CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208325Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208325	Submission Date(s): 08/24/2015
Brand Name (Proposed)	Parsabiv
Generic Name	Etelcalcetide
Clinical Pharmacology Reviewer	Ritesh Jain, Ph.D.
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OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	KAI Pharmaceuticals, Inc.
Submission Type; Code	505(b)(1); Standard
Formulation; Strength(s)	2.5 mg Etelcalcetide in 0.5 mL solution in a single-use vial 5 mg Etelcalcetide in 1 mL solution in a single-use vial 10 mg Etelcalcetide in 2 mL solution in a single-use vial
Proposed Indication	Indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis.

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1 Executive Summary

Etelcalcetide HCl (AMG 416) is a synthetic peptide of 7 D-amino acids linked to L-cysteine by a disulfide bond. Etelcalcetide is a calcium-sensing receptor agonist (calcimimetic agent) indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis.

Etelcalcetide is intended to be administered through intra venous (IV) route in CKD patients on hemodialysis. Recommended starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. To achieve the target parathyroid hormone (PTH) levels dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 208325 (dated 08/24/2015), and recommend approval.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The clinical program to support the proposed indication includes 16 clinical studies -five Phase 1 studies, three Phase 2 studies, and eight Phase 3 studies. The efficacy of etelcalcetide for the treatment of secondary hyperparathyroidism (HPT) in patients with CKD on hemodialysis is primarily supported by two pivotal, double-blind, placebo-controlled 26-week studies Phase 3 studies (study 20120229 and study 20120230). In addition, the clinical pharmacology program included 10 in-vitro studies that were conducted to evaluate permeability, plasma protein binding, potential metabolic drug-drug interactions, transporter interactions, biotransformation, red blood cell partition, dialysis clearance, and conjugation-deconjugation kinetics of etelcalcetide.

Pharmacokinetics

Absorption	• Dose-proportional PK (0.5 mg-10 mg dose range) in healthy subjects following single dose IV bolus administration. • Dose-dependent PK (5 mg-60 mg dose range) in CKD patients on dialysis, following single IV bolus administration. • In CKD patients, 12 fold increase in dose resulted in 7.86- and 14.1-fold increase in mean AMG 416 C_{max} and AUC_{65hr}

	respectively. • Multiple dosing for four weeks in CKD patients on dialysis is associated with etelcalcetide accumulation of 2-3 folds.
Distribution	• Based on the population pharmacokinetic analysis, the volume of distribution at steady state (V_{ss}) in CKD patients receiving hemodialysis is approximately 796 L. • Etelcalcetide is primarily bound to plasma albumin and the plasma non-covalent protein binding is less than 50%. • The blood to plasma ratio of etelcalcetide is approximately 0.6.
Metabolism	Based on the In-vitro study results : • The predominant biotransformation product, serum albumin peptide conjugate (SAPC), is formed by reversible covalent binding of the Etelcalcetide D-amino acid peptide backbone to albumin. Etelcalcetide is bio transformed by disulfide exchange with endogenous thiols. • Etelcalcetide is not metabolized and is not a substrate for cytochrome P450 enzymes. • Etelcalcetide is not shown to inhibit or induce cytochrome P450 enzymes. • Etelcalcetide is neither a substrate nor an inhibitor of common human efflux (P-glycoprotein, breast cancer resistance protein, bile salt export pump) and uptake (organic anion transporters 1 and 3, organic anion polypeptide transporters 1B1 and 1B3, organic cation transporter 2, and peptide transporters 1 and 2) drug transporters.
Excretion	• The effective half-life is around 5 to 7 days in CKD patients with hemodialysis. • Hemodialysis is the predominant route of etelcalcetide elimination in CKD patients requiring hemodialysis. • The hemodialysis clearance of etelcalcetide is 7.66 L/hr in CKD patients requiring hemodialysis. • Following a single radiolabeled dose of etelcalcetide, in CKD patients with secondary HPT requiring hemodialysis, approximately 60% of [^{14}C]-etelcalcetide is recovered in dialysate, and approximately 7% recovered in urine and feces combined over 175 days of collection period.

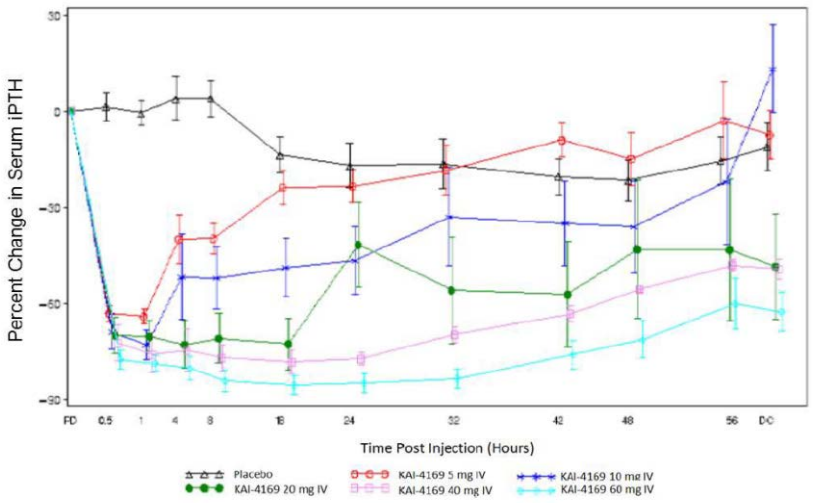
Pharmacodynamics

Healthy Subjects

- Single dose IV administration in healthy subjects showed a dose-dependent (0.5 mg-10 mg) serum parathyroid hormone (PTH) suppression with maximum suppression at 30 minutes post dose.
- In the single dose Phase 1 study, maximum observed serum PTH reduction from the baseline is 3.5%, 21.7%, 55.4%, 69.0%, and 72.6% following IV administration of placebo, 0.5, 2, 5, and 10 mg dose groups, respectively. The serum PTH levels gradually returned to baseline within 10 to 24 hours.

Hemodialysis Subjects with Secondary Hyperparathyroidism:

- Single dose IV administration of etelcalcetide, in hemodialysis subjects with secondary hyperparathyroidism subjects showed dose-dependent (5 mg-60 mg) PTH suppression with maximum suppression within one hour post dose.
- In the single dose study, etelcalcetide doses of 20 mg and greater is associated with sustained suppression throughout the approximately 3-day observation period (Figure 1).
- Single dose study in hemodialysis subjects, maximum observed serum PTH reduction from baseline is 36%, 65%, 73%, 75%, 83% and 86% following single dose IV administration of placebo, 5, 10, 20, 40, and 60 mg dose groups, respectively.
- Serum PTH levels gradually returned to baseline within 10 to 24 hours.



CKD = chronic kidney disease; DC = discharge; iPTH = intact parathyroid hormone; IV = intravenous; PD = predose; PTH = parathyroid hormone; SEM=standard error of the mean

Figure 1: Mean (± SEM) Percent Change From Baseline in Serum PTH Versus Time in Phase 1 Study 20130139.

Source: Sponsor report on Clinical Pharmacology Page 26

Starting Dose and Dose Titration

Dose titration scheme was used to achieve desired normal range levels for PTH and calcium based on individualized treatment goals. Dose-response data from Phase 1 and Phase 2 trials, showed reduction in serum PTH levels and formed the basis for selection of 5 mg administered three times a week (TIW) as the starting dose for the subsequent pivotal Phase 3 studies. Sponsor's starting dose of 5 mg TIW seems reasonable as the majority of patients were escalated to doses greater than 5 mg TIW with a maximum of 15 mg TIW dose in the two pivotal Phase 3 trials. Patients with higher baseline PTH levels needed higher doses upon titration, and yet efficacious with doses within the titration range. Majority of patients reached stable dose within 12 weeks generating ~75% response rate with the titration scheme. Thus, applicant's proposed dose titration scheme based on target PTH and corrected calcium (cCa) appears to be reasonable. Based on the proposed titration scheme, in the pivotal Phase 3 trials the primary efficacy endpoint (proportion of subjects achieving >30% reduction in PTH from the baseline) was 74.0% in Study 20120229 and 75.3% in Study 20120230.

Dose/Exposure-Response for Safety

Based on the population PKPD analysis, a clear dose-response relationship for corrected serum calcium levels was observed. Simulations based on the PK/PD analysis indicate that the proportion of subjects with corrected Ca <7.5 mg/dL following 2.5 mg, 5 mg, 10 mg, and 15 mg fixed doses increases with increasing dose. These simulations also show that the starting dose of 5 mg followed by titration algorithm implemented in phase 3 is expected to provide reasonable calcium lowering, while maintaining an acceptable safety profile, compared to other fixed dosing regimens.

No. One of safety concerns regarding dose titration scheme was the potential overdose resulting in excessive PTH reduction (less than 100 pg/mL) and thereby causing adynamic bone disease. A graphical assessment on doses for patients - with PTH less than100 pg/mL in comparison with those with PTH above 100 pg/mL indicates that these patients received lower dose than those with PTH above 100 pg/mL. Thus, this analysis supports that higher titrated dose does not necessary generate excessive PTH reduction in individual patients

Intrinsic/Extrinsic Factors

Based on the PopPK analysis, body weight (29 to 163 kg), sex, , race (White and Black), and age (20 to 93 years of age) do not influence the pharmacokinetics of etelcalcetide. Hepatic impairment PK study was not conducted. Based on the in vitro study results, no pharmacokinetic drug-drug interaction is expected with Etelcalcetide and was not conducted. Immunogenicity assessment from the phase 3 studies (trials # 20120230 and 20120229) indicates no significant impact of anti-AMG 416 antidrug antibody on the concentration of AMG 416 in the trial subjects over time.

Formulation Changes: Sponsor used Etelcalcetide (b) (4) parenteral drug product in the pivotal Phase 3 clinical studies and the proposed to be marketed formulation is a ready-to-use (RTU) liquid drug product. Sponsor is requesting a waiver for an in-vivo bioequivalence (BE) study between the Etelcalcetide (b) (4) parenteral clinical drug product used in phase 3 clinical studies and the Etelcalcetide ready-to-use (RTU) liquid

drug product intended for commercial use. Bio waiver request will be reviewed by OPQ Biopharmaceutics group.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

Etelcalcetide (AMG 416) is a novel calcimimetic being developed for the treatment of secondary HPT (HPT) in patients with chronic kidney disease (CKD) who are receiving hemodialysis. AMG 416 is a synthetic peptide comprised of 7 D-amino acids linked to an L-cysteine via a disulfide bond that acts as an allosteric activator of the calcium-sensing receptor (CaSR). AMG 416 suppresses secretion of parathyroid hormone (PTH) in a dose-dependent manner.

Etelcalcetide is intended to be administered through intra venous route in CKD patients on hemodialysis. Recommended starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH).

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Agency had several interactions with the sponsor during the development program of Etelcalcetide.

- In written responses to a meeting in 2011, Agency requested assessment of the distribution, metabolism and excretion of Etelcalcetide; given that it is a novel peptide. Results from Study 20120147, a phase 1, open-label, human ADME study, are provided in the current submission.
- In the EOP 2 meeting in July 2012, Agency agreed that no thorough QT/QTc study was necessary and agreed upon the timing of the ECG assessments included in the 2 Phase 3, placebo-controlled studies. Agency also agreed with the Sponsor's proposal to assess the potential for AMG 416 drug-drug interactions by conducting in-vitro studies as described in the Guidance on Drug Interactions Studies. Results from these in-vitro studies are provided in this marketing application.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Etelcalcetide, AMG 416 is a synthetic peptide comprised of 7 D-amino acids linked to L-cysteine by a disulfide bond. The molecular formula is $C38H73N21O10S2 \cdot xHCl$ ($4 \leq x \leq 5$) with a molecular weight of 1047.5 (monoisotopic; free base). The drug substance is hydrochloride salt in the form of a powder, white to off-white in color. The drug

substance is [redacted] water-soluble [redacted] amorphous, hygroscopic [redacted], with no known secondary and tertiary structures. The AMG 416 hydrochloride sequence formula is shown Figure 2 and the structural formula is shown in Figure 3.

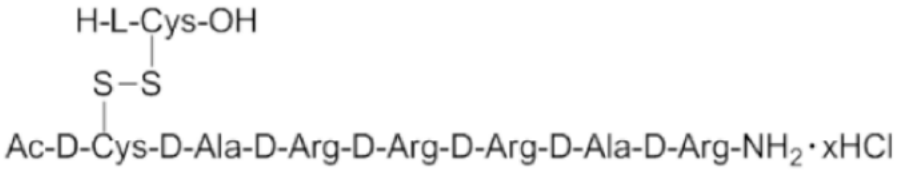


Figure 2: Etelcalcetide Sequence Formula

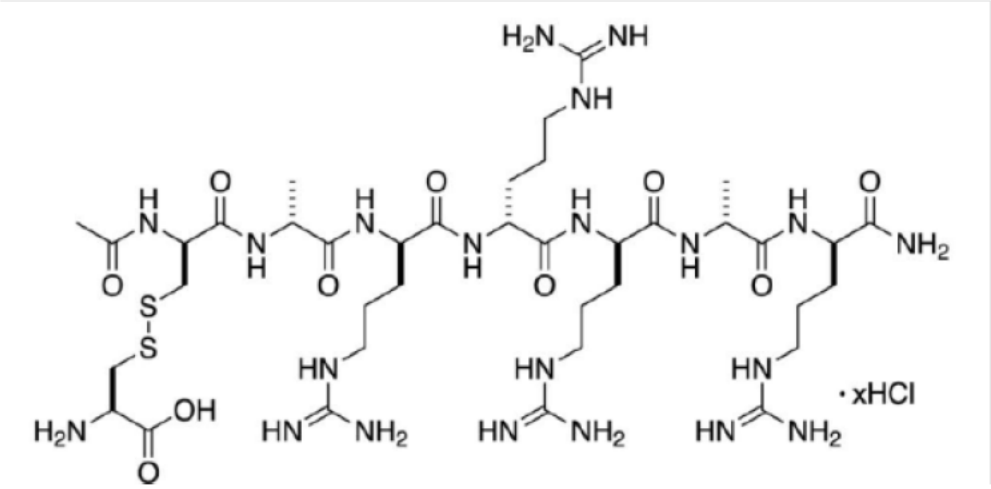


Figure 3:Etelcalcetide Structural Formula

Drug Product and Formulation:

AMG 416 drug product is supplied in 3 strengths (2.5 mg/0.5 mL, 5 mg/1.0 mL, and 10 mg/2.0 mL) for intravenous administration as a sterile, single-use, preservative-free liquid solution in 3 cc Type I glass vials with 13 mm stopper. The quantitative composition of Etelcalcetide liquid solution is shown in Table 1.

All the strength has the identical formulation (Table 1) and primary packaging components, and differs only in the deliverable volume. For each product strength, the concentration of AMG 416 as free base equivalent is 5 mg/mL, formulated with 10 mM succinic acid and 0.85% (w/v) sodium chloride, and adjusted to pH 3.3 with sodium hydroxide and/or hydrochloric acid. The deliverable volume and AMG 416 content for

each of the 3 strengths is as follows: 0.5 mL (containing 2.5 mg AMG 416 as free base equivalent), 1.0 mL (5 mg) and 2.0 mL (10 mg).

Table 1: Quantitative Composition of AMG 416 Drug Product

Component	Function	Standard	Concentration	Quantity per Vial for Stated Label Strength [a] 2.5 mg	5.0 mg	10 mg
AMG 416 Hydrochloride	Active Ingredient	In House[b]				(b) (4)
Sodium Chloride	(b) (4)	USP, PhEur, JP	8.5 mg/mL (0.85%)			(b) (4)
Succinic Acid		USP-NF, JP	1.2 mg/mL (10 mM)			
						(b) (4)
Hydrochloric Acid	pH adjustment	USP-NF, PhEur, JP	qs to pH	qs to pH	qs to pH	qs to pH
Sodium Hydroxide	pH adjustment	USP-NF, PhEur, JP[e]	qs to pH	qs to pH	qs to pH	qs to pH

qs = quantity sufficient to reach target

[a] Quantities are based on deliverable volume. Label strength is stated as AMG 416 quantity (free base equivalent).

[b] 3.2.S.4.1 (Specification)

[c] The concentration of AMG 416 as free base is determined (b) (4) See section 3.2.P.3.3

(b) (4)

(b) (4)

[e] A solution of sodium hydroxide may be used for pH adjustment. The supplier tests the sodium hydroxide (b) (4) to the stated compendial standards

Source: Sponsor's report of Quality Overall Summary, Page 62

2.1.3 What is the mechanism of action and therapeutic indication?

Secondary HPT is a disorder characterized by parathyroid gland hyperplasia and increased concentrations of circulating PTH. The principal regulator of PTH secretion is the calcium sensing receptor (CaSR) in parathyroid tissue. Calcimimetics target the CaSR in parathyroid tissue[1], [2] and regulates PTH levels. Etelcalcetide is a calcimimetic agent and binds to the CaSR receptors and suppress the secretion of PTH. Nonclinical and in-vitro studies have shown that etelcalcetide specifically binds to and activates the CaSR, which reduces PTH secretion from the parathyroid gland. Please also refer to Pharmacology and Toxicology review by Dr. Miyun Tsai-Turton for further details. In

[1]Brown EM, Hebert SC. A cloned extracellular Ca(2+)-sensing receptor: molecular mediator of the actions of extracellular Ca2+ on parathyroid and kidney cells? *Kidney Int.* 1996;49:1042-1046

[2] Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. *Nature*. 1993;366:575-580.

Phase 1 and Phase 2 trials etelcalcetide is shown to suppress PTH levels in a dose dependent manner.

Etelcalcetide is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis.

2.1.4 What are the proposed dosage and route of administration?

The recommended initial dose of Etelcalcetide is 5 mg administered by bolus injection 3 times per week.

Proposed Dosage and Administration:

The recommended initial dose of Etelcalcetide is 5 mg administered by bolus injection 3 times per week.

- Corrected serum calcium should be (b) (4) mg/dL prior to administration of first dose of Etelcalcetide, a dose increase of Etelcalcetide, or re-initiation of Etelcalcetide after a dose stop. Etelcalcetide doses are titrated so that dosages are individualized between 2.5 mg and 15 mg.
- Measure PTH after 4 weeks from initiation or dose adjustment of Etelcalcetide to determine the need for dose adjustment.
- The dose of Etelcalcetide may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target PTH. If PTH is below the target range, reduce the dose of Etelcalcetide or temporarily stop administration. If the dose is stopped, then reinitiate Etelcalcetide at a lower dose to achieve the desired PTH target.
- Do not administer Etelcalcetide more frequently than 3 times per week. If a regularly scheduled hemodialysis treatment is missed, do not administer any missed doses.
- If doses of Etelcalcetide are missed for more than 2 weeks, then administer Etelcalcetide at 5 mg (or 2.5 mg if that was the patient's last administered dose) and titrate to achieve the desired parathyroid hormone (PTH).

2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?

No. Sponsor is requesting a waiver for in-vivo bioequivalence (BE) study requirements to establish BE between the Etelcalcetide (b) (4) parenteral clinical drug product used in phase 3 clinical studies and the Etelcalcetide ready-to-use (RTU) liquid drug product formulation intended for commercial use. Sponsor has based their justification for bio waiver in accordance with 21 CFR 320.22(b), where self-evident BE is stipulated for parenterally administered drug products. Bio waiver request will be reviewed by OPQ- Biopharmaceutics group.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In the current application, 14 clinical studies (Figure 4) support the proposed use of AMG 416 for the treatment of secondary HPT in patients with CKD receiving hemodialysis. The clinical program consists of two studies that were conducted in healthy volunteers, and twelve studies were conducted in patients with secondary HPT receiving maintenance hemodialysis.

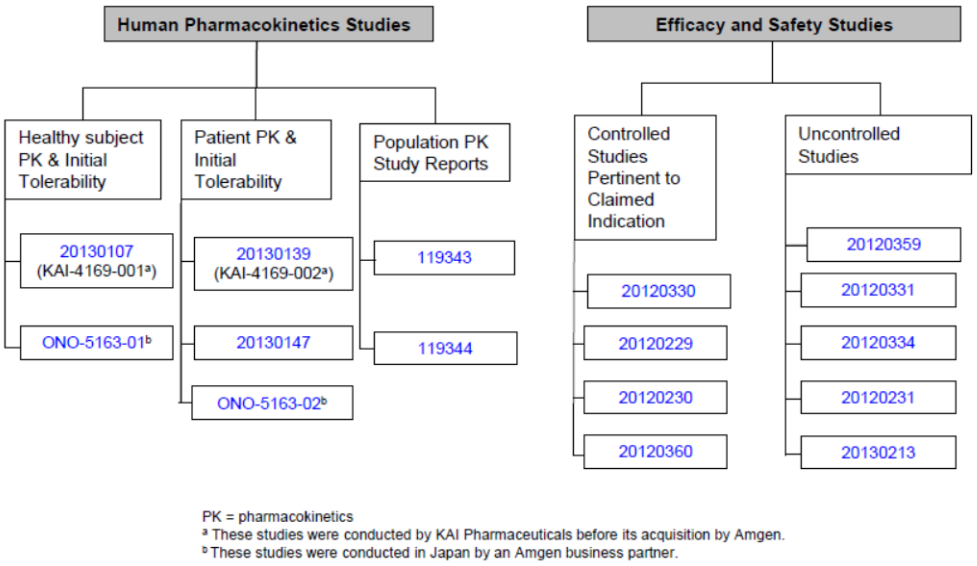


Figure 4: Overview of Etelcalcetide Clinical Development Program

Clinical Pharmacology Program:

In this application, three studies were primarily designed as clinical pharmacology studies which includes

- Study 20130107: PK and initial tolerability study in healthy volunteers ,
- Study 20130139: PK and initial tolerability study in subjects with CKD receiving hemodialysis and
- Study 20130147: ADME study in subjects with CKD receiving hemodialysis

In addition, Phase 2 studies (20120330, 20120331, and 20120334) and three pivotal Phase 3 studies (20120229, 20120230, and 20120231) in patients with CKD receiving hemodialysis also provided clinical pharmacology data in this application. Sponsor conducted population pharmacokinetic/pharmacodynamics analysis based on the study results of the Phase 1, Phase 2 and Phase 3 trials. Sponsor conducted two additional clinical pharmacology studies (ONO-5163-01 in healthy subjects and ONO-5163-02 in

CKD patients receiving hemodialysis) in the Japanese population. Data from Japanese trials were not reviewed in this application.

Sponsor also conducted ten in-vitro studies to evaluate permeability, plasma protein binding, potential metabolic drug-drug interactions, transporter interactions, biotransformation, red blood cell partition, dialysis clearance, and conjugation-deconjugation kinetics (Table 2).

