scheduled dialysis days, and at ET and on Day 55 (EOS).

[f] Subjects will remain supine for at least 5 minutes prior to recording 12-lead electrocardiogram (ECG). Screening 12-lead ECG will be recorded prior to hemodialysis. The Day -2 12-lead ECG will be recorded 15 minutes after hemodialysis rinse back. After the last dose of investigational product on Day 27, 12-lead ECGs will be recorded between 18 and 30 hours (recorded on day 28) post-dose.

[g] Adverse events including serious adverse events will be monitored and recorded from the time of informed consent through Day 55.

With:

[e] Subjects will remain seated for at least 10 minutes prior to measurement of predialysis **heart rate** and blood pressure. Vital signs will include blood pressure, heart rate, respiratory rate, and oral or ear temperature. Vital signs will be obtained pre-dialysis treatments on scheduled dialysis days, and at ET and on Day 55 (EOS).

[f] Subjects will remain supine for at least 5 minutes prior to recording 12-lead electrocardiogram (ECG). Screening 12-lead ECG will be recorded prior to hemodialysis. The Day -2 12-lead ECG will be recorded **within 4 hours** after hemodialysis rinse back. After the last dose of investigational product on Day 27, 12-lead ECGs will be recorded between 18 and 30 hours (recorded on day 28) post-dose.

[g] **Adverse events will be monitored and recorded from the dose of investigational product (AMG 416) or placebo.** Serious adverse events will be monitored and recorded from the time of informed consent through Day 55.

Section 7.1 Schedule of Assessments Table 1b Schedule of Laboratory Assessments

Add:

Table 1b. Schedule of Laboratory Assessments

Time	Assessment	Study Visit (Day)																			
		Screening	-2	1 (HD)	2	3 (HD)	6 (HD)	8 (HD)	10 (HD)	13 (HD)	15 (HD)	17 (HD)	20 (HD)	22 (HD)	24 (HD)	27 (HD)	28	29/ ET[a] (HD)	34 (HD)	41 (HD)	55 (HD)
Laboratory Assessments																					
Pre HD	Hematology, PT, aPTT[c]	X		X							X							X			X
	Clinical Chemistry	X		X							X							X			X
	Albumin[d]	X	X[b]	X		X		X			X			X		X		X	X	X	X
	Phosphorus	X	X[b]			X		X			X			X		X			X	X	X
	Calcium (cCa)[d]	X	X[b]	X				X			X			X		X		X	X	X	X
	Serum or Urine Pregnancy (females only)	X	X[b]																X		
	Serum FSH[g] (female only)	X																			
	Breath Alcohol Screen	X	X																		
	HIV, Hep C Ab, HBsAg	X																			
	iPTH	X	X[b]	X				X			X			X		X			X	X	X
	25(OH) vitamin D	X																			
	Kt/V or URR [e]	**X**																			
	Anti-drug antibodies[f]			**X**														X			X

Footnotes displayed on the next page

HD = hemodialysis; ET = early termination; cCa = albumin-corrected calcium; SDA = Study drug administration ; **Kt/V = measure of dialysis adequacy; URR = urea reduction ratio**

[a] If a treated subject withdraws from study before completion of dosing, the investigator will make every effort to obtain day 29 samples as close to 2 days after the last dose of investigational product as possible.

[b] **If screening albumin, phosphorus, cCa, pregnancy, and iPTH tests occur within 7 days prior to start of IP, then Day -2 lab tests can be waived.** ~~Pregnancy tests will be performed in women of child bearing potential within 7 days prior to start of investigational product.~~

[c] Blood sample for PT and aPTT will be drawn prior to heparin administration for dialysis. Day 1 hematology and coagulation tests will be performed only if day 1 occurs more than 2 weeks after the screening hematology and coagulation tests.

[d] Serum samples for albumin and calcium for screening and routine monitoring of predialysis cCa. When albumin is less than 4.0 g/dL, the calcium level will be corrected according to the formula: cCa (mg/dL) = total Ca (mg/dL) + (4 – albumin (g/dL))*0.8. Corrected calcium results will inform dosing/dose withholding at the next hemodialysis treatment.