Table 2: AMG 416 In-Vitro Studies With Human Biomaterial

Study Number	PK Assessment	Biomaterial	Species
119313	plasma protein binding	whole blood and plasma	human (HV, CKD); rat; dog
118052	drug transporter interactions	LLC-PK1, MDCKII, HEK293 cells transfected with and without human transporters; red blood cells	human
118358	biotransformation and blood to plasma ratio	whole blood; hepatocytes, liver and kidney S9 fractions	human, rat
119917	CYP metabolism	liver microsomes and liver S9 subcellular fractions	human
4169-NC-125	induction of CYP isoforms	hepatocytes	human
4169-NC-124, 119314	inhibition of CYP Isoforms	liver microsomes	human
119513	inhibition of BSEP transport	BSEP plasma membrane vesicles	human
119413	dialysis clearance	whole blood	bovine
119414	conjugation and deconjugation kinetics	whole blood	human

BSEP = bile salt export pump; CKD = chronic kidney disease; CYP = cytochrome P450; LLC-PK1 = polarized porcine kidney epithelial cells; MDCK = Madin-Darby Canin Kidney strain II cells; HEK = human embryonic kidney 293 cells; HV = healthy volunteer; PK = pharmacokinetics; S9 = supernatant fraction obtained from organ homogenate by centrifuging at 9000 rpm

Efficacy and Safety Program (Phase 2b/3 Program):

Etelcalcetide's efficacy for the intended indication has been demonstrated in two pivotal Phase 3, 26-week, placebo-controlled studies (studies 20120229 and 20120230) conducted in approximately 500 subjects each and a phase 3, active-controlled, 26-week study (Study 20120360) in 683 subjects comparing AMG 416 with cinacalcet, the only calcimimetic approved for the treatment of secondary HPT.

The primary efficacy endpoint for each Phase 3 study was the proportion of subjects with > 30% reduction from baseline in pre-dialysis PTH during the EAP, defined as Weeks 20 to 27, inclusive. In the Phase 3 trials, secondary endpoints included an evaluation of the proportion of subjects with pre-dialysis PTH ≤ 300 pg/mL during the EAP and percent change from baseline during the EAP for PTH, calcium, corrected calcium-phosphorus product (cCa x P), and phosphorus.

In all the Phase 3 studies, AMG 416 was administered intravenously (IV) as a bolus dose 3 times a week (TIW) at the end of each dialysis procedure. The starting dose of AMG 416 in these 3 studies was 5 mg, which was titrated to target pre-dialysis PTH ≤ 300 pg/mL. The minimum allowed AMG 416 titration dose was 2.5 mg and the maximum dose was 15 mg TIW.

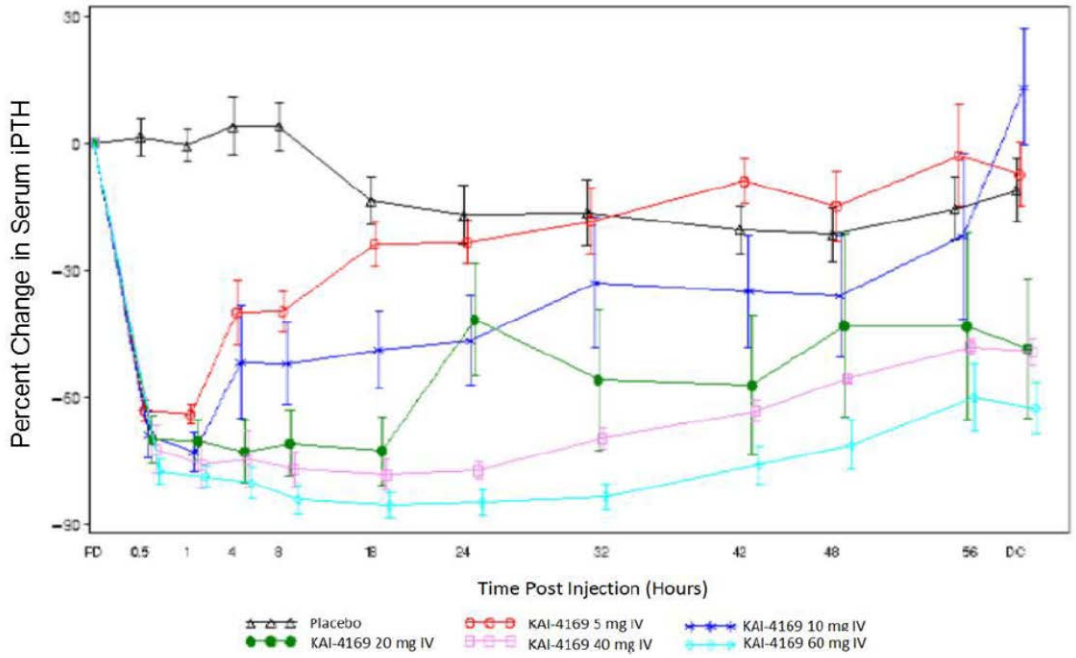
2.2.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Please refer to the analytical section (2.7) for details.

2.3 Exposure-Response

2.3.1 What was the rationale for Dose Selection in Phase 3 Program?

The starting dose of 5 mg AMG 416 is supported by the Phase 1 and 2 studies, which showed clinically relevant reduction in PTH from baseline in the patient population. In the Phase 1 trial, following single IV administration of AMG 416, a dose dependent effect in PTH reduction was observed across the dose group of 5 mg to 60 mg (Figure 5). In the Phase 2 study (study 20120330), AMG 416 administered 3 times weekly for 2 weeks (cohort 1) or 4 weeks (cohorts 2 and 3) in subjects with secondary



CKD = chronic kidney disease; DC = discharge; iPTH = intact parathyroid hormone; IV = intravenous; PD = predose; PTH = parathyroid hormone; SEM=standard error of the mean

Figure 5: Mean (± SEM) Percent Change From Baseline in Serum PTH Versus Time in Phase 1 Study 20130139.

Source: Sponsor report on Clinical Pharmacology Page 26

HPT who were receiving hemodialysis also showed dose dependent decrease in PTH levels (Table 3).

Table 3: Percent Change From Baseline in Serum PTH after 2 weeks (cohort 1, 5mg) or 4 weeks (cohort 2, 10 mg and cohort 3, 5 mg) of AMG 416 administration in subjects with secondary HPT who were receiving hemodialysis in Phase 2 Study 20120330.

	Cohort 1		Cohort 2		Cohort 3	
	Placebo	5 mg AMG 416	Placebo	10 mg AMG 416	Placebo	5 mg AMG 416
Baseline[a]						
N	4	6	21	21	13	13
Mean (SD)	636.3 (191.64)	588.3 (250.52)	601.5 (239.20)	765.1 (480.82)	619.4 (310.35)	662.1 (442.01)
Median	676.3	512.5	536.0	641.5	526.0	536.5
Minimum, maximum	369.5, 823.0	341.5, 1049.5	196.0, 1018.5	258.5, 2185.5	179.5, 1245.0	344.0, 1988.5
Percent change from baseline to endpoint						
N	4	6	21	21	13	13
Mean (SD)	0.3 (17.11)	-19.4 (20.65)	28.5 (70.39)	-49.4 (20.42)	2.3 (29.44)	-33.0 (26.28)
Median	1.0	-15.4	13.0	-54.5	0.0	-36.1
Minimum, maximum	-20.2, 19.3	-44.3, 11.6	-73.0, 293.9	-76.5, 3.8	-46.3, 47.1	-68.3, 20.7
LS mean[c]	2.2	-18.1	28.9	-48.0	1.9	-34.8
LS mean for difference[c]		-20.3		-76.9		-36.7
95% CI for difference[c]		-51.4, 10.8		-109.1, -44.8		-59.8, -13.6
P-value[c]				< 0.0001		0.0032
95% CI for difference[d]				-86.9, -50.0		
P-value[d]				< 0.0001		

Source: Sponsor's study report for trial Study Phase 2 Study 20120330

A dosing frequency of TIW at the end of hemodialysis sessions was selected because hemodialysis effectively removes plasma AMG 416 in patients (Study 119343). Plasma AMG 416 concentrations are near essentially at steady state after TIW dosing for 4 weeks which supports the every 4 week dose titration schedule in the phase 3 studies.

2.3.2 Is the proposed starting dose of 5 mg TIW and the titration scheme adequate?

Sponsor's proposed starting dose of 5 mg TIW seems reasonable as the majority of patients were escalated to doses greater than 5 mg TIW with maximum of 15 mg TIW dose in the two pivotal Phase 3 trials (Figure 6). Majority of patients reached stable dose within 12 weeks generating ~75% response rate with the titration scheme.

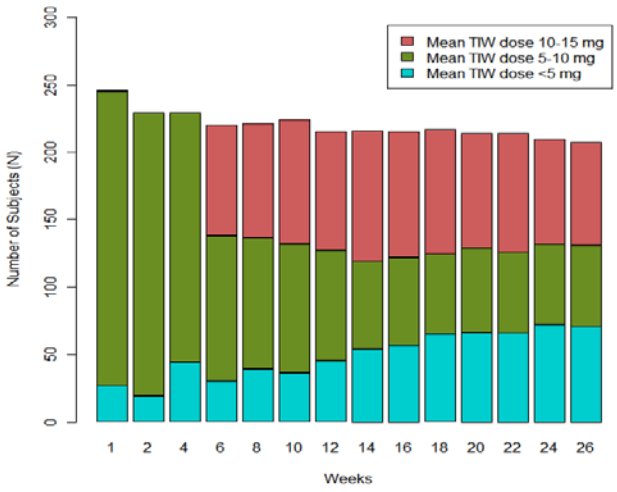


Figure 6: Number of subjects and change in mean TIW dose over time

Patients with higher baseline PTH levels needed higher doses upon titration and yet efficacious with the titrating dose range (Figure 7). Thus, starting with 5 mg dose and dose titration every four weeks based on the individual patient serum calcium and PTH levels is acceptable.

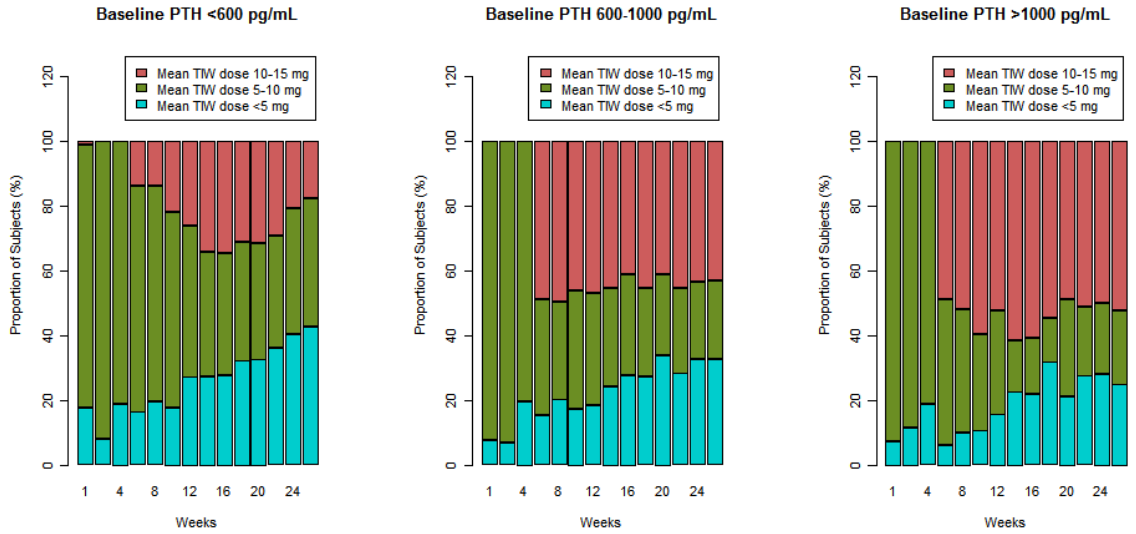


Figure 7: Proportion of subjects and change in mean TIW dose over time by baseline PTH

Based on the proposed titration scheme, in the pivotal Phase 3 trial the primary efficacy endpoint (proportion of subjects achieving >30% reduction in PTH from the baseline) was 74.0% in Study 20120229 and 75.3% in Study 20120230. See Pharmacometrics review in Appendix 4.2 for further details.

2.3.3 Is there any Dose/Exposure-Response for Safety?

Hypocalcemia is one of the safety concerns following etelcalcetide dosing. Simulations based on the population PK/PD analysis, indicate a clear dose-response relationship for corrected serum calcium levels. The simulation results also indicate that the proportion of subjects with corrected Ca <7.5 mg/dL following 2.5 mg, 5 mg, 10 mg, and 15 mg fixed doses increases with increasing dose. The results also suggest that the starting dose of 5 mg followed by titration algorithm implemented in phase 3 is expected to provide reasonable Ca lowering, while maintaining an acceptable safety profile, compared to other fixed dosing regimens simulated (Figure 8).

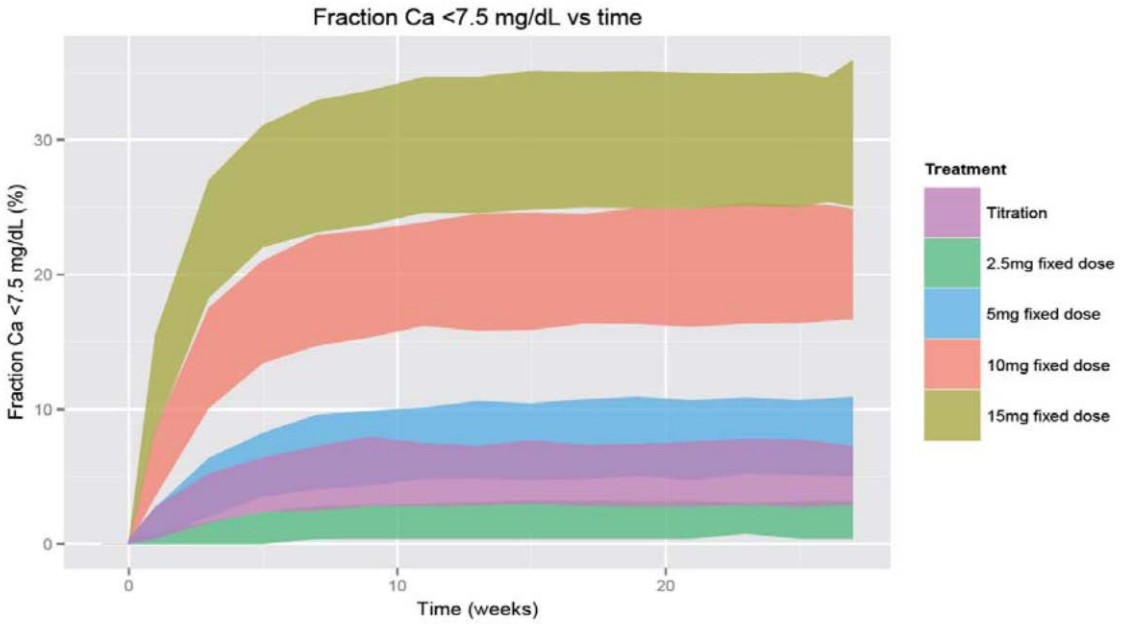


Figure 8. Simulations of the Effects of Titration Dose Safety: The proportion of subjects expected to be experiencing serum cCa levels <7.5 mg/dL, over the course of the study (at the different scheduled potential titration visits) and 90% prediction interval.

(Source: Population PKPD report, Figure 24, page 316)

2.3.4 Is there an overtreatment effect on PTH generating excessive PTH reduction with the titration scheme?

No. One of safety concerns regarding dose titration scheme was the potential overdose resulting in excessive PTH reduction (less than 100 pg/mL) and thereby causing adynamic bone disease. A graphical assessment on doses for patients - with PTH less than100 pg/mL in comparison with those with PTH above 100 pg/mL indicates that these patients received lower dose than those with PTH above 100 pg/mL. Thus, this analysis supports that higher titrated dose does not necessary generate excessive PTH reduction in individual patients (Figure 9).

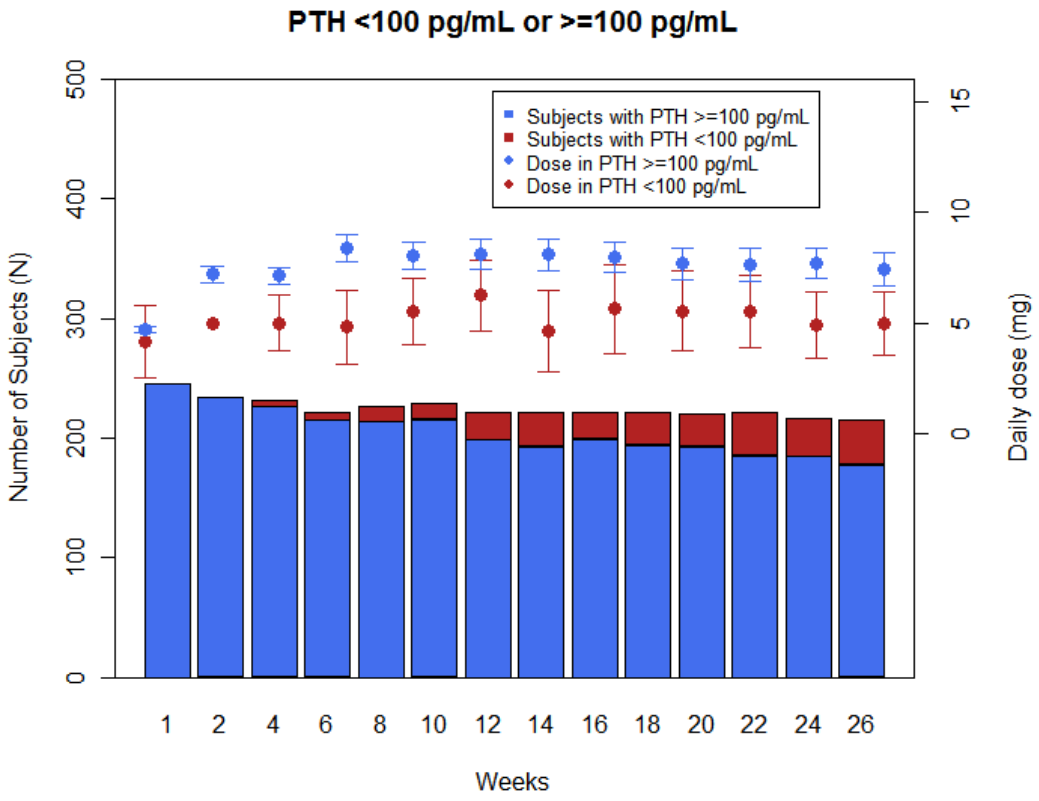


Figure 9: Change in dose in patients with PTH<100 pg/mL or PTH≥100 pg/mL

2.4 What are the PK characteristics of the drug?

2.4.1 What are the single and multiple dose PK characteristic of Etelcalcetide in healthy and in CKD patients on hemodialysis?

Single Dose Pharmacokinetics in Healthy Subjects:

Phase 1 single ascending dose study (#20130107) characterized the pharmacokinetics of etelcalcetide in healthy subjects following intravenous administration. In this study 4 cohorts: 0.5, 2, 5 and 10 mg AMG 416 administered by IV bolus injection were evaluated.

After IV bolus administration, plasma AMG 416 concentration-time profiles exhibited tri-exponential decays (Figure 10). Plasma AMG 416 C_{max} and AUC_{inf} values increased approximately dose-dependent manner. The terminal elimination half-life ranged from 18.4 to 20.0 hours across the dose range evaluated. Mean clearance ranged from 5.38 to 8.11 L/hr and mean volume of distribution at the steady state (V_{ss}) ranged from 113 to 160 L. A summary of PK parameters, by treatment group, are presented in Table 4.

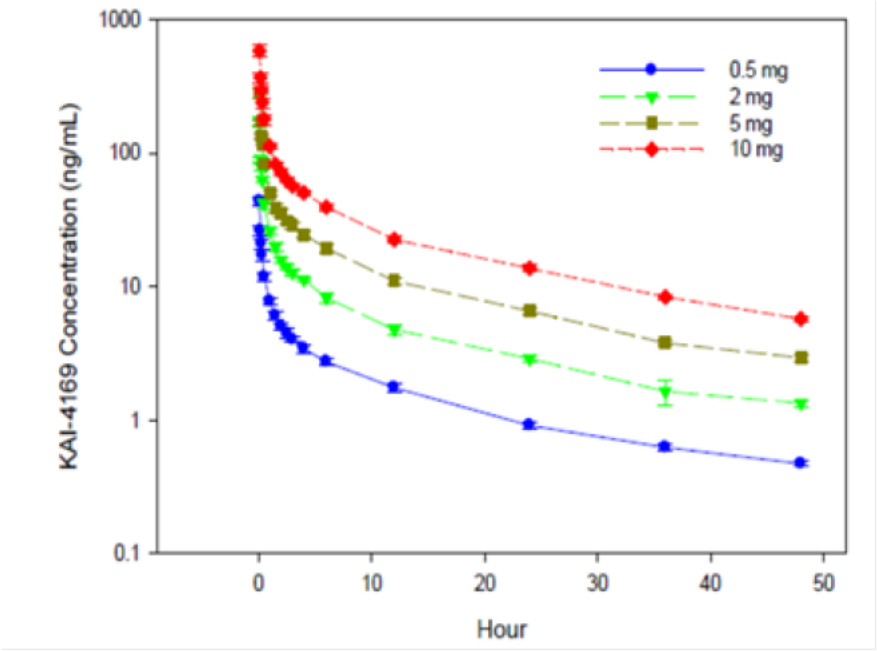


Figure 10: Figure Showing Plasma Concentration-Time Profile for Etelcalcetide Following Single Dose IV Administration of 0.5 mg, 2 mg, 5 mg and 10 mg Etelcalcetide Dose (Study 20130107).

Table 4: Summary of Baseline-Adjusted Pharmacokinetic Parameters for Etelcalcetide (Study 20130107)

Cohort/Dose	Statistic	Cmax (µg/L)	AUCall (hr*µg/L)	AUCINFobs (hr*µg/L)	HLλz (hr)	Clobs (L/hr)	Vssobs (L)
1/ 0.5 mg	N	6	6	6	6	6	6
	Mean	43.5	81.1	94.3	19.5	5.38	113
	SD	7.86	11.7	12.5	1.35	0.675	19.6
2/ 2.0 mg	N	6	6	6	6	6	6
	Mean	171	256	294	20.0	6.87	138
	SD	35.6	32.5	34.1	2.25	0.750	26.0
3/ 5.0 mg	N	6	6	6	6	6	6
	Mean	280	544	623	18.6	8.11	160
	SD	59.3	57.7	71.5	2.51	0.928	21.0
4/ 10.0 mg	N	6	6	6	6	6	6
	Mean	583	1130	1290	18.4	7.83	152
	SD	144	129	116	2.21	0.755	30.0

Source: Sponsor's report on Summary of Clinical Pharmacology

Reviewer's Comment: *Incurred sample reanalysis for study 20130107, showed that approximately 50% of the samples reanalyzed have differences in value of greater than 20% of the original value (sample from cohort 1 and cohort 2 of the trial). Sponsor provided investigational summary and attributed this to matrix related instability of the plasma samples. Sponsor in their report showed that when plasma was maintained in a poorly-controlled ice bath (temperature up to 14.3°C), a time-dependent decrease in AMG 416 concentration was observed. However, when plasma was maintained in a well-controlled ice bath (4 to 7°C), AMG 416 was stable and no time-dependent decrease in AMG 416 concentration was observed. Sponsor in their mid-cycle communication mentioned temperature control was maintained for rest of the samples and that none of the other studies were affected due to matrix related instability. Bioanalysis for remainder of the samples from phase 1 clinical studies (20130107, cohorts 3 and 4; 20130139, all cohorts) was performed in a well-controlled ice bath operated according to a new Standard Operating Procedure (SOP) (* (b) (4) *LCMS0016.01) and the samples passed the incurred sample reanalysis. Sponsor's rationale/investigation for higher deviations from the original values from Incurred sample reanalysis is acceptable. . It is recommended that the prescribing information include PK data from patients rather than from this healthy subject PK study.*

Single Dose Pharmacokinetics in Hemodialysis Subjects With Secondary Hyperparathyroidism:

Single dose pharmacokinetics in hemodialysis subjects with secondary hyperparathyroidism were assessed in the Phase 1 study (study 20130139). In this phase 1 study subjects received single intravenous etelcalcetide dose of 5 mg, 10 mg, 20 mg, 40 mg, and 60 mg and subjects did not receive hemodialysis during an approximate 3 day observation period.

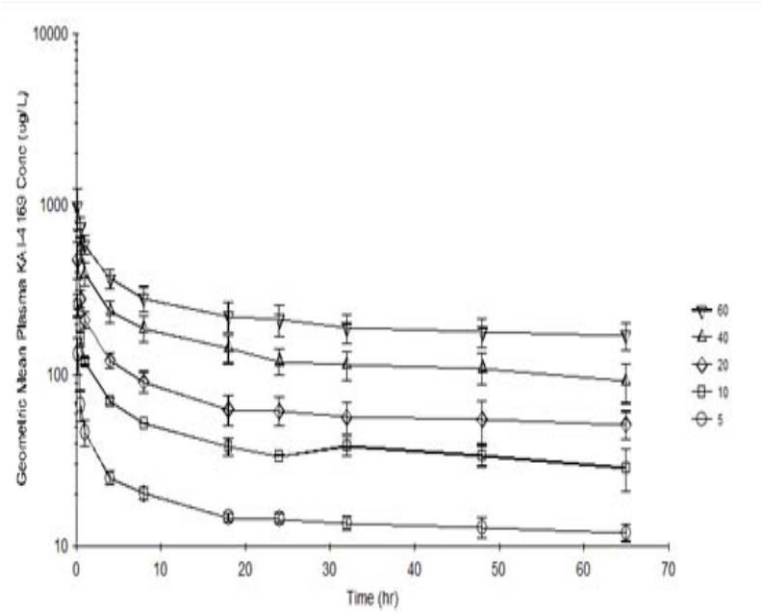


Figure 11: Figure Showing Geometric Mean (±SE) Plasma Concentration-Time Profile for Etelcalcetide Following Single Dose IV Administration of 5 mg, 10 mg, 20 mg, 40 mg and 60 mg Etelcalcetide Dose (study 20130139).

Source: Sponsor's amended PK report Pg:12

Plasma AMG 416 declined quickly from the peak concentration and exhibited a multiple exponential decay (Figure 11). AMG 416 plasma C_{max} and AUC_{65hr} increased in a dose-related manner over the dose range evaluated. The observed increase in C_{max} values was less than dose proportional; however, the increase in AUC_{65hr} was approximately dose proportional over the dose range evaluated (Table 5). Mean AMG 416 C_{max} and AUC_{65hr} values increased 7.86- and 14.1-fold, respectively, over a 12-fold dose range.

Table 5: Summary of Etelcalcetide PK Parameters Following Single Dose IV Administration of 5 mg, 10 mg, 20 mg, 40 mg and 60 mg Etelcalcetide Dose (study 20130139).

Cohort/Dose	Statistic	Cmax (µg/L)	AUC65hr (hr*µg/L)
1/ 5 mg	N	4	4
	Mean	145	1110
	SD	64.8	182
2/ 10 mg	N	3	3
	Mean	263	2820
	SD	67.2	458
3/ 20 mg	N	4	4
	Mean	511	4920
	SD	230	1650
4/ 40 mg	N	4	3
	Mean	726	9560
	SD	278	3340
4/ 40 mg	N	4	4
	Mean	1140	15700
	SD	428	5100

Reviewers Comment: *Etelcalcetide is primarily cleared by hemodialysis in CKD patients and in this study in the absence of hemodialysis, t1/2 could not be reliably determined from the pharmacokinetic profile recorded from 0 to 65 hours post dose. The pharmacokinetic parameters AUC_{inf}, CL, and V_{ss} could not be reliably calculated. These parameters are not reported by the sponsor. Population pharmacokinetic analysis from Phase 1, Phase 2 and Phase 3 provides the pharmacokinetic information for labeling purposes.*

2.4.2 What are the characteristics of drug absorption?

Absorption and other non-IV routes of administration of AMG 416 are not studied in this application as AMG 416 is to be administered IV. In Phase 2 study (20120330), in CKD patient on dialysis, repeat TIW dosing of AMG 416 over four week duration resulted in 2-3 fold Etelcalcetide accumulation. Based on the population PK analysis of data from Phase 1, Phase 2 and Phase 3 studies, the plasma accumulation ratio of AMG 416 was 2- to 3-fold by week 4 and 3- to 5-fold by month 6.

2.4.3 What are the characteristics of drug distribution?

Phase 1 and Phase 2 data demonstrates that following IV administration, plasma Etelcalcetide exhibited a multiple exponential decay characterized by rapid initial distribution followed by a prolonged elimination phase (Figure 10 and Figure 11). Based on the population pharmacokinetic analysis, the volume of distribution at steady state (Vss) in CKD patients receiving hemodialysis is approximately 796 L. Non covalent binding to human plasma protein is less than 50%. Etelcalcetide is primarily bound to plasma albumin, In-vitro 53 to 69% of the added dose being covalently bound to plasma proteins in whole blood; predominantly in the form of serum albumin peptide conjugate (SAPC). The blood to plasma ratio of etelcalcetide is approximately 0.6.

2.4.4 What are the characteristics of drug metabolism and excretion?

In this application sponsor conducted an open-label, single-dose study to evaluate the pharmacokinetics, biotransformation and excretion of [^{14}C] AMG 416 in six patients with end stage renal disease receiving dialysis (study 20130147) . In this study, a total of 6 adults with ESRD receiving hemodialysis were enrolled to receive a single dose of 10 mg AMG 416 combined with 750 nCi of ^{14}C-labeled AMG 416.

Hemodialysis is the predominant route of etelcalcetide elimination in CKD patients requiring hemodialysis. The hemodialysis clearance of etelcalcetide is 7.66 L/hr in CKD patients. Based on PopPK analyses, the clearance of etelcalcetide by routes other than hemodialysis is 0.47 L/h, suggesting hemodialysis is the primary route for the clearance etelcalcetide from the systemic circulation. Following a single radiolabeled dose of etelcalcetide, in CKD patients with secondary HPT requiring hemodialysis, approximately 60% of [^{14}C]-etelcalcetide is recovered in dialysate, and approximately 7% recovered in urine and feces combined over 175 days of collection period.

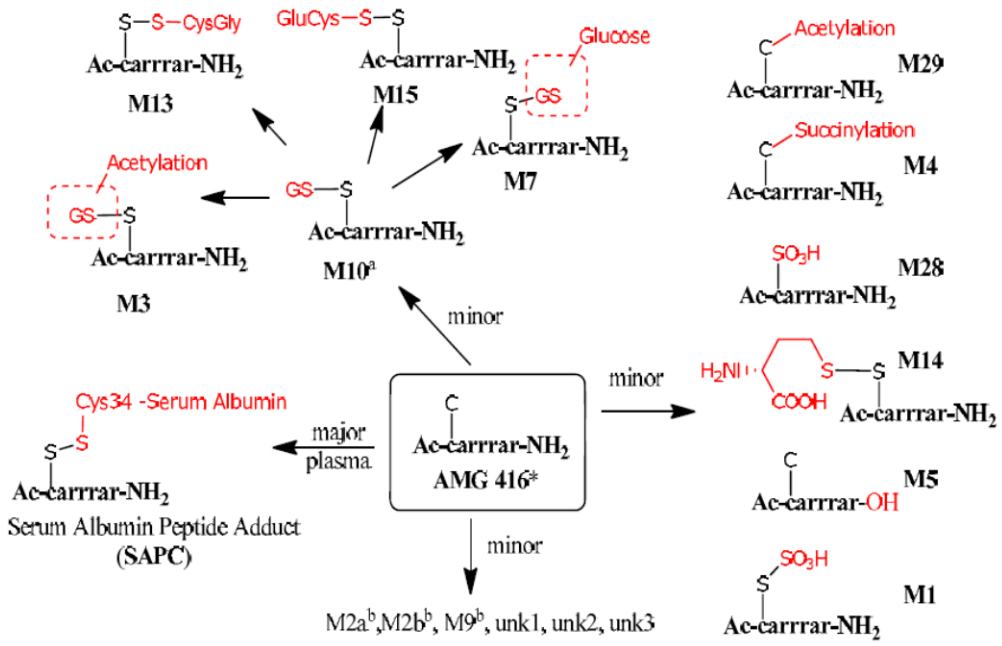
Following IV administration, biotransformation of AMG 416 is primarily the result of disulfide exchange with endogenous thiols rather than metabolism by enzymes such as proteases or CYPs. Sponsor's proposed biotransformation scheme for AMG 416 in humans is illustrated in Figure 12.

Intact AMG 416 accounted for approximately 17% of the total radioactive $AUC_{0\text{-}68hr}$ in plasma before the first dialysis after dose administration. The predominant biotransformation product, serum albumin peptide conjugate (SAPC), is formed by reversible covalent binding of the disulfide conjugation of the D-cysteine in the AMG 416 peptide backbone to L-cysteine at position 34 in serum albumin. SAPC represented 73% of the total radioactivity in the AUC pooled plasma.

M11 (also known as AMG2940944; sequence structure Ac-D-Cys(SH)-D-Ala-D-Arg-D-Arg-D-Arg-D-Ala-DArg- NH2) is the sulfhydryl (reduced) form of the D-amino acid peptide backbone in AMG 416. M11 can also be liberated by chemical reduction of all AMG 416-related mixed disulfides with an intact D-amino acid backbone that was present in plasma. In this ADME study, sponsor performed chemical reduction with Tris (2-carboxyethyl) phosphine (TCEP), a disulfide bond reducing agent. The M11 formed upon TCEP reduction is referred to as "Total M11" because it represents all AMG 416

related material present in plasma. Plasma ^{14}C and Total M11 concentrations were similar, indicating that [^{14}C] AMG 416 and all of its biotransformation products were present in a form that could be quantitatively converted to Total M11 by chemical reduction of disulfide bonds.

The plasma exposure of biotransformation products is approximately 5-fold higher than that of etelcalcetide. The concentration-time profile of biotransformation products parallels that of etelcalcetide plasma concentration time profile Figure 13.



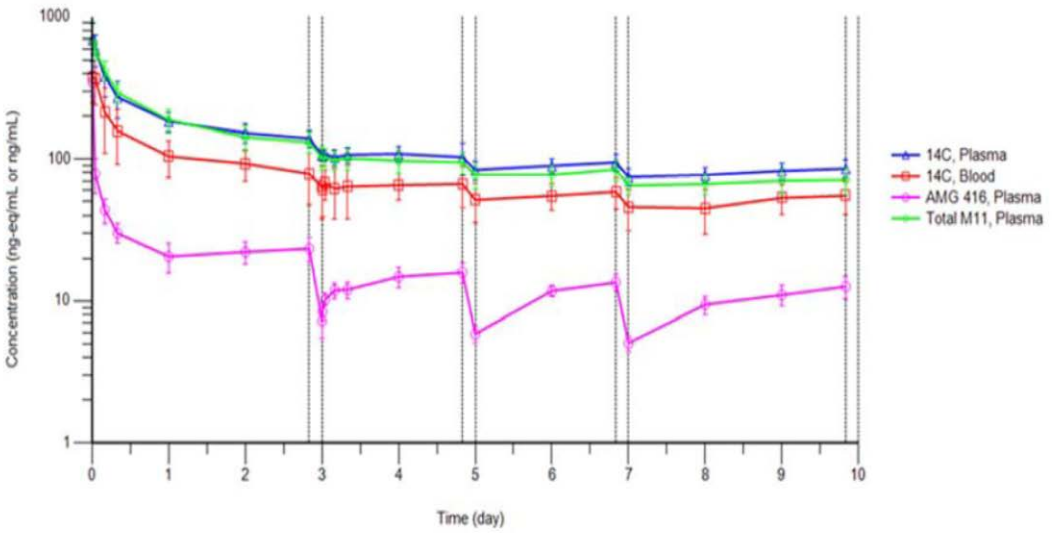
GS = L-glutathione; minor = each < 5% of ^{14}C dose (urine) or ^{14}C chromatogram (plasma)

* Lower and upper case single letter aminoacid abbreviation refer to D- and L-aminoacids, respectively

[a] The structure was confirmed by an authentic standard.

[b] The structure has an intact peptide backbone, but the exact modification could not be determined; observed mass to charge ratio and mass shift are shown in the table below.

Figure 12: Proposed Biotransformation Scheme for [^{14}C]AMG 416 in Humans



14C = [^{14}C]AMG 416-derived radioactivity; CKD = chronic kidney disease; IV = intravenous; nCi = nanocurie; SD = standard deviation

Vertical dashed lines represent the hemodialysis periods.

Figure 13: Mean (±SD) Concentration-Time Profiles of [^{14}C]AMG 416-derived Radioactivity in Blood and Plasma, AMG 416 in Plasma, and Total M11 in Plasma Following a Single IV Bolus Administration of [^{14}C]AMG 416 (10 mg; 750 nCi) to CKD Subjects Receiving Dialysis

Metabolism:

In-vitro study (study 119917) in human liver microsomes showed that Etelcalcetide is not metabolized by and is not a substrate for cytochrome P450 enzymes. In human liver microsome, Etelcalcetide (concentration up to 5µg/mL) is not shown to inhibit (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4) or induce (concentration up to 10 µg/mL) (1A2, 2B6, or 3A4) cytochrome P450 enzymes (studies 4169-NC-125, 4169-NC-124, 119314).

In-vitro studies showed that etelcalcetide is neither a substrate nor an inhibitor of common human efflux (P-glycoprotein, breast cancer resistance protein, bile salt export pump) and uptake (organic anion transporters 1 and 3, organic anion polypeptide transporters 1B1 and 1B3, organic cation transporter 2, and peptide transporters 1 and 2) drug transporters (study 118052, 119513). No transport or enzyme inhibition of the probe substrates was observed in the presence of etelcalcetide at concentrations up to 50µM (~50 µg/mL).

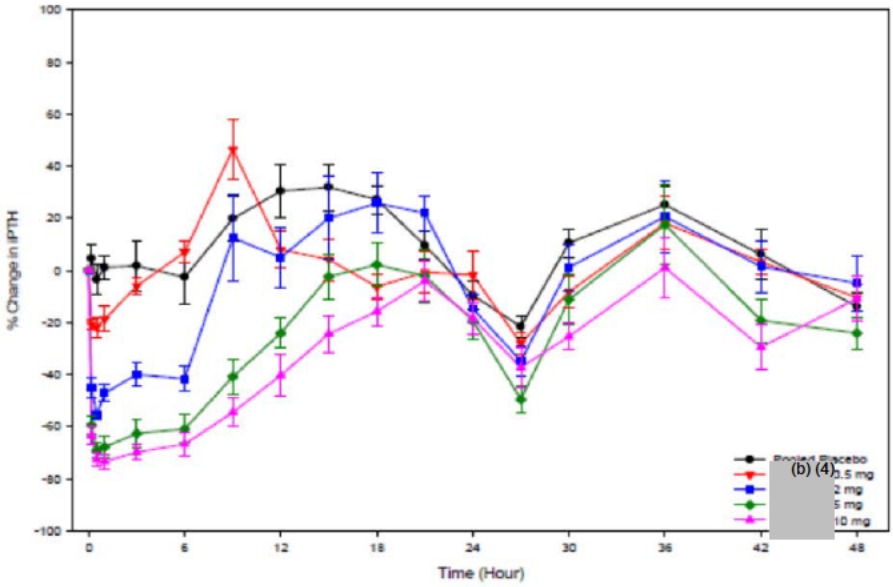
Reviewers Comment: Based on the single dose study with 5 mg dose in patients with secondary hyperthyroidism mean maximum concentration observed is 145 ng/mL. Also, based on population PK analysis, 5 mg TIW dose results in maximum concentration of around 200 ng/mL at steady state. Thus, concentrations observed in in-vivo studies are

much less than that are tested in the in-vitro settings (5-50 µg/mL), confirming that no inhibition or induction with etelcalcetide is expected in in-vivo settings.

2.4.5 ***What are the pharmacodynamic properties of Etelcalcetide in healthy and CKD patients on hemodialysis?***

Healthy Subjects:

Following single dose IV administration of AMG 416 the maximum mean percent change from baseline in PTH levels were 3.5%, 21.7%, 55.4%, 69.0%, and 72.6%, for the 0.5, 2, 5, and 10 mg dose groups, respectively (Figure 14). After a single IV dose of AMG 416, PTH decreased maximally by 30 minutes and in a dose-dependent manner. The maximum PTH suppression was transient and serum PTH levels gradually returned to baseline within 10 to 24 hours in healthy volunteers.



PTH = parathyroid hormone; SEM = standard error of the mean

Source: Figure12 of Study 20130107 CSR

Figure 14: Mean (± SEM) Percent Change From Baseline in Serum PTH Over Time in Healthy Volunteers Following Single Dose IV Administration of 0.5 mg, 2 mg, 5 mg and 10 mg Etelcalcetide Dose.

Hemodialysis Subjects With Secondary Hyperparathyroidism:

In hemodialysis subjects with secondary hyperparathyroidism (study 20130139), after a single IV dose of AMG 416, a dose-dependent decrease in serum PTH levels were observed. In this study, maximum PTH reduction was observed within 30 minutes of the Etelcalcetide administration. Following single dose IV administration the duration of maximal PTH reduction and time to return to baseline appeared to be dose-related (Figure 15). At 65 hours post-dose, serum PTH was suppressed -48.5%,-49.3%, and -62.6%, in the 20, 40, and 60 mg dose groups, respectively

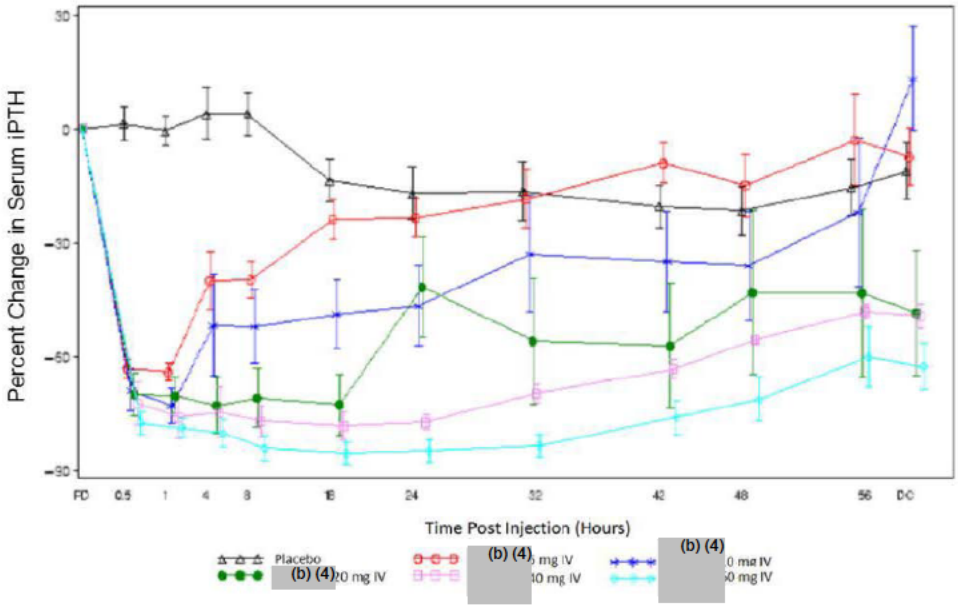


Figure 15: Mean (± SEM) Percent Change From Baseline in Serum PTH Versus Time Study 20130139 (b) (4) CKD Patients With Secondary HPT Receiving Hemodialysis

2.5 Intrinsic Factors

2.5.1 What intrinsic factors (e.g., age, sex, race, weight, height, , pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response(PD)?

Renal Impairment: No formal pharmacokinetic studies of etelcalcetide have been conducted in patients with mild to severe kidney impairment.

- Etelcalcetide is indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease (CKD) patients on hemodialysis. Phase 2 and Phase 3 studies were conducted in hemodialysis patient population, which provides the pharmacokinetic, safety and efficacy data in this patient population.

Hepatic Impairment: No formal studies of Etelcalcetide have been performed in patients with hepatic impairment. Etelcalcetide, based on the in-vitro studies, is not metabolized by metabolic enzymes and is primarily eliminated by renal route. Hepatic impairment should not have any effect on the pharmacokinetics of Etelcalcetide.

Age, Sex, Race, and Body Weight: Based on the PopPK analysis, body weight (29 to 163 kg), sex, race (White and Black), and age (20 to 93 years of age) do not influence the pharmacokinetics of etelcalcetide. No dosing adjustment is warranted for these specific populations. Please refer to Pharmacometrics review Appendix 4.2 for further details.

Immunogenicity: Sponsor's analysis of pooled data from the two Phase 3, multi-center, randomized, double-blind, placebo-controlled studies (#20120229 and #20120230) showed that out of 503 patients, 11.1% (56) were found with anti-AMG 416 antibodies. Of these 56 patients, 43 had preexisting anti-drug antibodies (ADA), and 13 developed ADA only after exposure to AMG 416.

Figure 16 shows dose-normalized plasma concentrations of AMG 416 based on the immunogenicity status. The study result suggests that there is no significant impact of anti-AMG 416 ADA on the concentration of AMG 416 in the trial subjects over time, irrespective of whether they had pre-existing ADA or developed ADA over the course of the timeframe of the clinical trial. Please refer to immunogenicity consult by Dr. Bruce Huang DARRTs dated 04/08/2016 for further details on the assay used to assess the anti-drug antibody.