[e] **Perform Kt/V or URR assessment at screening unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available**. ~~Baseline iPTH is the average of predialysis iPTH levels on day -2 (may be collected up to -4 if needed) and day 1.~~

[f] Serum samples for anti-drug antibodies will be collected predialysis on **days 1**, 29, and 55. Any subjects with positive titers for antibodies to AMG 416 may be asked to return to the clinical research unit to provide additional serum samples.

[g] Luteinizing hormone and estradiol levels may additionally be collected if deemed necessary for confirmation of postmenopausal status as described in exclusion criteria section 4.2.4.

Section: 7.2 General Study Procedures

Add:

Study tests and procedures will be performed only after written informed consent is obtained. All screening procedures must be completed within 22 days before investigational product administration (Day 1). Eligible subjects will be admitted to the clinical research facility on Day -2 at which time continued eligibility will be reconfirmed and baseline safety assessments will be performed. Subjects will be administered AMG 416 or placebo on Day 1 **after completion of baseline assessments.**

Section: 7.2 General Study Procedures

Add:

Every effort should be made to conduct study procedures as scheduled. Acceptable windows for the timing of PK are as follows:

- **Plus or minus 2 mins for the 10 min sample**
- **Plus or minus 5 mins for the 30 min sample**
- **Plus or minus 10 mins for the 60 min sample**
- **Plus or minus 15 mins for the 90 min sample**
- **Plus or minus 4 hours for the 18-30 hour post dose samples**

Section: 7.2.1 Screening

Add:

- Laboratory assessments (all pre-hemodialysis samples)
  - Clinical hematology
  - Clinical chemistry
  - PT, aPTT
  - Albumin, Phosphorus, Calcium (cCa)
  - Serum or urine pregnancy test (women of child-bearing potential only; within 7 days prior to first study drug administration)
  - Serum FSH (females only)
  - Breath alcohol screen
  - HIV, Hepatitis C Antibody, Hepatitis B surface antigen
  - iPTH
  - 25(OH) vitamin D
  - **Kt/V or URR**

Subjects who meet the eligibility criteria after completion of all screening, Day -2 procedures will be considered enrolled in the study.

If screening albumin, phosphorus, cCa, pregnancy, and iPTH tests occur within 7 days prior to start of IP, then Day -2 lab tests can be waived.

Day -2 assessments will be performed 2 days before investigational product administration. Day -2 assessments will include recording the date and time of the last hemodialysis treatment before investigational product administration.

Evaluations obtained as part of routine medical care may be performed prior to informed consent and may be used in place of the study specific evaluations, provided they are performed within 22 days prior to Day 1 and meet the time windows described above.

Section: 7.2.2 Day -2

Add:

Two days before dosing (day -2) the following baseline procedures will be performed **and confirmed to meet eligibility requirement:**

Section: 7.2.2 Day -2

Delete:

iPTH ~~**(may be collected up to day -4 if needed)Anti-Drug Antibodies**~~

Section: 7.2.3 Treatment (Day 1-27) and Follow up Periods (Day 28-55)

Delete:

On the ~~**morning of**~~ day 1 the following predose activities will be conducted:

Section: 7.2.3 Treatment (Day 1-27) and Follow up Periods (Day 28-55)

Add:

- Laboratory assessments and predose collections (pre-hemodialysis samples):
    - Hematology, PT, aPTT
    - Clinical chemistry
    - Calcium (cCa)
    - iPTH
    - Albumin
    - **Anti-Drug Antibodies**
    - Pre-hemodialysis PK sample

Section: 7.3.10 Table 2 Chemistry, Hematology

Add:

Chemistry	Hematology	Other Labs
Sodium Potassium Chloride Total protein Albumin Glucose (Random) Blood urea nitrogen Creatinine Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Calcium Adjusted Calcium Creatinine phosphokinase Phosphorus Thyroid-stimulating hormone (TSH)[a]	Red blood cells Hemoglobin Hematocrit Mean corpuscular volume Platelets White blood cells Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Antidrug Antibodies Hep B surface antigen Hep C antibody HIV Pregnancy Intact PTH (iPTH) 25-hydroxyvitamin D PK PT aPTT FSH[b] Luteinizing hormone[b] Estradiol[b] Syphilis[c] **Urea/BUN[d]**

[a] Only required at screening for subjects who have a history of hyper- or hypothyroidism and do not have available TSH results within 6 months prior to screening
[b] Females only, and only collected if deemed necessary for confirmation of postmenopausal status as described in exclusion criteria section 4.2.4
[c] Only collected at screening when investigator consider it is necessary
d Urea/BUN measurement to be performed locally for Kt/V or URR assessment at screening, unless a qualifying Kt/V or URR measurement from within 4 weeks prior to screening assessments is available.