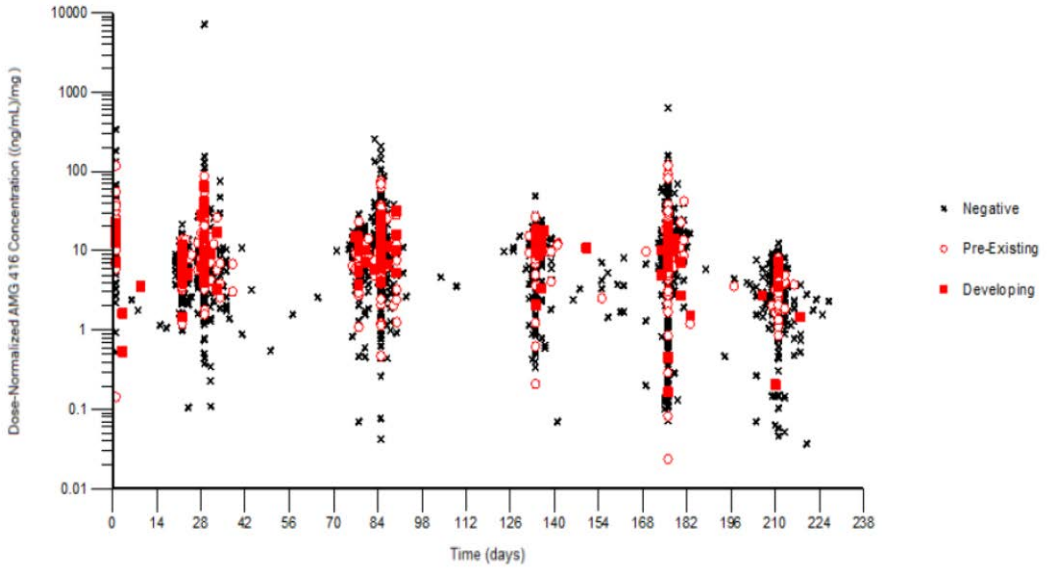


Figure 16: Individual Plasma AMG 416 Concentrations for Subjects Whose Samples Tested as Pre-existing and/or Developing for Anti-AMG 416 Antibody as Compared to Other Subjects Treated With AMG 416

Source: Sponsor's summary of clinical pharmacology report, page 56.

Pediatric Subjects: No clinical studies in pediatric subjects are conducted under this NDA. Sponsor has an agreed initial Pediatric Study Plan (iPSP) for:

- A waiver for the pediatric clinical studies in preterm and newborn infants (0 to (b) (4) days) on the basis that necessary studies are impossible or highly impracticable owing to the prevalence of the condition in the pediatric population.
- A partial deferral of the pediatric clinical studies (b) (4) (1 month to < 2 years), children (2 to 11 years) and adolescents (12 to < 18 years) until safety and efficacy profile in adults has been established.

2.6 Extrinsic Factors

2.6.1 *What extrinsic factors (drugs, herbal products) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?*

In this NDA, sponsor has not conducted any clinical drug-drug interaction studies. Based on the results of the in-vitro studies, no transporter or enzyme based drug interaction for etelcalcetide is expected.

2.7 General Biopharmaceutics

In the clinical development program (Phase 1-Phase 3 clinical studies) sponsor used (b) (4) as the investigational drug product. The (b) (4) for intravenous administration. The (b) (4) contained (b) (4)

The formulation used in the clinical development program is different than the commercial formulation that is proposed to be marketed. The proposed to-be-marketed commercial formulation is a ready-to-use (RTU) liquid drug product (Table 7). Sponsor has not conducted any bioequivalence study to bridge the formulations. Sponsor is requesting a waiver from in-vivo bioequivalence (BE) study requirements to establish BE between the Etelcalcetide (b) (4) parenteral clinical drug product used in phase 3 clinical studies and the Etelcalcetide ready-to-use (RTU) liquid drug product intended for commercial use. Sponsor based their justification for bio waiver in accordance with 21 CFR 320.22(b), where self-evident BE is stipulated for parenteral administered drug products. Bio waiver request will be reviewed by OPQ- Biopharmaceutics group.

Table 6: Comparison of AMG 416 (b) (4) and RTU Liquid Formulations

Component or Attribute	(b) (4)	Liquid Formulation
(b) (4)		Sodium Chloride (0.85%)
pH		Succinic Acid (10 mM) (b) (4)
(b) (4)		

In open label extension studies (20120231, 20130213) sponsor utilized ready-to-use (RTU) liquid commercial drug product. RTU liquid drug product used in the open label extension studies was supplied as a sterile, preservative free, aqueous solution containing 10 mg AMG 416, (b) (4) sodium chloride and (b) (4) succinic acid in a single-use 3 mL glass vial. The liquid drug product has a (b) (4) As requested by FDA at the

End-of-Phase 2 CMC Meeting (IND 109773, SN0080), Sponsor conducted a a local tolerance study in dogs (Study 117458) to address any discomfort that may result from the (b) (4) pH of the liquid formulation.

Table 7: Qualitative and Quantitative Composition of AMG 416 RTU Liquid Drug Product

Component	Function	Reference to Standard	Conc.	Quantity per Vial[a] 2.5 mg	5.0 mg	10 mg
AMG 416[b]	Active Ingredient	(b) (4)				
Sodium Chloride	(b) (4)	USP, PhEur, JP	8.5 mg/mL (0.85%)			(b) (4)
Succinic Acid		USP-NF	1.2 mg/mL (10 mM)			(b) (4)
(b) (4)						(b) (4)
Hydrochloric Acid or Sodium Hydroxide	pH adjustment	USP, PhEur, JP	N/A	As needed		

a. Based on deliverable volume

(b) (4)

c. 3.2.S.4.1 (Drug Substance Specification)

2.8 Analytical

2.8.1 How are the active moieties identified and measured in the plasma?

In this NDA, LC-MS/MS assays were developed to measure AMG 416 and Total M11 in human plasma. An overview of the analytical methods and the studies for which they were used is provided in AMG 416 and Total M11 Table 8. The method parameters are summarized in Table 9. Stability of AMG 416 in human plasma is presented in Table 10.

Table 8:Analytical Methods for AMG 416 and Total M11

Method	Compound	Use in Clinical Study
100085KSC4169HPL_S	AMG 416	20130107 (KAI-4169-001) 20130139 (KAI-4169-002)
100989ATC4169HPL_S	AMG 416	20120330 (KAI-4169-003) 20120331 (KAI-4169-005) 20120334 (KAI-4169-005-01)
TM12-241	AMG 416	20120229 20120230 20120231 20130147
MET-003548[a]	Total M11	20120330
MET-003622	Total M11	20130147

[a] Qualified analytical procedure

Table 9: Summary of Bioanalytical Method Parameters for AMG 416 and Total M11 Analysis in Human Plasma

	AMG 416			Total M11
Study Number	118438[a]	116951[b]	4169-NC-115[c]	118480[d]
Plasma Acid Status	acidified	acidified	non-acidified	acidified
Sample Volume (mL)	0.2	0.1	0.2	0.05
Internal Standard	$^{13}C_3D_3{}^{15}N$-KAI-4169			$^{13}C_3D_3{}^{15}N$-KAI-4169
Sample Preparation Technique	SPE	SPE	SPE	TCEP & PPT
Linear Range (ng/mL)	0.2-100	0.2-100	0.2 to100	50 to 2000
LLOQ (ng/mL)	0.2	0.2	0.2	50
ULOQ with Dilution (ng/mL)	2500	1000	1000	20000
QC Bias and CV	≤ 15% (20% at LLOQ)			≤ 15% (20% at LLOQ)

CV = coefficient of variation; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LLOQ = lower limit of quantification; PPT = Protein Precipitation; QC = quality control; SPE = solid phase extraction; TCEP = tris(2-carboxyethyl)phosphine); a disulfide bond reducing agent; ULOQ = upper limit of quantification

[a] Study 118438: Method Validation of AMG 416 (KAI-4169) in Acidified Human Plasma by (b) (4) LC/MS/MS

[b] Study 116951: HPLC/MS/MS Assay Validation for the Determination of AMG 416 from Human Acidified K2EDTA Plasma

[c] Study 4169-NC-115: Method Validation for the Quantitation of KAI-4169 in Human Plasma by (b) (4) (b) (4) LC/MS/MS

[d] Study 118480: Method Validation: Determination of Total AMG2940944 (M11; metabolite of AMG 416) in Human Plasma using LC/MS/MS after reduction with TCEP

Table 10: Stability of AMG 416 in Human Plasma

	AMG 416				Total M11
	Healthy Volunteer			Subjects with CKD	Healthy Volunteer
Plasma Acid Status	Acidified[a]	Acidified[b]	Acidified[c]	Acidified[b]	Acidified[d]
Storage at -20°C (days)	205	204	NA	66	91
Storage at -70°C (days)	208	539	68	147	91
Freeze/thaw cycles (-70°C to RT)	5	6	5	--	3
Storage at RT (hours)	24	6	2 (1 hr at RT and 1 hr over ice)	--	5

CKD = chronic kidney disease patients receiving hemodialysis; hr = hours; RT = room temperature

[a] Study 118438

[b] Study 116951

[c] Study 4169-NC-115

[d] Study 118480

Reviewers Comments: *In the analysis of study samples from Phase 2 and Phase 3 studies, sponsor identified that most of the runs have carryover effect from one sample to another. The carry over effect was identified on each day by injecting a double blank sample after ULOQ sample. In each batch a double blank sample near the beginning of the batch was injected immediately after a ULOQ sample. No Carryover effect is assumed if the AMG 416 peak area response in this blank following ULOQ sample was ≤ 20% of the mean peak area response for the AMG 416 LLOQ calibration samples in the batch. If the AMG 416 peak area response was > 20% of the mean LLOQ peak area response, the batch carryover factor (COF) was calculated using mean peak area ratios from triplicate ULOQ and blank samples (including IS). Using the COF, the potential extent of carryover for all test samples within that batch was determined, and any samples with a potential bias of > 15% were reanalyzed.*

In the mid-cycle communication sponsor clarified that most of the runs did not have carryover that might have introduced bias in the quantification. Indeed, only 28 samples out of 10,235 samples (<0.3%; Table 11) required reanalysis according to the criteria described above. In addition, COF itself was not determined at any other concentration except the ULOQ. This was a worst-case scenario based on an assumption that the carryover would be the greatest at the highest concentration. Thus, carry over effect observed in the analysis was observed in very few samples (<0.3% of total samples analyzed) and the samples were reanalyzed based on the pre-specified criteria.

Table 11: Summary of Number Batches and Sample Reanalysis due to Carryover Factor (COF)

Study	Number				
	Accepted batches	Samples analyzed[1]	Batches where COF was assessed	Batches with samples to reanalyze due to COF[2]	Samples reanalyzed due to COF (% total)
20120229	70	2760	56	6	25 (0.91%)
20120230	45	1868	31	3	3 (0.16%)
20120231	143	5607	85	0	0
Sum Total	258	10,235	165	9	28 (0.27%)

[1] Reportable results

[2] COF = carryover factor; COF definition and reanalysis criteria described in (b) (4) SOP (b) (4)

3 DETAILED LABELING RECOMMENDATION

The following are the labeling recommendations relevant to clinical pharmacology for NDA 208325. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

7 DRUG INTERACTIONS

(b) (4)

Reviewers Comment: Not clinically relevant. This information is moved to section 12.

(b) (4)

Reviewers Comment: This section should capture (b) (4) *In the absence of such information these sections should be deleted. Pharmacokinetic information should be captured in section 12.*

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

The pharmacokinetics of etelcalcetide [redacted] is linear and do not change over time following single (5 to 60 mg) and multiple IV doses (2.5 to 20 mg) in CKD patients with secondary HPT requiring hemodialysis. Etelcalcetide exhibited tri-exponential decay following IV administration. [redacted] three times a week IV dosing at the end of each 3- to [redacted]6-hour hemodialysis session in CKD patients, etelcalcetide plasma levels reached [redacted] steady state in [redacted]-8-[redacted]weeks after dosing with an [redacted] accumulation ratio of [redacted]3- to [redacted]-fold, and the effective half-life was ~~3~~ [redacted] to [redacted] days. [redacted]

Metabolism

Etelcalcetide is not metabolized by CYP450 enzymes. Etelcalcetide is biotransformed in blood by reversible disulfide exchange with endogenous thiols to predominantly form conjugates with serum albumin.

Following a single radiolabeled dose of etelcalcetide in CKD patients with secondary HPT requiring hemodialysis, the plasma exposure of biotransformation products is approximately 5-fold higher than that of etelcalcetide and their concentration-time course parallels that of etelcalcetide.

Excretion

Etelcalcetide is rapidly cleared in patients with normal renal function, while hemodialysis is the predominant elimination pathway in CKD patients requiring hemodialysis. [redacted] Etelcalcetide was [redacted] removed with a hemodialysis clearance value of 7.66 L/hr. Following a single radiolabeled dose of etelcalcetide in CKD patients with secondary HPT requiring hemodialysis, approximately 60% of [^{14}C]-etelcalcetide was recovered in dialysate, and approximately 7% recovered in urine and feces combined over 175 days of collection period.

[redacted]Specific Populations

[redacted]

Effects of Body Weight, Sex, Race, and Age

Results of population pharmacokinetic analyses indicate that body weight (29 to 163 kg), gender, race (b) (4) and age (20 to 93 years of age) do not influence the pharmacokinetics of etelcalcetide.

(b) (4)

(b) (4)

In vitro, etelcalcetide did not inhibit or induce CYP450 enzymes, and (b) (4) not a substrate (b) (4) CYP450 enzymes. In vitro, etelcalcetide was not a substrate of efflux and uptake transporter proteins (P-glycoprotein [Pgp], breast cancer resistance protein [BCRP], organic anion transporter [OAT] 1 and 3, organic anion polypeptide transporter [OATP] 1B1 and 1B3, organic cation transporter [OCT] 2, and peptide transporter [PEPT] 1 and 2).

In vitro, etelcalcetide was also not an inhibitor of common transporter proteins (Pgp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, or bile salt export pump [BSEP]).

4 APPENDIX

4.1 OCP FILING MEMO

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208325	**SDN**	0000
Applicant	Amgen	**Submission Date**	08/24/2015
Generic Name	Etelcalcetide	**Brand Name**	
Drug Class	Calcium-sensing receptor agonist		
Indication	Indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis.		
Dosage Regimen	Starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH)		
Dosage Form	2.5 mg Etelcalcetide in 0.5 mL solution in a single-use vial 5 mg Etelcalcetide in 1 mL solution in a single-use vial 10 mg Etelcalcetide in 2 mL solution in a single-use vial	**Route of Administration**	Intravenous
OCP Division	DCPII	**OND Division**	DMEP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Ritesh Jain	Jayabharathi Vaidyanathan	
Pharmacometrics	Jee Eun Lee	Nitin Mehrotra	
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	10/23/2015	**74-Day Letter Date**	11/6/2015
Review Due Date	4/28/2016	**PDUFA Goal Date**	8/24/2016

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑ Yes ☐ No If no list reason(s)
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ☐ Yes ☑ No If yes list comment(s)
Is there a need for clinical trial(s) inspection? ☐ Yes ☑ No If yes explain

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No

1

Reference ID: 3835140

Bioanalytical and Analytical Methods ☑ Yes ☐ No			Labeling ☑ Yes ☐ No
Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☑ Metabolism Characterization		5	Study#119917 CYP metabolism, Study#4169-NC-125 induction of CYP isoforms, Study# 4169-NC-124, 119314 inhibition of CYP Isoforms, Study#118358 biotransformation and blood to plasma ratio
☑ Transporter Characterization		2	Study#118052 drug transporter interactions, Study#119513 inhibition of BSEP transport
☑ Distribution		3	Study#119313 plasma protein binding, Study#119413 dialysis clearance, Study#119414 conjugation and deconjugation kinetics
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Study # 20130107 PK and Tolerability Study in Healthy Volunteers
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Study # 20130139PK and Tolerability Study in Hemodialysis Subject with HPT
	☐ Multiple Dose		
☑ Mass Balance Study		1	Study# 20130147ADME Study in CKD Patients on Hemodialysis
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects			
☑ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects		1	Study # 20130107 PK and Tolerability Study in Healthy Volunteers

2

☑ Patients	1	Study # 20130139PK and Tolerability Study in Hemodialysis Subject with HPT
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	2	Report #119343, Report#119344: Phase I/ II/III Population PK or PK/PD reports Population PK/PD analysis includes data from one Phase 1, two Phase 2 and two Phase 3 trials
☑ Exposure-Efficacy		
☑ Exposure-Safety		

Total Number of Studies	**In Vitro**	10	**In Vivo**	5
Total Number of Studies to be Reviewed		10		5

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☑No ☐N/A	Bio-waiver request for in-vivo bioequivalence (BE) study between the AMG 416 (b) (4) parenteral drug product used in n phase 3 clinical studies and the AMG 416 ready-to-use (RTU) liquid drug product intended for commercial use.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2	☑Yes ☐No ☐N/A	

summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?		
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic	☑Yes ☐No ☐N/A	

requirements for approvability of this product?		
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	

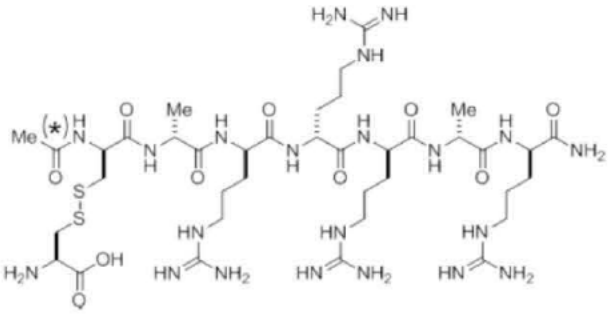
Filing Memo

Indication and Dosage Administration: Etelcalcetide (AMG416) is a calcium-sensing receptor agonist indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis. Recommended starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH).

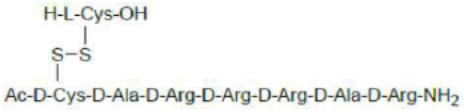
Drug Molecule and Its Mechanism of Action: AMG 416 is a synthetic peptide with a molecular weight of 1048.3 Da comprised of a 7 D-amino acid backbone and L-cysteine linked via a disulfide bond to a D-cysteine in the backbone (Figure 1). AMG 416functions as an allosteric activator of the calcium-sensing receptor (CaSR) and lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium.

Figure 1. (A) Molecular Structure and (B) Amino Acid Sequence of AMG 416 (Free Base)

(A)



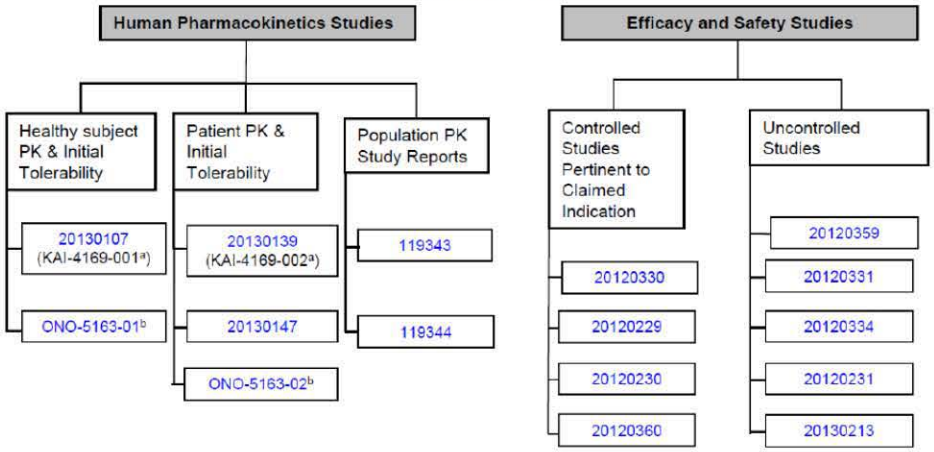
(B)



Clinical Program: The clinical program in this NDA consists of 10 vitro studies. These studies were conducted using human biomaterial to evaluate permeability, plasma protein binding, potential metabolic drug-drug interactions, transporter interactions, biotransformation, red blood cell partition, dialysis clearance, and conjugation-deconjugation kinetics.

Clinical studies in this application include 5 Phase 1 studies, 3 Phase 2 dose studies and 8 Phase 3 trials. Figure below shows the listing of clinical studies conducted in this program.

Figure 1. Organization of AMG 416 Clinical Studies



PK = pharmacokinetics
[a] These studies were conducted by KAI Pharmaceuticals before its acquisition by Amgen.
[b] These studies were conducted in Japan by an Amgen business partner.

Summary: This NDA is file able from Office of Clinical Pharmacology standpoint. No inspection is needed for Clinical Pharmacology Studies. The Clinical Pharmacology Review for this NDA will focus on the following key review questions

1. What are the PK and PD features of AMG416?
2. What is the exposure/Dose relationship for safety and efficacy?
    a. Is the starting dose and dosing frequency adequate?
    b. Is the proposed titration scheme adequate?
    c. Is there any dose/exposure relationship to Hypocalcemia?
3. Does population PK or PK/PD analysis suggests any need for dose adjustment based on covariates?

Filing Meeting Slides:

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Filing Meeting
NDA 208325
AMG416 (Etelcalcetide)

Amgen

Clinical Pharmacology Review Team

Ritesh Jain
Jaya Vaidyanathan
Nitin Mehrotra

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Background: AMG416

Indication:

- AMG416 is a calcium-sensing receptor agonist indicated for Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

Dosage and Administration:

- Starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse back or intravenously after rinse back
- Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH)

Dosage Form and Strengths:

- 2.5 mg etelcalcetide in 0.5 mL solution in a single-use vial
- 5 mg etelcalcetide in 1 mL solution in a single-use vial
- 10 mg etelcalcetide in 2 mL solution in a single-use vial

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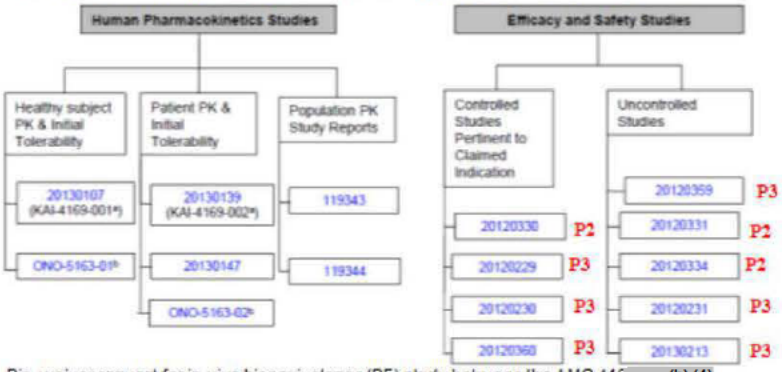
Overview: Clinical Program

Total 16 Clinical Trials: 5 Phase 1 Trials, 3 Phase 2 Trials, 8 Phase 3 Trials



Bio-waiver request for in-vivo bioequivalence (BE) study between the AMG 416 (b) (4) parenteral drug product used in phase 3 clinical studies and the AMG 416 ready-to-use (RTU) liquid drug product intended for commercial use.

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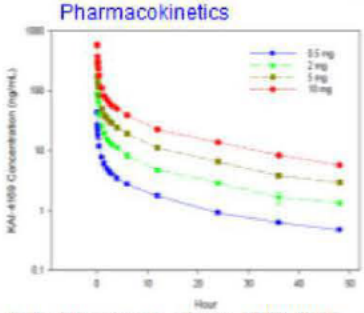
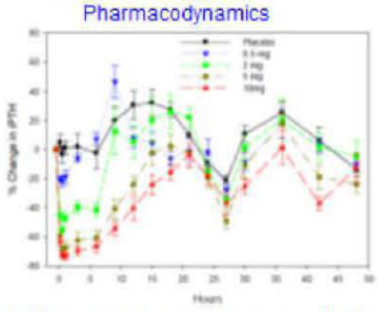
Overview: PK/PD Healthy Subjects

Pharmacokinetics



Pharmacodynamics



- In healthy subjects, plasma AMG 416 C_{max} and AUC_{inf} values increased approximately dose-proportionally. The terminal elimination half-life ranged from 18.4 to 20.0 hours
- Maximum decrease in PTH occurred by 30 mins. PTH levels gradually returned to baseline within 10 to 24 hours.
- The maximum serum PTH reduction from baseline at 30 minutes post-dose in the placebo, 0.5, 2, 5, and 10 mg dose groups was 3.5%, 21.7%, 55.4%, 69.0%, and 72.6%, respectively.

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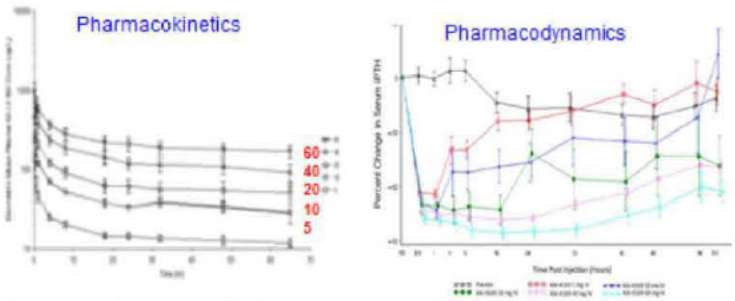
Overview: PK/PD CKD Patients with HPT



- The terminal elimination half-life ranged from 81 to 175 hours (data not sufficient)
- Maximum decrease in PTH occurred by 30 min.
- At 65 hours post-dose, serum PTH was suppressed -48.5%,-49.3%, and -62.6%, in the 20, 40, and 60 mg dose groups, respectively

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Overview: ADME

- AMG 416 is not metabolized by cytochrome P450 enzymes. AMG 416 was not a substrate of human cytochrome P450 enzymes in vitro
- AMG 416 was bio transformed upon administration in blood by disulfide exchange with endogenous thiols. It also forms covalent binding with serum proteins.
- The elimination of AMG 416 and its biotransformation products was presumed to be predominantly by renal excretion in healthy subjects.
- The elimination of AMG 416 in CKD patients receiving hemodialysis was slow, predominantly by hemodialysis and by nonspecific elimination.

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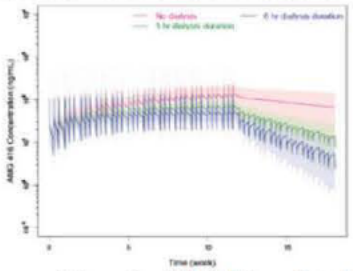
Overview: Population PK

Figure 20. Simulation of AMG 416 PK After 5 mg TIW Dosing for 12 Weeks Followed by 6 Weeks Washout at Dialysis Duration of 0, 3 or 6 hours



- The plasma accumulation ratio of AMG 416 was 2- to 3-fold by week 4.
- The effective half-life is 3 to 5 days following a TIW dosing and dialysis schedule.
- At week 4 plasma concentration are near steady state and after 6-10 weeks of dosing steady state concentrations are reached.

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Pivotal Phase 2 Study Results (20120330)

- AMG 416 administered 3 times weekly for 2 weeks (cohort 1) or 4 weeks (cohorts 2 and 3) in subjects with secondary HPT who were receiving hemodialysis.

Table 9-1. Summary of iPTH at Endpoint (MITT Population)

	Cohort 1		Cohort 2		Cohort 3	
	Placebo	5 mg AMG 416	Placebo	10 mg AMG 416	Placebo	5 mg AMG 416
Baseline*						
N	4	6	21	21	13	13
Mean (SD)	636.3 (191.64)	588.3 (250.52)	601.5 (239.20)	765.1 (480.82)	619.4 (310.35)	662.1 (442.01)
Median	676.3	512.5	536.0	641.5	526.0	536.5
Minimum, maximum	369.5, 823.0	341.5, 1049.5	196.0, 1018.5	258.5, 2185.5	179.5, 1245.0	344.0, 1988.5
Percent change from baseline to endpoint						
N	4	6	21	21	13	13
Mean (SD)	0.3 (17.11)	-19.4 (20.66)	28.5 (70.39)	-49.4 (20.42)	2.3 (29.44)	-33.0 (26.28)
Median	1.0	-15.4	13.0	-54.5	0.0	-36.1
Minimum, maximum	-20.2, 19.3	-44.3, 11.6	-73.0, 293.9	-76.5, 3.8	-46.3, 47.1	-68.3, 20.7
LS mean*	2.2	-18.1	28.9	-48.0	1.9	-34.8
LS mean for difference*		-20.3		-76.9		-36.7
95% CI for difference*		-51.4, 10.8		-109.1, -44.8		-59.8, -13.6
P-value*				< 0.0001		0.0052
95% CI for difference*				-86.9, -50.0		
P-value*				< 0.0001		

Dose Selection Rationale for Phase 3 Trials

- **The starting dose of 5 mg AMG 416 is supported by:**
  - The phase 1 and 2 studies, which showed clinically relevant reductions in PTH in the patient population
  - In addition, the phase 3 studies (Studies 20120230 and 20120229) confirmed that the 5 mg starting dose is reasonable because at the first titration step (Week 4), 35 to 37% of patients stayed at 5 mg and 53% titrated upward to achieve desired PTH control.
  - Approximately 18% to 23% of subjects required titration to the highest dose of 15 mg by week 17 in an effort to achieve target PTH levels of ≤ 300 pg/mL
  - The remainder of patients (approximately 10%) either had their dose withheld (5 to 6%), missed a dose (1 to 2%), or titrated down (3 to 4%).

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Phase 3 Efficacy Results

Table 15. Percent Change in PTH During the Efficacy Assessment Phase - Mixed-effects Model Repeated Measures (Studies 20120229 and 20120230 and 6-month Placebo-controlled Combined Dataset – Full Analysis Set)

	20120229		20120230		Total placebo-controlled studies	
	Placebo (N = 254)	AMG 416 (N = 254)	Placebo (N = 260)	AMG 416 (N = 255)	Placebo (N = 514)	AMG 416 (N = 509)
Baseline PTH (pg/mL)						
n	254	254	260	255	514	509
Mean	819.74	848.70	851.67	845.03	835.89	846.86
SE	24.22	32.65	34.23	29.08	21.04	21.83
Mean PTH (pg/mL) during the EAP						
n	219	229	237	227	456	456
Mean	897.39	383.57	960.28	363.35	930.07	373.51
SE	32.21	25.40	48.09	26.26	29.40	18.25
Percent change from baseline in PTH during the EAP (%)						
n	219	229	237	227	456	456
Mean	13.00	-55.11	13.72	-57.39	13.37	-56.25
SE	2.81	1.94	2.59	1.91	1.87	1.36
Treatment difference (AMG 416 - Placebo) from adjusted analysis*						
Estimate		-71.11		-71.34		-71.30
SE		3.59		3.15		2.31
(95% CI)		(-77.77, -64.46)		(-77.53, -65.14)		(-75.84, -66.76)
p-value		< 0.001		< 0.001		< 0.001

CI = confidence interval; EAP = efficacy assessment phase; PTH = parathyroid hormone; SE = standard error
Full analysis set: all randomized subjects in the dataset
*Mixed-effects model includes treatment and stratification factors as covariates. For individual study, stratification factors were screening PTH level, prior cinacalcet use, and region; for integrated studies, stratification factors were screening PTH level, prior cinacalcet use, region, and study.
Source: ISE Table 4.5

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Clinical Pharmacology Review Focus

- What are the PK and PD features of AMG416?
- What is the exposure/Dose relationship for safety and efficacy?
  - Is the starting dose and dosing frequency adequate?
  - Is the proposed titration scheme adequate?
  - Is there any dose/exposure relationship to Hypocalcemia?
- Does population PK or PK/PD analysis suggests any need for dose adjustment based on covariates?

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Conclusions

- This NDA is filable from Office of Clinical Pharmacology standpoint.
- No inspection is needed for Clinical Pharmacology Studies.
- No comments for the 74 Day letter.

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/s/

RITESH JAIN
10/19/2015

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10/19/2015

4.2 Pharmacometrics Review

4.2.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.2.1.1 Is there evidence of an exposure-response for etelcalcetide in the treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis?

Yes. The primary efficacy endpoint (<30% reduction in PTH from the baseline) increases as dose of etelcalcetide increases. As shown in Figure 17, the predicted fraction PTH decrease by >30% following 2.5 mg, 5 mg, 10 mg, and 15 mg fixed doses with the population PKPD model show a clear dose-response relationship. Furthermore, the predicted fraction PTH decrease by >30% following the proposed dose titration with 5 mg starting dose supports the dose titration rationale for patients whose PTH level is lower than the target range.

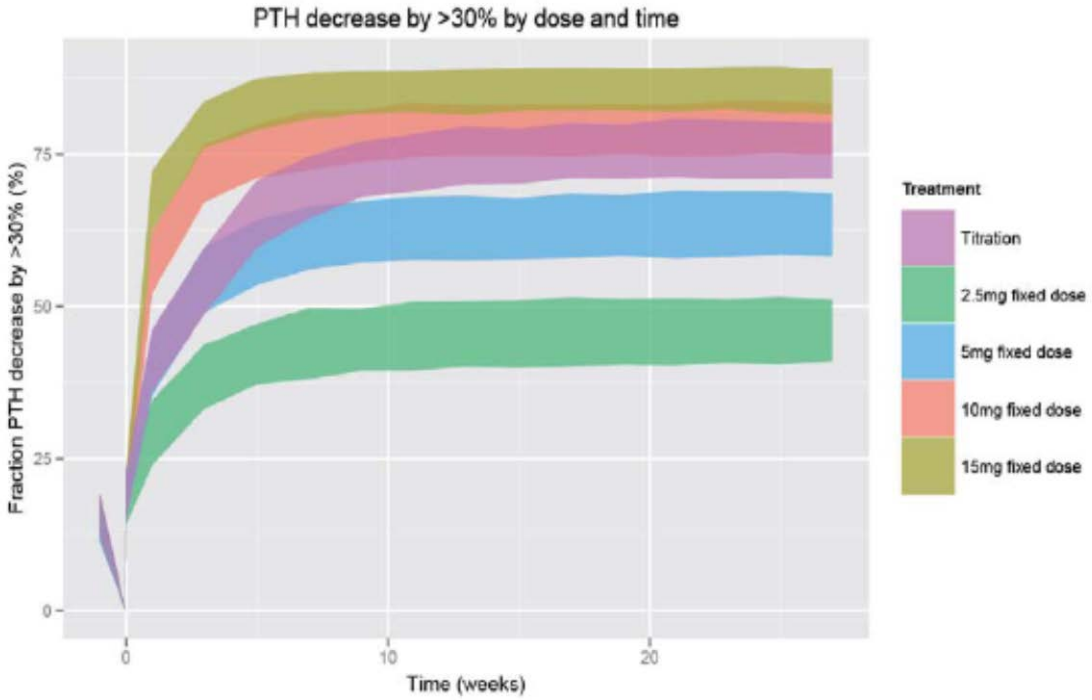


Figure 17: The proportion of subjects expected to achieve the primary efficacy endpoint of >30% reduction in iPTH relative to individual baseline value, over the course of the study and 90% prediction interval.

(Applicant's simulation with the population PKPD model)

4.2.1.2 Is the proposed starting dose for the overall population appropriate?

- Is there a need have a lower starting dose in patients whose PTH level drops below < 100 pg/ml during the trial?

Yes. The applicant's proposed dose titration based on target PTH and corrected Ca appears to be reasonable. Given the dose titration scheme, the majority of patients escalated dose to >10 mg TIW with maximum of 15 mg TIW dose (Figure 18) and the efficacy endpoint (proportion of subjects achieving >30% reduction in PTH from the baseline) was 74.0% in Study 20120229 and 75.3% in Study 20120230. Although patients with severe disease condition tended to receive higher dose upon titration, the final doses were still within the range of the proposed titrating doses and the proposed starting dose of 5 mg TIW was adequate for patients with any level of baseline PTH.
Moreover, the change of iPTH and cCa relative to baseline following 5 mg TIW dosing for 4 weeks show that the changes in iPTH and cCa at Week 4 (Day 21) and Week 5 (Day 28) are comparable. Thus, the sampling at Week 4 and titrating dose at Week 5 seems appropriate.

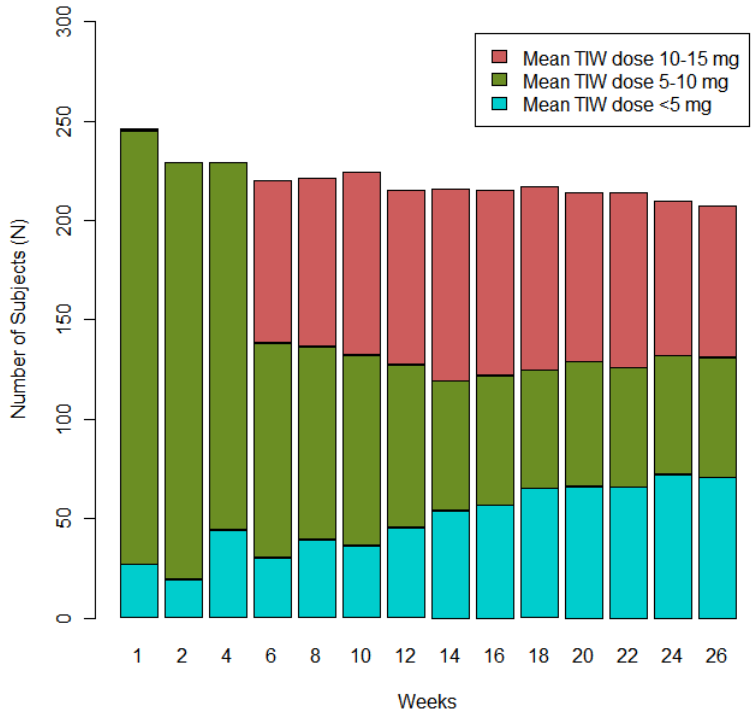


Figure 18: Number of subjects and change in mean TIW dose over time

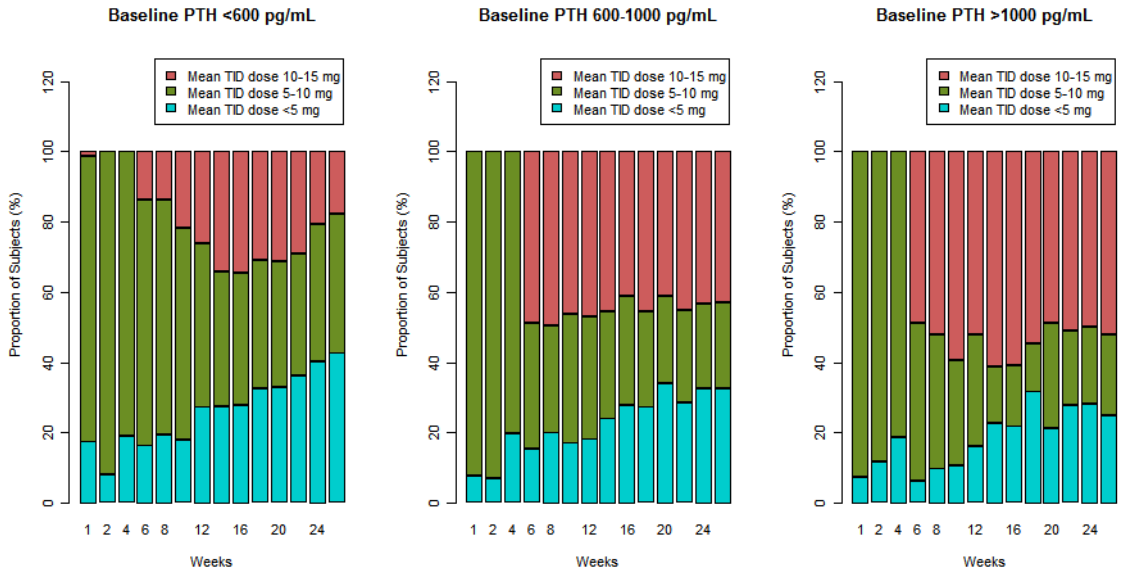


Figure 19: Proportion of subjects and change in mean TIW dose over time by baseline PTH

Furthermore, dose-response relationship for PTH <100 pg/mL indicates that higher titrated dose does not necessary generate over-reduction in PTH in individual patients (Figure 20). One of safety concerns regarding dose titration scheme was the potential overdose resulting in over-reduction in PTH and thereby causing adynamic bone diseases. As shown in Figure 20, subjects whose PTH was less than 100 pg/mL received lower dose than those whose PTH was above 100 pg/mL. This analysis result also supports that dose titration scheme based on individual response.

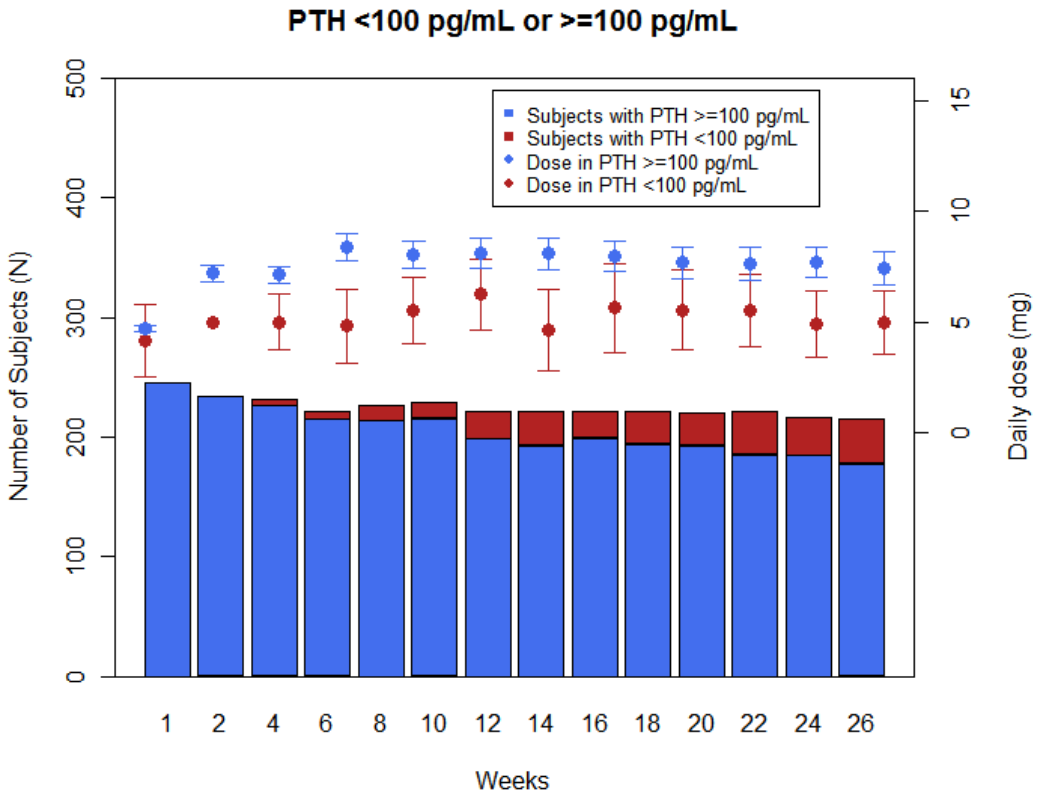


Figure 20: Change in dose in patients with PTH<100 pg/mL or PTH≥100 pg/mL

4.2.2 Recommendations

The office of Clinical Pharmacology Division of Pharmacometrics has reviewed the information provided in the submission and consider the data are acceptable for supporting the approval of etelcalcetide for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.

4.2.3 Labeling Statements

Detailed labeling recommendations are included in section 3.

4.2.4 Applicant's Analysis

4.2.4.1 Introduction

Due to the variability of PTH and Ca responses to treatment, dose was intended to be titrated based on PTH and serum Ca levels following a few weeks of treatment. The titration scheme aims at lowering PTH and Ca levels with minimal safety risks that may result from low serum calcium levels.

First, the sponsor conducted a population PK analysis to characterize the PK of etelcalcetide after intravenous administration and evaluate various covariates to explain inter-patient variability in exposure, such as demographic factors, liver function

biomarkers, baseline alkaline phosphatase, disease characteristics, and concomitant medications.
Second, a population PKPD analyses were performed to characterize the effects of AMG416 on the time course of PTH and serum Ca in the patients with sHPT. Model-based simulations were performed to support the efficacy and safety of the dose titration scheme which was utilized in the phase 3 trials.

4.2.4.2 Datasets

Data from one phase 1 study (2013039), two phase 2 studies (20120331 & 20120330) and two phase 3 studies (20120229 & 20120230) were used in the AMG416 population PK analysis. These studies are summarized in Table 12.

Table 12: Summary of Clinical Studies Conducted in CKD Patients with SHPT Receiving HD

Study	Phase	AMG 416 Dose in mg (number of subjects)	Dosing Schedule	PK Sampling Scheme
20130139 (KAI-4169-002)	1	Placebo only (n=9) Placebo/Treatment (cross over): 5 mg (n=4) 10 mg (n=3) 20 mg (n=4) +Treatment only: 40 mg (n=4) 60 mg (n=4)	Single dose treatment	Pre-dose, 0.17, 0.5, 1, 4,8, 18, 24, 32, 48 hour and on day 4 at discharge and after HD
20120330 (KAI-4169-003)	1	Placebo: 38 5 mg (2 wks) (n=6) 5 mg (4 wks) (n=13) 10 mg (4 wks) (n= 21)	TIW dose for 2 weeks (cohort 1) or 4 weeks (cohort 2, 3)	Pre-dose and on day 1, 3, 6, 8, 10, 13, 15, 20, 27 and 41 after the start of treatment.
20120331 (KAI-4169-005)	2	doses titrated ranging from 2.5 – 20 mg (n=37); starting dose: 5 mg	TIW dose for 12 weeks starting at 5 mg; and titrated on week 5 and 9	Day 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 82/83, 85, 99, 113 and end of study (EOS)
20120229	3	N=500, dose titrated ranging from 5-15mg; starting dose: 5 mg	TIW dose for 26 weeks starting at 5 mg; and titrated on week 5, 9, 13, and 17	Day 1, week 5, 13, 26
20120230	3	N=500, dose titrated ranging from 5-15mg; starting dose: 5 mg	TIW dose for 26 weeks starting at 5 mg; and titrated on week 5, 9, 13, and 17	Day 1, week 4, 5, 12, 13, 20, 26 and EOS

HD: hemodialysis; TIW: thrice weekly

AMG416 PK was evaluated in a total of 583 subjects. In the 2 phase 1 studies, fixed dose of AMG416 was administered. In phase 2 and 3 studies, titrated dose of AMG416 was administered TIW and ranged from 2.5 to 20 mg. The dataset for the population PK analysis only included data from sHPT patients since the difference in PK between healthy volunteers and the sHPT patients was well established. Renal excretion was one of the major elimination pathways while hemodialysis was the major route of elimination in sHPT patients and the impact of renal impairment was minimal.