Section: 7.3.11 Follicle Stimulating Hormone Test (Females Only)

Replace:

Serum FSH is not required for subjects who have had a hysterectomy, and/ or who are at least 6 weeks post-surgical bilateral oophorectomy (with or without hysterectomy) as documented in medical history and verified with an operative note, if available.

With:

Serum FSH is required for subjects as described in exclusion criteria section 4.2.4 (age < 55 years and spontaneous menses within the past 1 years, but currently amenorrheic).

Section 10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Add:

Treatment groups will be blinded to the investigator (other than unblinded pharmacist), subjects, and the Amgen study team (other than unblinded role, eg, unblinded CRA)

Section 11.1 Informed Consent

Delete:

~~**The investigator is also responsible for asking the subject if he/she 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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the subject or legally acceptable representative.**~~

Section 12.5 Language

Replace:

CRFs must be completed in the local language.

With:

CRFs must be completed in **English.**

Amendment 2

Protocol Title: A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects with Chronic Kidney Disease on Hemodialysis

Amgen Protocol Number AMG 416, 20140197

Amendment Date: 20 Sep 2017

Rationale:

The protocol is being amended to:

1. Correct the typo of the range of intact PTH level.
2. Move 25(OH) vitamin D testing from Day1 to screening because a vitamin D level taken within the screening window before Day 1 should be representative of Day 1 as vitamin D level is not likely to change much in such a short time.
3. Add Albumin testing on Day 1 and Day 29 because corrected Calcium is needed so albumin will be necessary.
4. Add oral temperature as an additional alternative besides ear temperature. Ear temperature has been the general practice for most of the China sites. This will be more flexible for the investigators.
5. Add syphilis, B ultrasound testing as the optional tests when the investigator consider it necessary. Syphilis testing is recommended to be done in screening for clinical trials and the subjects with chronic kidney disease on hemodialysis will perform syphilis testing twice a year so it's optional. B ultrasound is recommended to be optional in the screening to exclude ovarian cancer.
6. Remove 'Bicarbonate' from Chemistry. Some sites do not conduct this testing and it is not critical testing for this study.
7. Add 'urine pregnancy testing' as an additional alternative besides serum pregnancy testing. Some sites prefer to use urine pregnancy testing instead of serum pregnancy testing. This will be more flexible for the investigators.
8. Modify the language of the timing of randomization to 'prior to dosing' in order to accurately clarify when the randomization happens.
9. Delete the 'Monday' to 'Sunday' in the schedule of assessments to make it more flexible for the investigators.
10. Modify the collection date of baseline iPTH up to Day -4 if needed in order to get result prior to dosing.

Amendment 1

Protocol Title: A Phase 1, Multiple Dose, Randomized, Double-blind, Placebo-controlled Study to Evaluate Pharmacokinetics, Safety and Tolerability of AMG 416 Administered Intravenously to Chinese Subjects With Chronic Kidney Disease on Hemodialysis

Amgen Protocol Number AMG 416, 20140197

Amendment Date: 08 March 2017

Rationale:

The protocol is being amended to:

1. Add IVR/IWR for this study
2. Align with the latest version of DES
3. Simplify some study procedures, for example, weight, vital sign and ECG
4. Make administrative, typographical and formatting changes throughout the protocol. Updates have been implemented to align with the current template.
5. Delete all the relevant verbiage related to M11 throughout the protocol because the team considers M11 assay as too variable
6. Delete the verbiage " Day -2 assessments will be performed 2 days before IP administration and Day-2 and Day -1 are not HD days." in order to provide the flexibility on the scheduling of HD prior to Day 1.
7. Some deleted text has been involved in other section (for example, a paragraph in Section 7.2 has been already involved in Section 7.5)