4.2.4.3 Methods

PK Model was developed in three steps: structural model selection, covariates analysis, and model refinement. Three-compartment model with IV bolus input with an additional route of drug elimination vis hemodialysis was established to describe the PK of etelcacetide. The covariates were evaluated including demographic factors (body

weight, age, sex, race), liver function biomarker (aspartate aminotransferase, alanine aminotransferase, serum albumin, total bilirubin, and alkaline phosphatase), and disease markers iPTH, corrected calcium, phosphorus, serum creatinine, and concomitant medications (vitamin D, phosphate binders and calcium supplements).

Refinement of the established PK model was attempted with the data in the pooled dataset and found a different residual error model appeared to explain without converge failure. However, the addition of the new error parameter did not have statistically significant difference in objective function value, thus the originally developed model was maintained as the final model.

PK model-based simulations were performed to explore the effect of dialysis durations on AMG416 exposure and accumulation following the administration of 5 mg IV TIW dosing. Furthermore, the effects of covariates were evaluated using simulation exercises.

The development of the population PKPD model was performed using a sequential process and individual parameters obtained from the population PK model was used to predict the individual intact AMG416 serum concentration-time profile. These predicted individual PK profiles in turn were used as an input function of the exposure-response in the population PKPD model.

A mechanism-based population PKPD model was fitted to the data and the individual Bayesian estimates were utilized to evaluate the effects of covariates with visual inspection and stepwise linear regression for the relationship between the individual Bayesian model parameters and the covariates. The structure model was refined by examination of correlation of covariates, residual error distribution, and parameter precision, etc. Models were evaluated further with visual predictive check and Monte Carlo importance sampling expectation maximization for the development of the final model.

PKPD model-based simulations were performed to evaluate the effect of selected covariates (e.g., disease severity described by iPTH baseline) on the changes in serum cCa and iPTH, evaluate the interplay between AMG416 PK, iPTH and cCa, and to support the dose titration scheme implemented in phase 3 trials. For comparison, the time courses of iPTH and cCa following the treatment fixed dosing of 2.5, 5, 10 and 15 mg TIW were also simulated.

Finally, following measures of efficacy, safety and adequacy of titration scheme were calculated and reported:

- The proportion of subjects expected to achieve the primary efficacy endpoint of 30% reduction in iPTH relative to individual baseline value, over the course of the study (at the different scheduled potential titration visits, or at different disease severity level

- The proportion of subjects expected to be experiencing serum cCa levels <7.5 mg/dL, over the course of the study (at the different scheduled potential titration visits, or at different disease severity level
- The proportion of subjects expected to be on each dose level (5 mg, 10 mg and 15 mg), over the course of the study (at the different scheduled potential titration visits)
- The proportion of subjects expected to be experiencing up-titration, down-titration or dose suspensions over time, over the course of the study (at the different scheduled potential titration visits)

*4.2.4.4 **Results: PK***

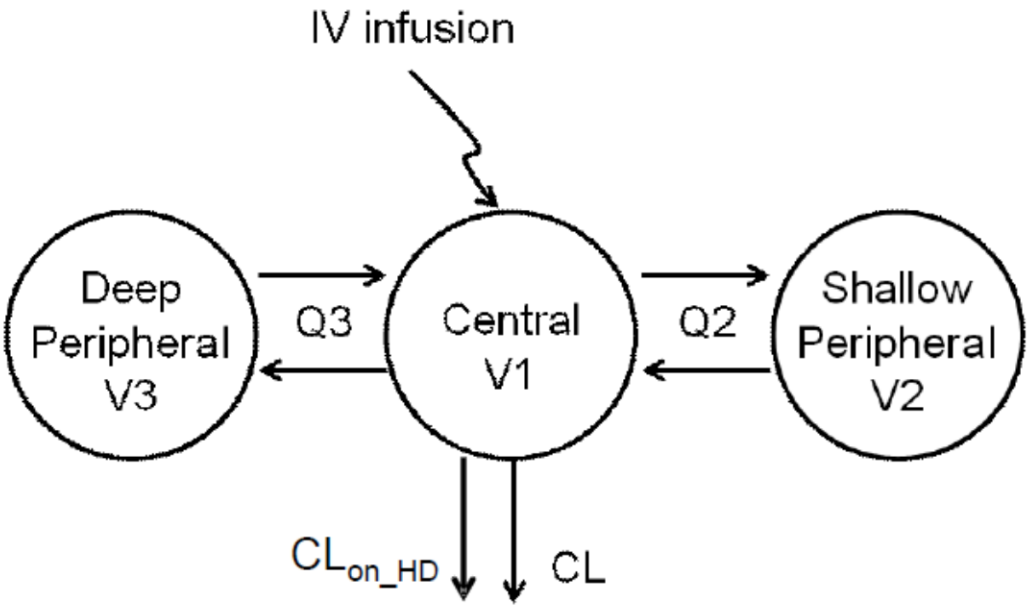


Figure 21: Structural model for AMG416 pharmacokinetics

The 3-compartment model with instantaneous input and first order elimination along with additional route of drug elimination via hemodialysis was developed as the structural model (Figure 21). The 3-compartment model was parameterized in terms of systemic clearance (CL), hemodialysis clearance (CL_{on_HD}), volume of distribution for the central compartment (V1), volume of distribution for the shallow peripheral compartment (V2), volume of distribution for the deep peripheral compartment (V3), intercompartmental clearance between central and shallow peripheral compartment (Q2), and intercompartmental clearance between central and deep peripheral compartment (Q3). The parameter estimates of the final model are summarized in Table 13.

Table 13: Parameter Estimates for the Final Model

Parameter	Estimate	RSE(%)
CL (L/h)	0.479	7.22
V1 (L)	50.4	5.86

Q2 (L/h)	33.2	8.94
V2 (L)	119	5.05
Q3 (L/hr)	3.44	8.52
V3 (L)	624	3.16
$CL_{on\ HD}$ (L/h)	21.9	4.02
ωCL (%)	70	14.3
ωV1 (%)	90.8	7.3
Cor CL-V1	0.18	36
ωQ2 (%)	71.8	17.9
ωV2 (%)	-	-
ωQ3 (%)	81.55	15.5
ωV3 (%)	37.4	17.0
ωCLon_HD (%)	-	-
σ_{prop} (%)	32.5	0.47
σ_{add} (SD)	2.16	7.21

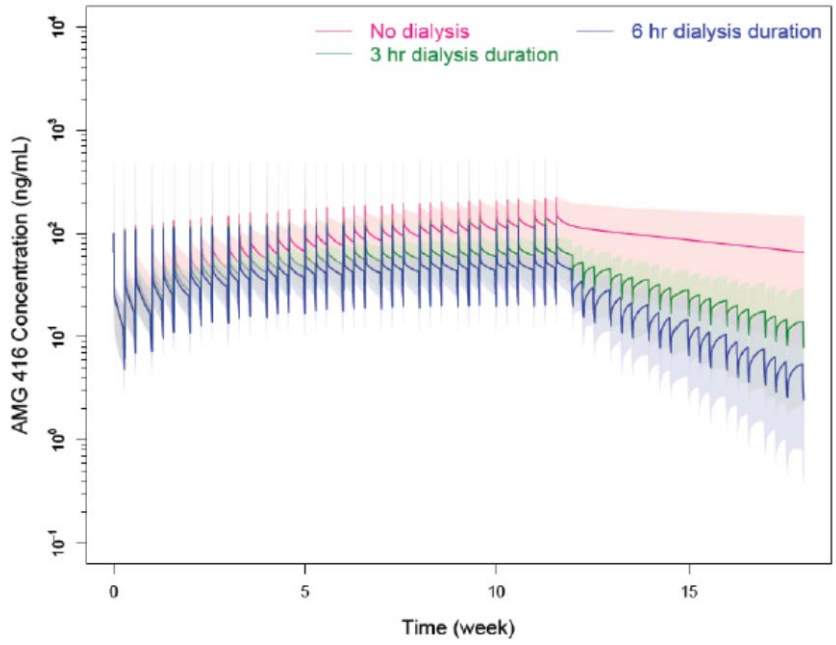
(Source: Population PK report, Table 6, page 59)

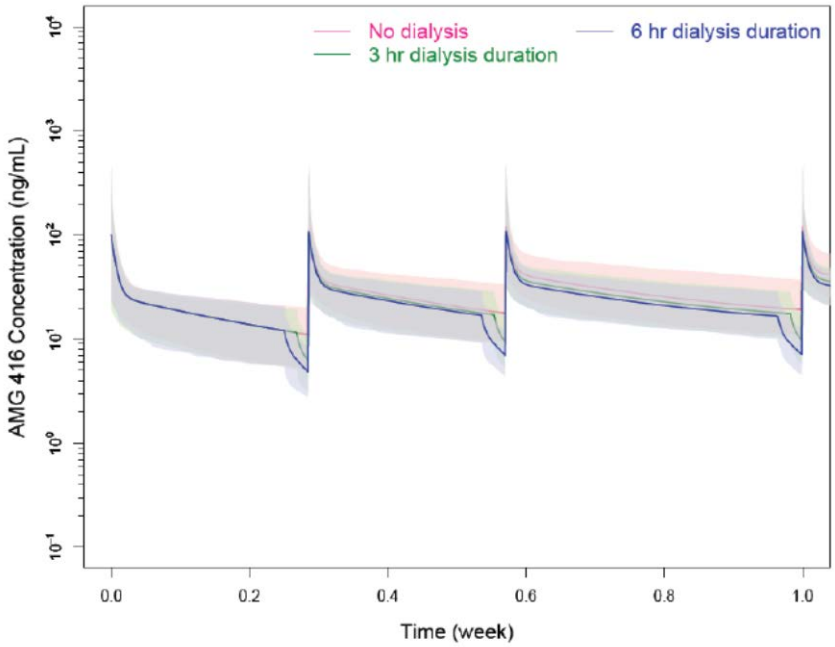
Simulation results for the plasma AMG416 concentration versus time profile following 5 mg IV TIW dosing with 0, 3 and 6 hour dialysis duration (Figure 22) indicate that increasing the dialysis duration from 3 hour to 6 hours is expected to result in reduced accumulation ratio and effective half-life by 27% and 33%, respectively. The mean steady-state exposure of AMG416 ($AUC_{48hr,ss}$) in sHPT patients with 6 hour dialysis duration is expected to be approximately 40% higher than that with 3 hour dialysis duration (Table 14).

Table 14: Summary of Mean Accumulation Ratio, Effective Half-life, Time to Steady State

Dialysis duration	$AUC_{48hr,ss}$ (ng*hr/mL)	Accumulation Ratio		Effective Half-life (day)		Time to 90% Steady State	
		Based on C_{min}	Based on AUC	Based on C_{min}	Based on AUC	Based on C_{min}	Based on AUC
No dialysis	6148 [2595.2, 9857.0]	10.6 [4.3, 22.5]	6.8 [3.1, 13.7]	14.0 [5.2, 30.5]	8.7 [3.5, 18.3]	69.0 [53.0, 74.0]	67.0 [47.9, 74.0]
3 hr	3225.4 [1704.3, 4282.2]	5.5 [2.8, 11.2]	3.6 [2.3, 6.6]	6.9 [3.2, 14.9]	4.3 [2.4, 8.4]	57.9 [33.9, 66.9]	53.0 [32.0, 65.0]
6 hr	2299.9 [1428.0, 3043.8]	3.8 [2.2, 7.6]	2.6 [1.9, 4.4]	4.6 [2.3, 9.8]	2.9 [1.8, 5.4]	40.8 [24.8, 57.8]	46.0 [25.0, 65.0]

(Source: Population PK report, Table 8, page 61)


No dialysis
6 hr dialysis duration
3 hr dialysis duration
AMG 416 Concentration (ng/mL)
Time (week)


No dialysis
6 hr dialysis duration
3 hr dialysis duration
AMG 416 Concentration (ng/mL)
Time (week)

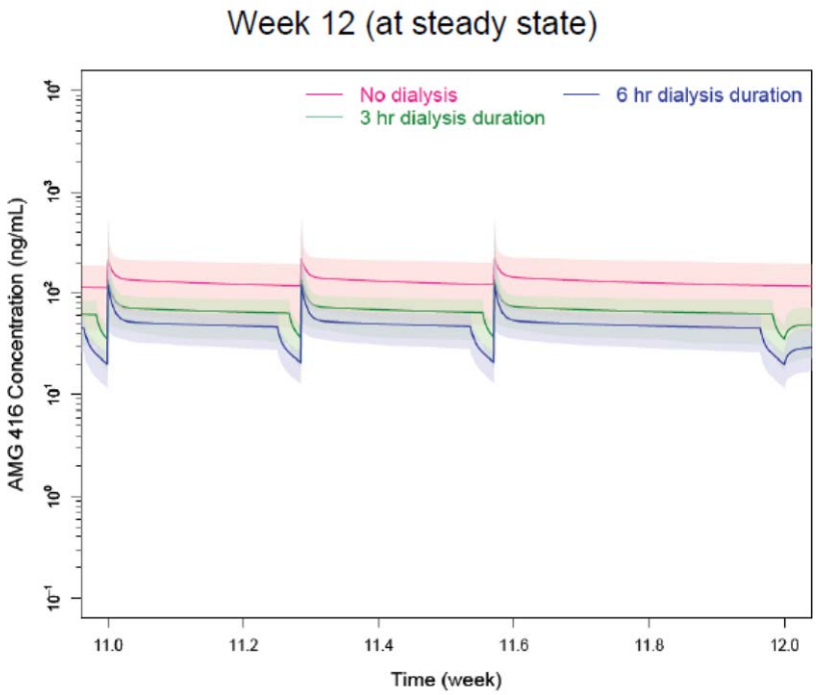
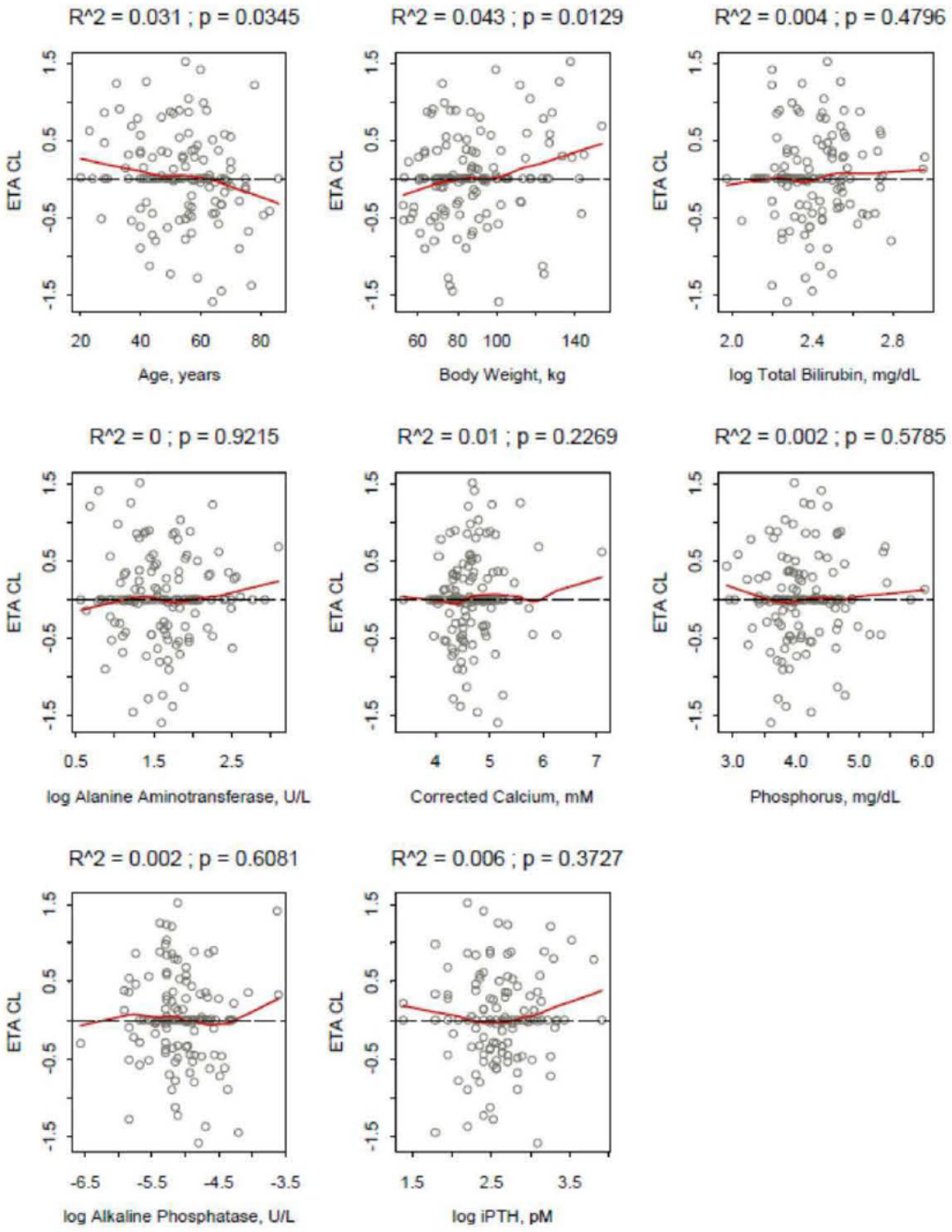


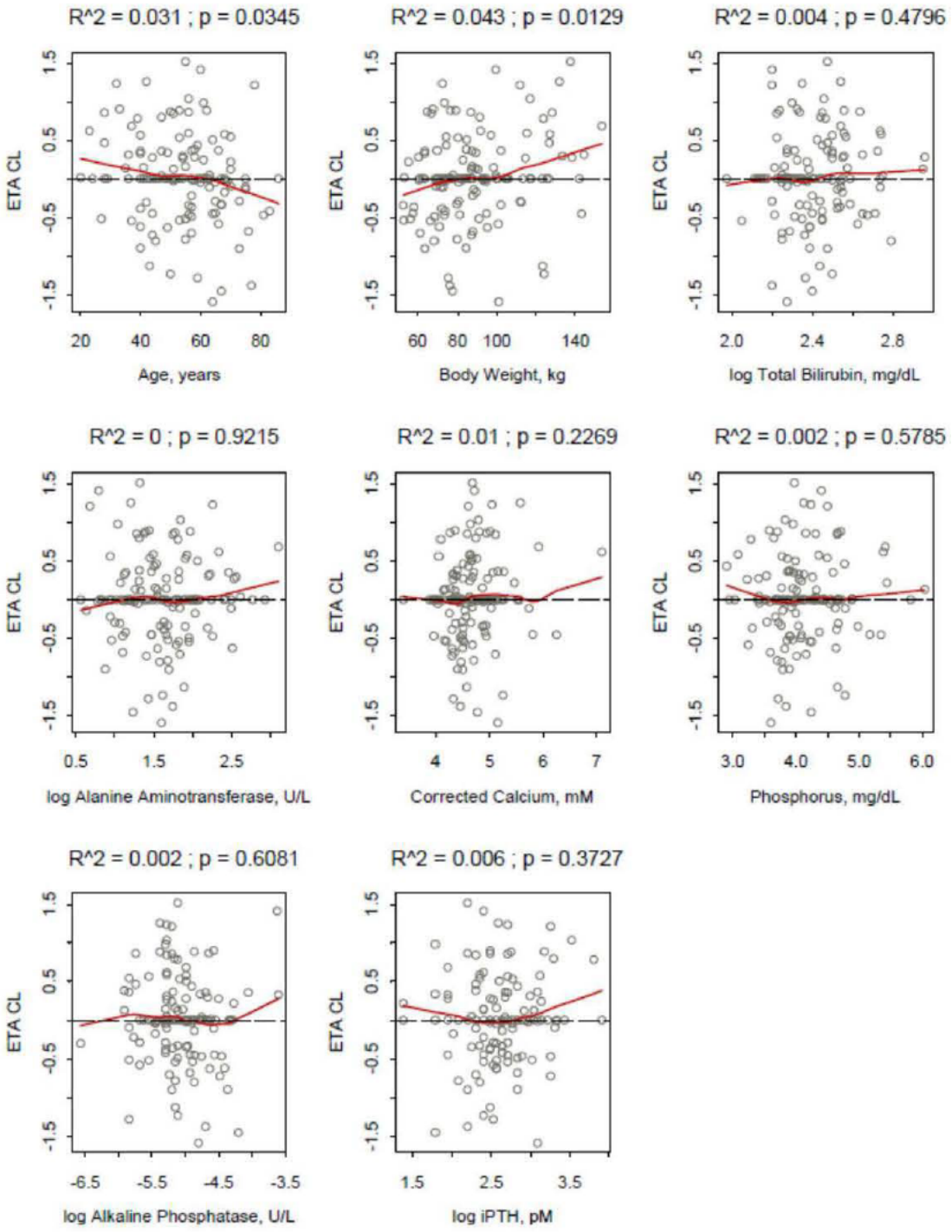
Figure 22: Simulation of AMG416 PK following 5 mg TIW dosing for 12 weeks followed by 6 weeks washout at dialysis duration of 0, 3, 6 hours

(*Source: Population PK report, Figure 30, page 94*)

The terminal half-life was estimated to be 1270 hours and it was longer in patients compared to healthy volunteers. Based on results from simulations, dialysis duration was on the main determinants of accumulation ratio and effective half-life. The mean Cmin-based steady-state effective half-life was 5.5 days with the 3-hour dialysis duration. These findings support the dosing scheme of TIW since the drug lost due to dialysis needs to be replaced to maintain effective exposures and this dosing does not appear to results in unacceptable accumulation of the drug.

The distribution of variability on CL by demographic and laboratory covariates were evaluated using graphical assessment (Figure 23) and most covariates but body weight did not show significant effect. As body weight increases the variability on CL appear to increase but its clinical impact seems minimal.





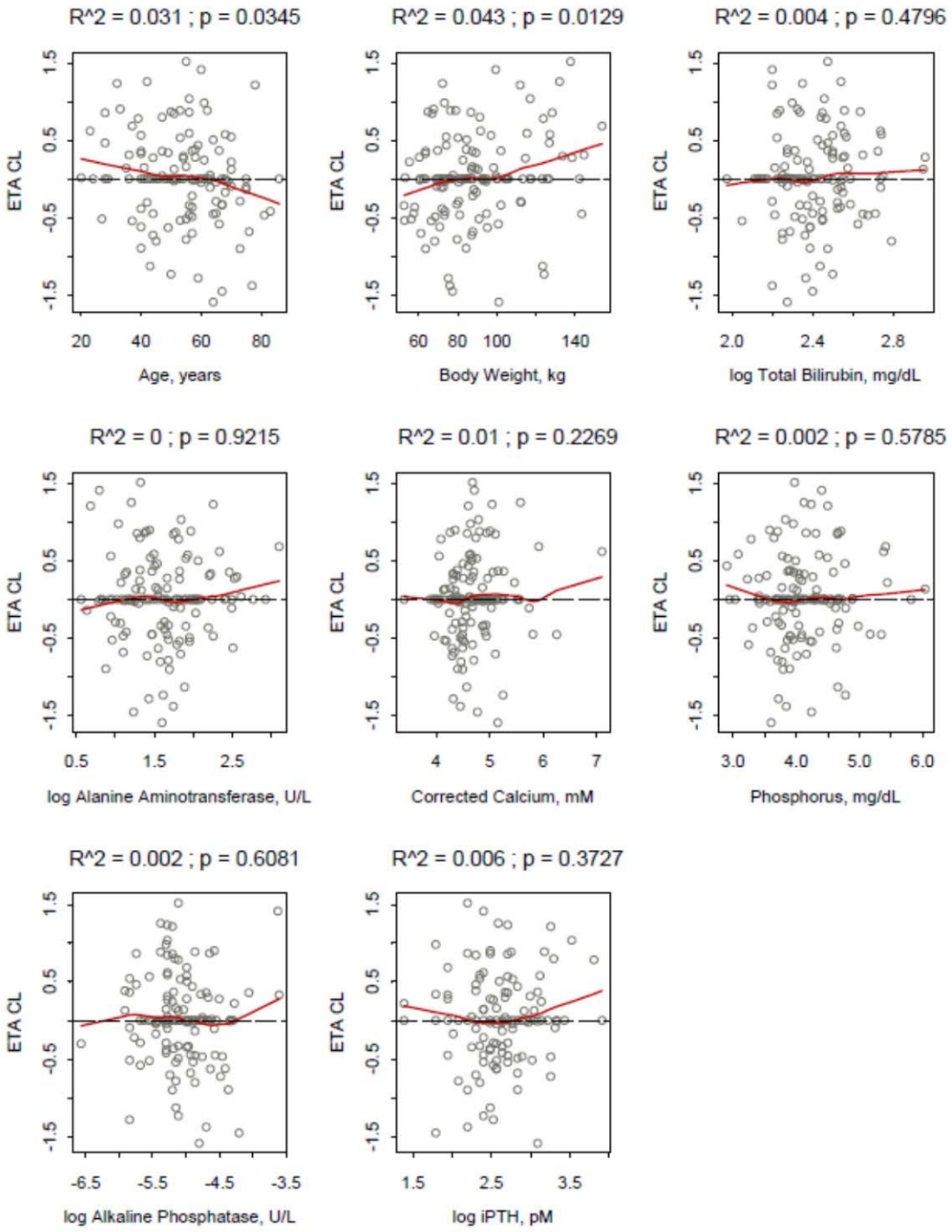


Figure 23: Relationship between the interindividual random effect for CL and covariates for the structural model (source: Population PK report, Figure 18, page 82)

Forest plots were generated to evaluate vitamin D, sex, and body weight on AMG416 steady state exposures (Figure 24). Within the range of the given body weight,

steady-state AUC $_{0\text{-}48}$ exposures are expected to be within 20% of difference from a typical individual (80 kg male not using vitamin D). The effects of vitamin D and sex were also within 20% of difference from a typical individual.

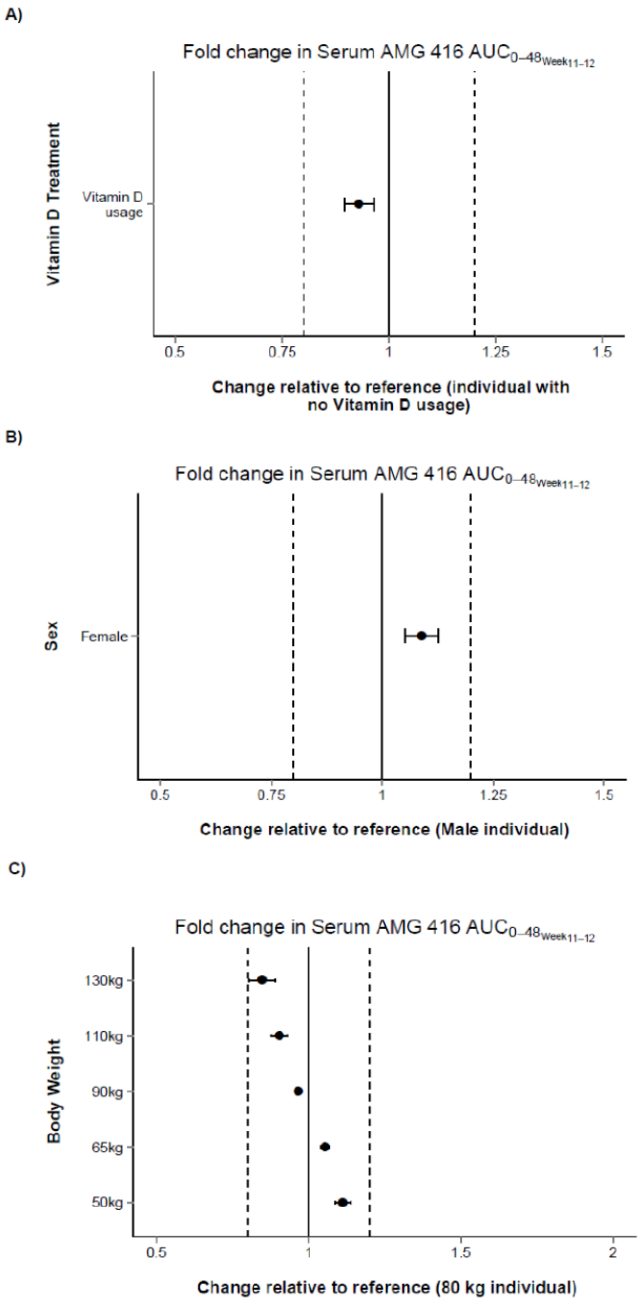


Figure 24: Forest plots based on the simulated parameters with uncertainty for covariate vitamin D treatment (A), Sex (B) and Body weight (C) from the final covariate model

Reviewer's comments: The final population PK model appears to be reasonable to explain the PK of etelcalcetide following 5 mg TIW IV administration. Following

intravenous bolus, the systemic clearance (CL), CL on hemodialysis (C_{on_HD}) and central volume of distribution (V1) were estimated to be 0.472 L/hr, 22.4 L/h and 49.9 L, respectively. The volumes of distribution for the two peripheral compartments were estimated to be 119 L (shallow) and 624 L (deep). The estimates of interindividual variability (IIV) for CL and V1 were 70.3% and 88.3%, respectively. No significant covariates were identified as predictors of PK variability. The effect of dialysis duration was evaluated using simulation with the developed model and the results confirm that TIW dosing in patients with dialysis could provide adequate exposure for treatment effect. Conclusively, the proposed labeling statements based on the population PK analysis are acceptable.

*4.2.4.5 **Results: PKPD***

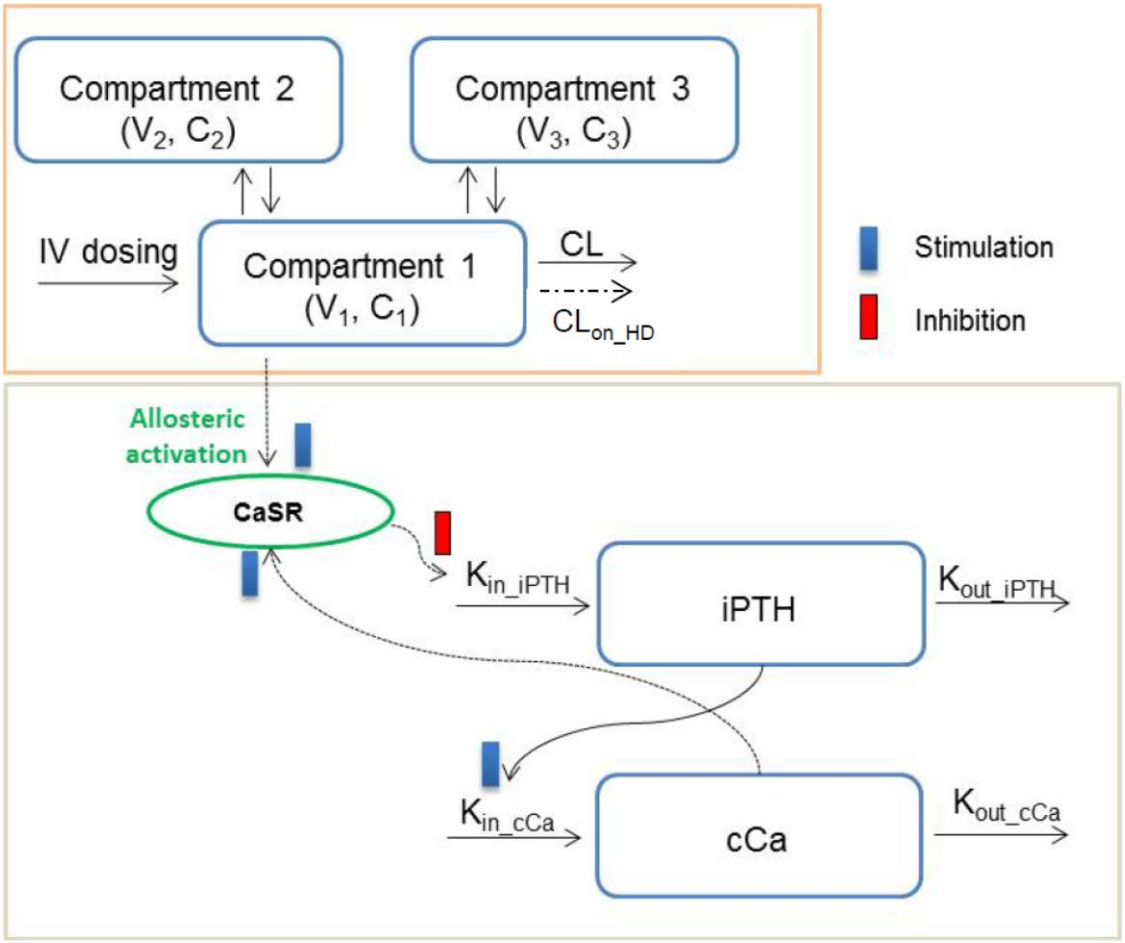


Figure 25: Schematic diagram of the PKPD model for AMG416.

(Source: Population PKPD report, Figure 1, page 278)

The physiological interaction between the iPTH, cCa and mechanism-based (allosteric activation) effect of AMG416 were introduced in the structural model (Figure 25). Both

cCa and iPTH production were described using zero-order processes and cCa production is stimulated by increases in iPTH from baseline through a linear relationship, while iPTH production is inhibited by increases in CaSR receptor occupancy by the innate ligand, Ca, relative to the baseline occupancy. Both cCa and iPTH was assumed to be eliminated by first order kinetics.
In the absence of drug, fractional occupancy of CaSR by calcium is defined as

$$\rho = \frac{Ca}{K_D + Ca}$$

where, K_D, the equilibrium dissociation constant of Ca, is assumed to be 1.2 mM.
The fractional change in CaSR occupancy relative baseline is the driving force in iPTH production, and PTH turnover is described by

$$\frac{diPTH}{dt} = K_{in,iPTH}\left(\frac{\rho}{\rho_0}\right)^{\lambda} - K_{out,iPTH} \cdot iPTH$$

where, $K_{in,iPTH}$ is the zero-order production rate of PTH, ρo is the Ca/CaSR occupancy at baseline, λ is a constant determining the strength of the effect of changes in ρ on iPTH production, and $K_{out,iPTH}$ is the first-order elimination rate constant for iPTH. As an increase in receptor occupancy is expected to lead to a decrease in iPTH production rate, λ is expected to be negative.
Ca turnover is described by

$$\frac{dCa}{dt} = K_{in,ca}(1 + s(iPTH - iPTH_0)) - K_{out,ca} \cdot Ca$$

where Kin,Ca is the zero order production rate of Ca, s is the slope relating changes in iPTH from baseline to Ca production, iPTH0 is baseline iPTH and Kout,Ca is the first order elimination rate for Ca.
AMG416 is believed to be an allosteric activator and assumed to increase the affinity of the CaSR for Ca, resulting in increased CaSR occupancy by Ca and stimulation of PTH production for the same Ca concentration. In the presence of the allosteric activator AMG416, the model is described as

$$\rho = \frac{\frac{Ca}{K_D} \cdot (1 + \frac{\alpha \cdot C_p}{K_i})}{\frac{Ca}{K_D} \cdot (1 + \frac{\alpha \cdot C_p}{K_i}) + \frac{C_p}{K_i} + 1}$$

where K_i is the equilibrium dissociation constant for AMG416 at the CaSR, α is less than one, the interaction is negatively cooperative, but if α is greater than one, the interaction is positively cooperative (i.e., the affinicty of the CaSR for Ca is increased).
The baseline cCa and iPTH values, cCa0 and iPTH0 were estimated and Kin,Ca and Kin,iPTH were calculated as

$$K_{in,Ca} = Ca_0 \cdot K_{out,Ca}$$

$$K_{in,iPTH} = iPTH_0 \cdot K_{out,iPTH}$$

The parameter estimates for the PKPD model are summarized in Table 15.

Table 15: PD Parameter Estimates of the PKPD Model

Parameter	Estimate	RSE (%)
Slope (s)	0.00269	4
Lambda(λ)	-12.1	-3
$K_{out,iPTH}$ (1/hour)	1.93	3
$K_{out,Ca}$ (1/hour)	0.03	9
K_i (ng/mL)	536.81	10
Alpha (α)	3.41	7
PTH_0	76.9	2
Ca_0	2.4	0.2
ωPTH_0	46	4
ωCa_0	6	5
ωK_i	53	7
ωslope	67	8
$\sigma_{prop,Ca}$ (%)	3.5	1

$\sigma_{prop,PTH}$ (%)	27.5	2

(source: Population PKPD report, Table 5, page 274)

As physiologically expected, high correlation between interindividual variability estimated on baseline iPTH and cCa (r2=0.08, p<0.001) was observed. As shown in Table 15, all PD parameters were estimated with good precision (RSE<30%) and the shrinkage on s, Ki baseline iPTH, and cCa were 40.7%, 33.3%, 2.5%, and 1.9%, respectively. Interindividual variability in the slope of the relationship between calcium production to the change in PTH from the baseline, and equilibrium dissociation constant for AMG416 were relatively moderate (50-60%).

The feedback mechanism of CaSR and PTH production is well reflected in the model with the value of the magnitude parameter λ=-12.1. The negative sign reflects the negative effect (inhibitory effect) on PTH production. Low interindividual variability (<10%) on baseline Ca indicates that calcium level was tightly regulated in the body.
The covariates included in the assessment were demographic factors (body weight, age, sex, race), disease severity characteristic (time on dialysis and baseline serum phosphorus), and co-medicating with Vitamin D supplements. No statistically significant covariates on baseline iPTH and baseline cCa were identified.

Simulation results with the final PKPD model for the fraction of subjects expected to achieve primary efficacy, experience the cCa safety endpoint with different dosing schemes are shown in Figure 26 and Table 16. The simulation results suggested that the iPTH suppression for the 5 mg starting dose and implementing the titration regimen are generally between the results of 5 mg and 10 mg fixed dose. Approximately 75% of subjects are expected to achieve the primary efficacy endpoint following 12 weeks of titration. This fraction is expected to be maintained throughout the study with the titration scheme. About 10% higher efficacy is expected with starting dose of 5 mg with titration than 5 mg fixed dosing regimen without titration. For the fraction of subjects that experience cCa<7.5 mg/dL, the results of 5 mg starting dose with titration are between the results of 2.5 mg and 5 mg fixed dose. On average, the fraction of subjects experiencing hypocalcemia of cCa<7.5 mg/dL are expected to be less than 6% with titration and approximately 8-9% with 5 mg fixed dosing regimen without titration.

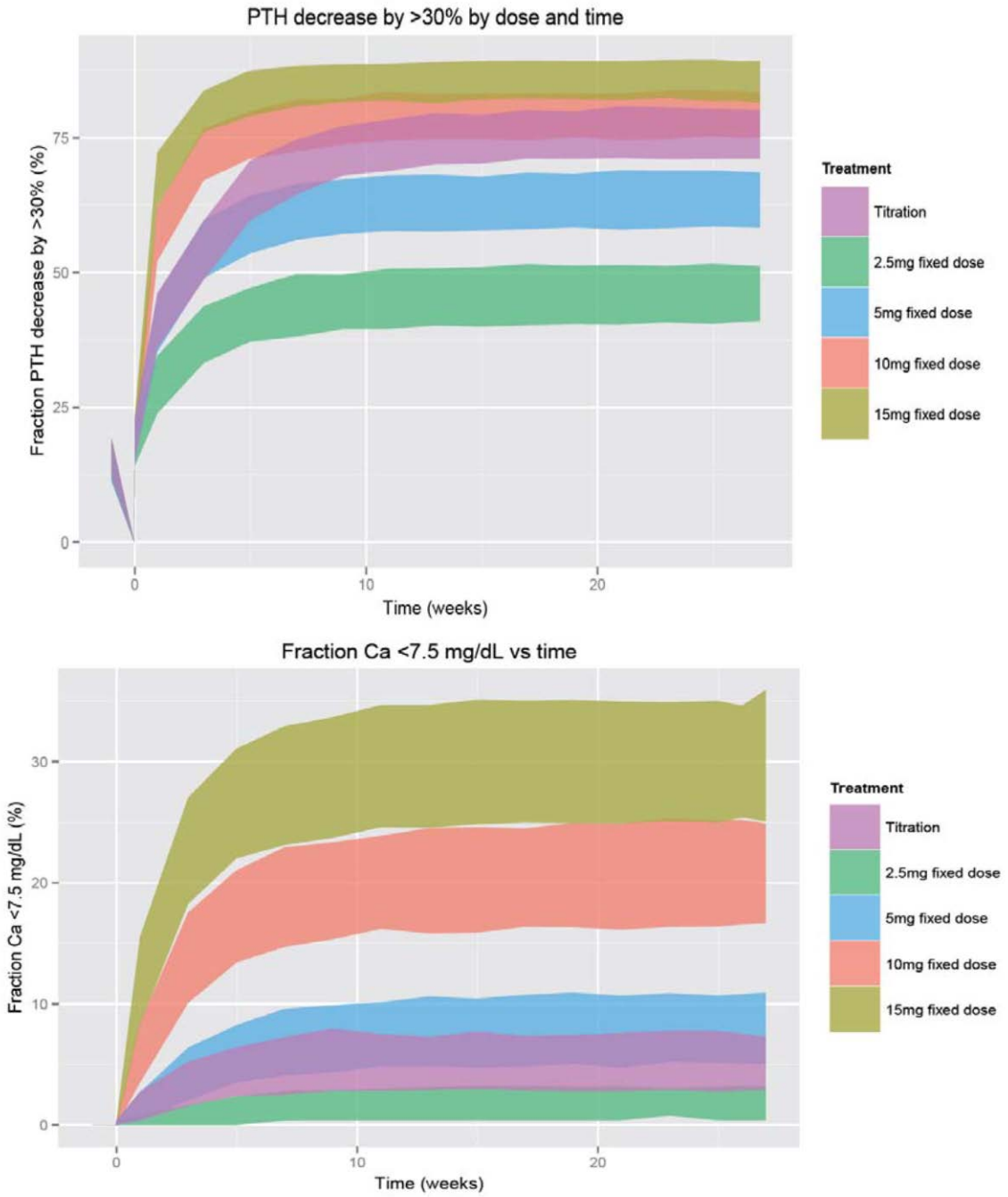


Figure 26: Simulations of the Effects of Titration Dose on Efficacy and Safety: (a) The proportion of subjects expected to achieve the primary efficacy end point of >30% reduction in iPTH relative to individual baseline value, over the course of the study and 90% prediction interval. (b) The proportion of subjects expected to be experiencing serum cCa levels <7.5 mg/dL, over the course of the study (at the different scheduled potential titration visits) and 90% prediction interval.

(Source: Population PKPD report, Figure 24, page 316)

Table 16: Summary of Fraction of Subjects Expected to Achieve Primary Efficacy and Safety Endpoint Over Time

	>30% Reduction in iPTH relative to baseline			Serum cCa < 7.5 mg/dL		
Dosing Regimen	Week 4	Week 12	Week 24	Week 4	Week 12	Week 24
Titration starting 5 mg	54.3	73.5	75.5	3.1	4.9	5.1
	[48.6 - 59.5]	[68.9-78.4]	[71.0 -80.6]	[1.6 - 5.2]	[2.8 - 7.5]	[2.9 - 7.8]
2.5 mg fixed dosing	38.3	45.2	46.0	0.8	1.6	1.6
	[33.2 - 43.7]	[39.5 -50.7]	[40.8 - 51.2]	[0.0 - 1.7]	[0.4 - 3.0]	[0.8 - 3.0]
5 mg fixed dosing	54.1	62.7	63.5	4.1	7.3	7.8
	[49.0 - 59.7]	[57.7 -68.0]	[58.2 - 68.9]	[2.0 - 6.4]	[4.8 - 10.1]	[5.2 - 10.9]
10 mg fixed dosing	71.6	78.7	79.4	13.6	20.0	21.0
	[67.1 - 76.6]	[74.5 - 83.6]	[74.7 - 83.8]	[10.1 - 17.6]	[16.2 - 23.9]	[16.4 -25.3]
15 mg fixed dosing	80.3	85.5	85.7	22.5	29.5	30.2
	[76.1 - 83.7]	[81.9 - 88.7]	[82.4 - 89.5]	[18.3 - 27.0]	[24.6 - 34.7]	[25.1 -34.9]

* The values are represented as median [90%CI]

(source: Population PKPD report, Table 6, page 275)

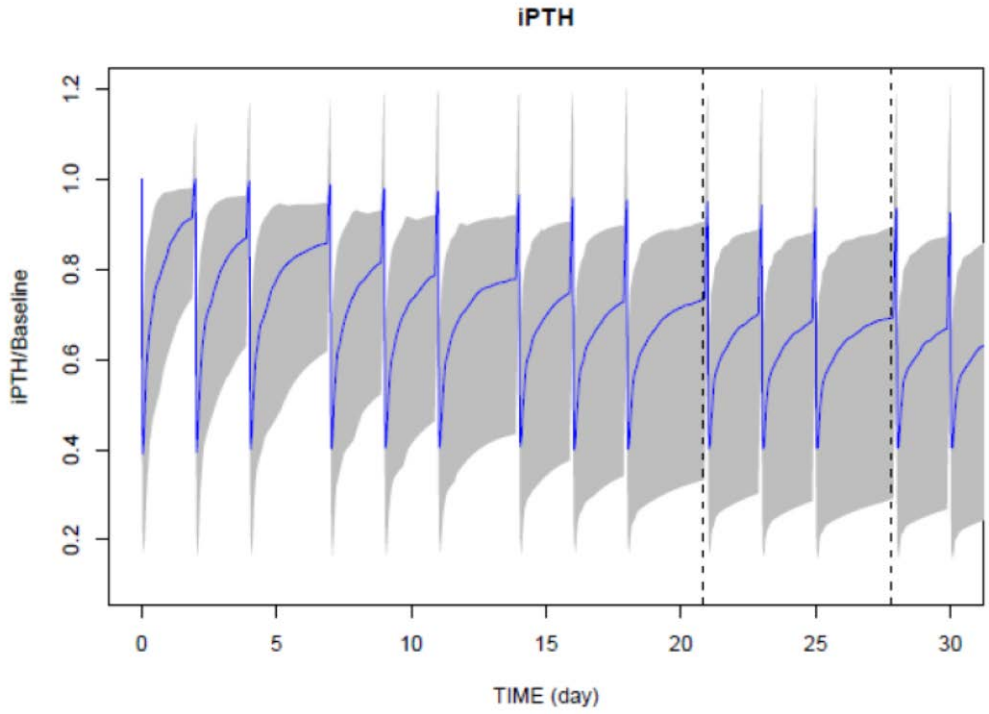
The simulation results for the effect of disease severity on iPTH and cCa are summarized in Table 17. Regardless of disease severity at baseline, the titration is expected to result in a higher fraction with iPTH<30% suppression compared to 5 mg fixed dose, but lower fraction than 10 mg and 15 mg fixed dose regimen. Conclusively, the effect of disease severity appears to be minimal.

Table 17: Summary of Fraction of Subjects Expected to Achieve Primary Efficacy and Safety Endpoint at Week 24 with Different Disease Severity

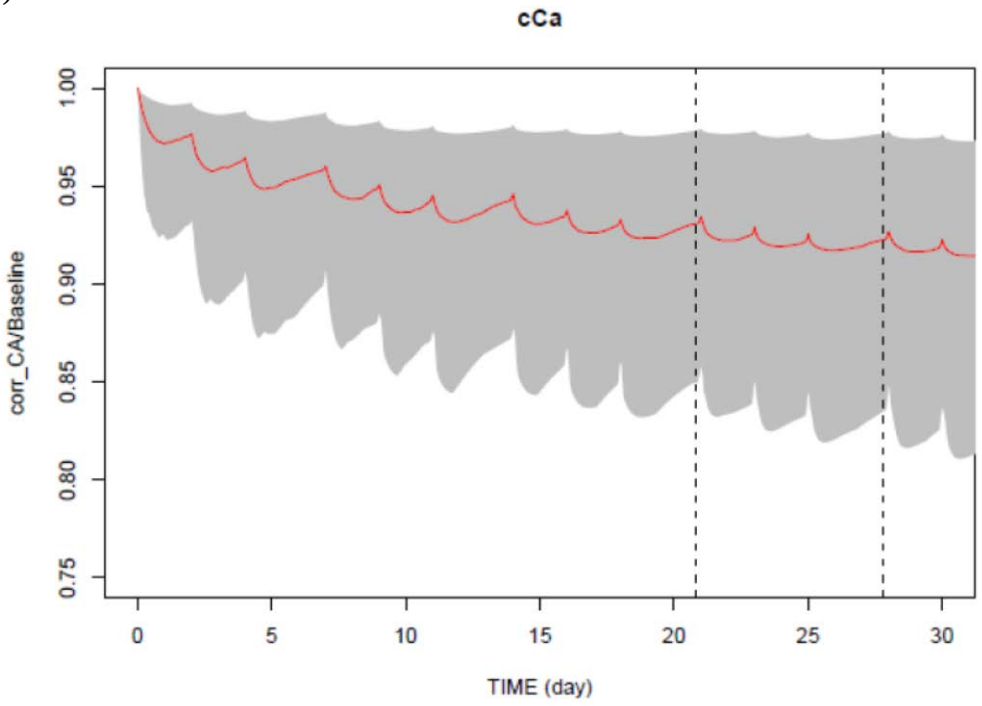
	>30% Reduction in iPTH relative to baseline*			Serum cCa < 7.5 mg/dL*		
Dosing Regimen	Mild (iPTH baseline < 694 pg/mL)	Moderate (694 pg/mL <= iPTH baseline < 1080 pg/mL)	Severe (iPTH baseline >= 1080 pg/mL)	Mild (iPTH baseline < 694 pg/mL)	Moderate (694 pg/mL <= iPTH baseline < 1080 pg/mL)	Severe (iPTH baseline >= 1080 pg/mL)
Titration starting 5 mg	75.3	75.9	75.9	2.80	4.88	7.14
	[66.6 - 83.3]	[68.6 - 85.4]	[67.1 - 82.9]	[0.00 - 7.14]	[2.17 - 9.30]	[2.35 - 11.30]
2.5 mg fixed dosing	39.8	44.4	53.2	1.22	1.27	2.15
	[30.5 - 50.0]	[35.7 - 52.6]	[44.6 - 63.9]	[0.00 - 3.87]	[0.00 - 3.82]	[0.00 - 5.19]
5 mg fixed dosing	61.0	62.9	67.4	5.68	7.60	9.88
	[51.6 - 69.7]	[54.2 - 71.8]	[58.4 - 74.7]	[2.17 - 10.90]	[3.57 - 12.50]	[4.23 - 15.70]
10 mg fixed dosing	79.5	79.5	79.7	15.60	20.50	26.50
	[71.0 - 86.2]	[71.6 - 85.7]	[71.5 - 86.8]	[9.09 - 22.60]	[13.70 - 28.80]	[18.70 - 35.40]
15 mg fixed dosing	86.6	85.9	85.1	21.80	29.20	38.70
	[80.6 - 91.6]	[80.3 - 91.7]	[78.7 - 91.1]	[15.00 - 29.20]	[22.10 - 37.30]	[29.90 - 47.70]

* The values are represented as median [90%CI]

Adequacy of sampling at Week 4 and titrating at Week 5 after starting dose of 5 mg was also evaluated by simulation with the final PKPD model. The change of iPTH and cCa relative to baseline following 5 mg TIW dosing for 4 weeks show that the changes in iPTH and cCa at Week 4 (Day 21) and Week 5 (Day 28) are comparable. Thus, the sampling at Week 4 and titrating dose at Week 5 seems appropriate.



(a)



(b)

Figure 27: Simulations of iPTH (a) or cCa (b) change relative to baseline following 5 mg TIW dosing

(Source: Population PKPD report, Figure 26, page 323)

Reviewer's comments: The applicant's population PKPD model appears reasonable in explaining observation. The model was established and evaluated adequately and the output table from the final PKPD analysis was utilized for the reviewer's analysis along with the observed data.

4.2.5 Reviewer's Analysis

4.2.5.1 Introduction

The applicant performed population PK and population PKPD analyses to characterize the pharmacokinetics following 5 mg TIW IV administration and pharmacodynamics of AMG416 following 5 mg TIW with various titration schemes. None of covariates evaluated were identified as a significant covariate on either PK or PD. The reviewer acknowledge the applicant's analysis results and perform additional supportive analysis to evaluate the adequacy of the starting dose of 5 mg.

4.2.5.2 Objectives

Analysis objectives are:
1. To evaluate the adequacy of starting dose of 5 mg TIW by assessing proportion of subjects titration during trial
2. To evaluate the adequacy of titration scheme utilized in the trials by assessing potential overdose of AMG416 in patients whose PTH levels decreased below 100 pg/mL during the trial.

4.2.5.3 Methods

The changes in dose and PTH over time in terms of proportion of subjects receiving designated dose range were graphically evaluated.

4.2.5.4 Data sets

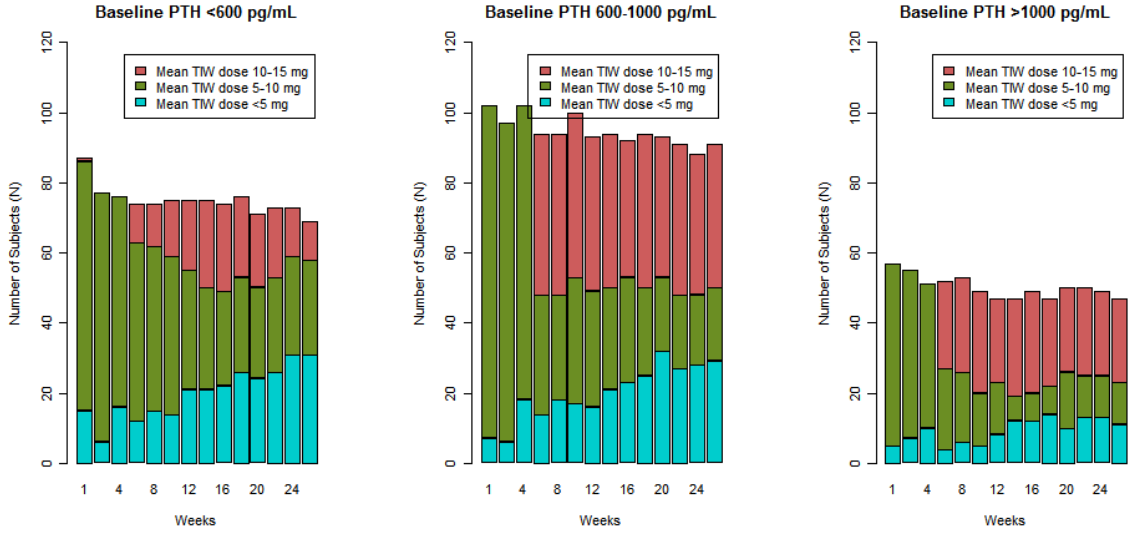
Study Number	**Name**	**Link to EDR**
adex.xpt adsl.xpt adae.xpt adlb.xpt		\\cdsesub1\evsprod\NDA208325\0000\m5\datasets\20120229\analysis\adam\datasets\
adex.xpt adsl.xpt adae.xpt adlb.xpt		\\cdsesub1\evsprod\NDA208325\0000\m5\datasets\20120230\analysis\adam\datasets\

4.2.5.5 Software

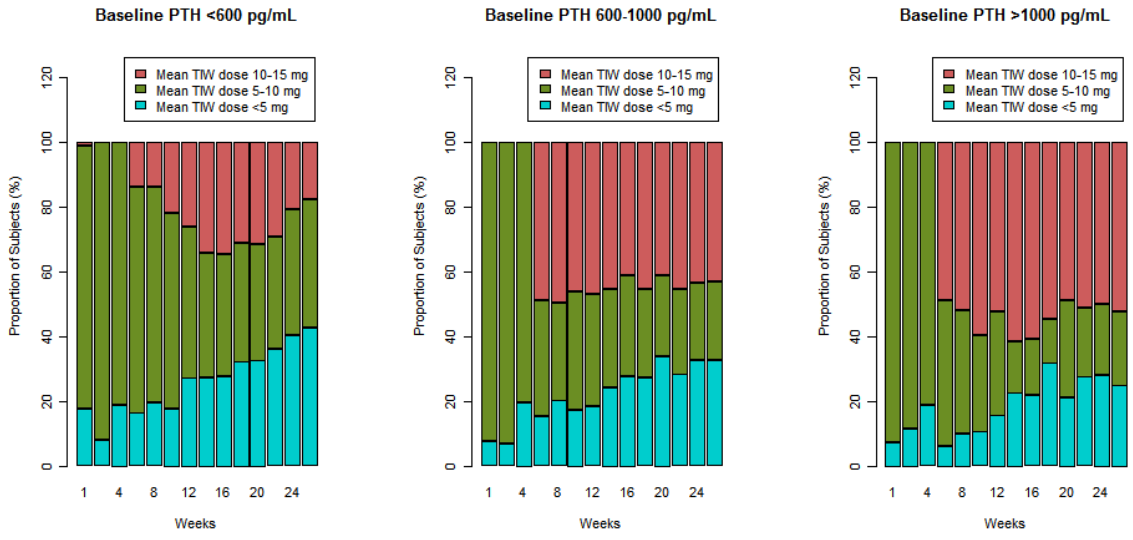
Graphical assessment was performed with R (version 2.13.1)

4.2.5.6 Starting dose of 5 mg

The number and the proportion of subjects by the mean TIW dose over time were graphically evaluated to assess the trend in dose change with the titration scheme. As shown in Figure 28, etelcacetide dose was up-titrated for the majority of subjects after Week 5 and most of them received > 5 mg with maximum of 15 mg. Less proportion of subjects whose baseline PTH<600 pg/mL ended up receiving the higher mean TIW dose of 10-15 mg (Figure 28 (b), however, the proportion of patients achieving >30% reduction in PTH with etelcalcetide was significantly higher than placebo with the proposed titration scheme in the overall population, there is lack of evidence for increasing or decreasing the proposed starting dose of 5 mg. The trend is similar to all group of patients with various baseline PTH level (Figure 28), indicating the proposed starting dose of 5 mg is appropriate regardless of the disease severity.



(a)

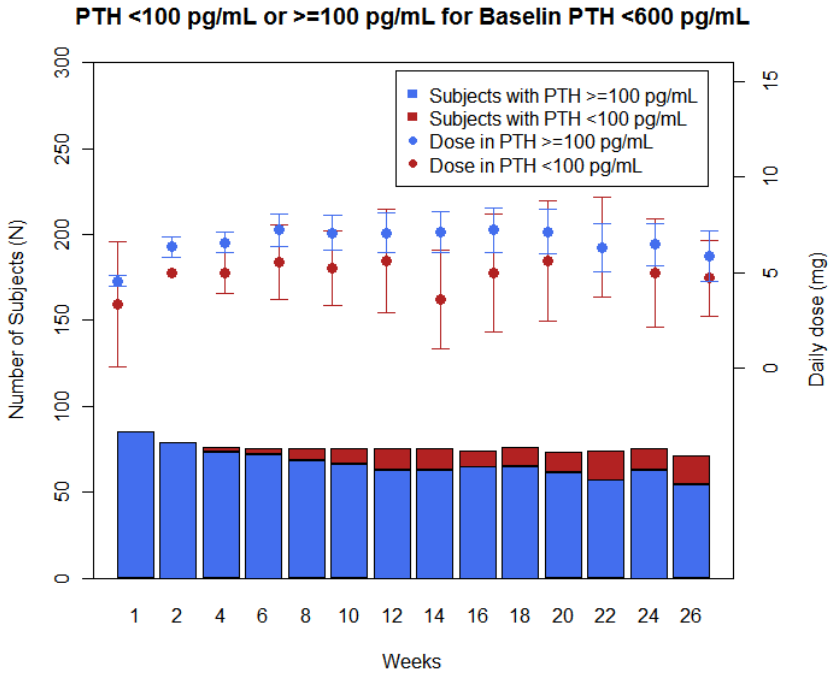


(b)

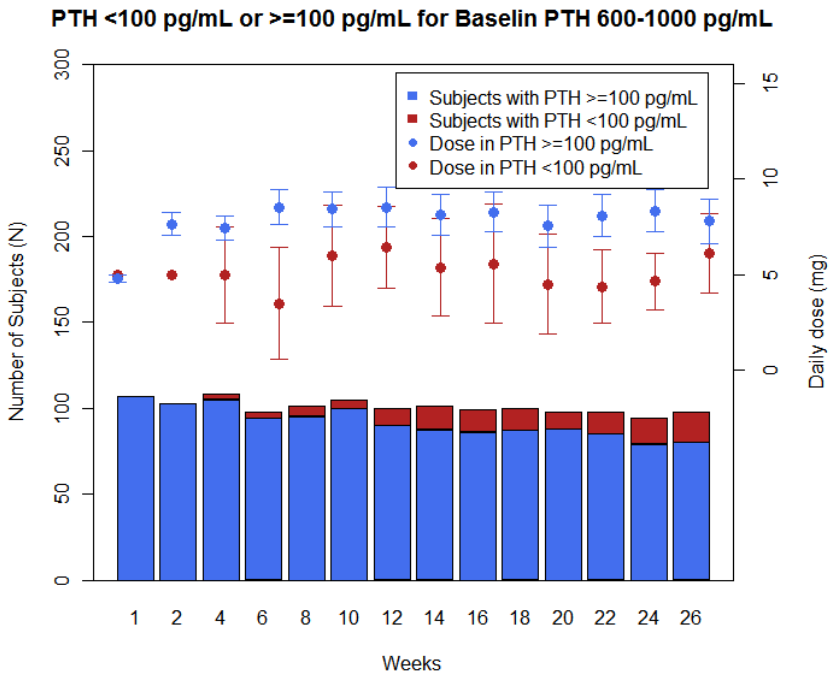
Figure 28: Number (a) and proportion (b) of subjects and change in mean TIW dose over time by baseline PTH

4.2.5.7 Evaluating doses in patients with PTH < 100 pg/mL

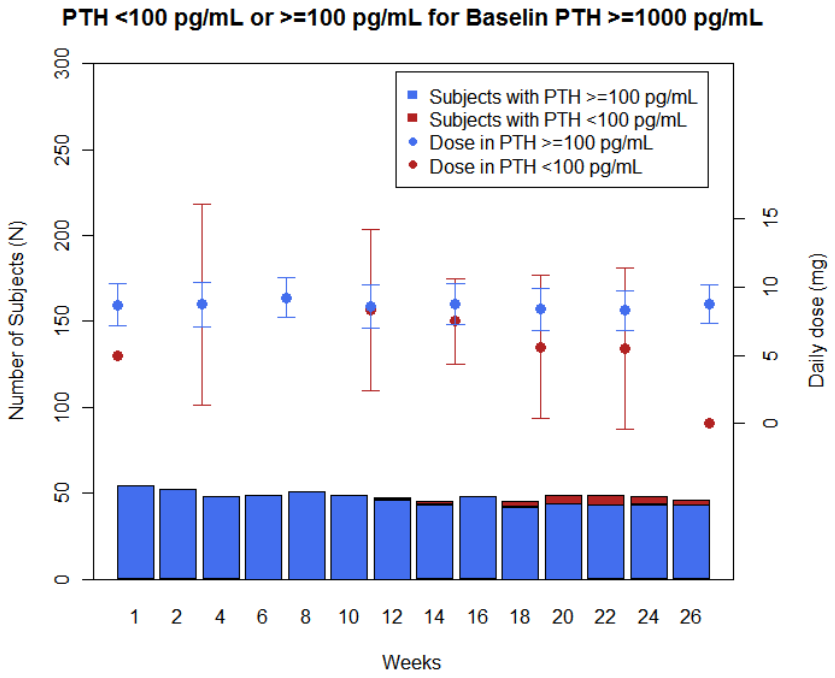
One of the safety concerns pointed out by the clinical review team is that for some patients, the PTH level becomes too low (<100 pg/mL) due to overdose of etelcalcetide, which is not desirable and may trigger adynamic bone disease. The reviewer's analysis was conducted to evaluate if the doses were higher in patients who had PTH<100 pg/mL during the course of the trial. The analysis results showed, however, subjects whose PTH<100 pg/mL during the trial did not receive higher dose than those whose PTH ≥100 pg/mL (Figure 29). It is likely that the patients with less severe disease condition (lower baseline PTH) may have higher sensitivity to etelcalcitide, however, there is no strong evidence that these patients need lower dose than the proposed dose. The trend is similar among subgroups of patients with various baseline PTH levels, although few patients had baseline PTH >1000 pg/mL (Figure 29).



(a)



(b)



(c)

Figure 29: Change in dose over time in patients with PTH<100 pg/mL or PTH≥100 pg/mL ((a) Baseline PTH <600 pg/mL (b) Baseline PTH 600 – 1000 pg/mL (c) Baseline PTH ≥1000 pg/mL

4.2.5.8 Exposure-safety relationships for etelcalcetide

Since the dosing was stopped for the safety (corrected Ca) endpoint, corrected Ca levels in the analysis dataset do not include the values above the safety threshold (>7.5 mg/dL). Thus, the evidence for the exposure-safety relationship for etelcalcetide is not available. The model-predicted corrected Ca levels ranged between 1.64 and 2.80 mg/dL with the given concentration range of etelcalcetide concentration.

4.2.5.9 Listing of analyses codes and output files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
ER_etelcalcetide.R	Dose response for PTH	Reviews\Ongoing PM Reviews\etelcacetide_NDA208325_JEL\

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RITESH JAIN
05/05/2016

JEE E LEE
05/05/2016

NITIN MEHROTRA
05/05/2016

JAYABHARATHI VAIDYANATHAN
05/05/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208325	**SDN**	0000
Applicant	Amgen	**Submission Date**	08/24/2015
Generic Name	Etelcalcetide	**Brand Name**	
Drug Class	Calcium-sensing receptor agonist		
Indication	Indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis.		
Dosage Regimen	Starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH)		
Dosage Form	2.5 mg Etelcalcetide in 0.5 mL solution in a single-use vial 5 mg Etelcalcetide in 1 mL solution in a single-use vial 10 mg Etelcalcetide in 2 mL solution in a single-use vial	**Route of Administration**	Intravenous
OCP Division	DCPII	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Ritesh Jain	Jayabharathi Vaidyanathan
Pharmacometrics	Jee Eun Lee	Nitin Mehrotra
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	10/23/2015	**74-Day Letter Date**	11/6/2015
Review Due Date	4/28/2016	**PDUFA Goal Date**	8/24/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies ☑ Yes ☐ No Clinical Pharmacology Summary ☑ Yes ☐ No

Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☑ Metabolism Characterization		5	Study#119917 CYP metabolism, Study#4169-NC-125 induction of CYP isoforms, Study# 4169-NC-124, 119314 inhibition of CYP Isoforms, Study#118358 biotransformation and blood to plasma ratio
☑ Transporter Characterization		2	Study#118052 drug transporter interactions, Study#119513 inhibition of BSEP transport
☑ Distribution		3	Study#119313 plasma protein binding, Study#119413 dialysis clearance, Study#119414 conjugation and deconjugation kinetics
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Study # 20130107 PK and Tolerability Study in Healthy Volunteers
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Study # 20130139PK and Tolerability Study in Hemodialysis Subject with HPT
	☐ Multiple Dose		
☑ Mass Balance Study		1	Study# 20130147ADME Study in CKD Patients on Hemodialysis
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects			
☑ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects		1	Study # 20130107 PK and Tolerability Study in Healthy Volunteers

☑ Patients	1	Study # 20130139PK and Tolerability Study in Hemodialysis Subject with HPT
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	2	Report #119343, Report#119344: Phase I/ II/III Population PK or PK/PD reports Population PK/PD analysis includes data from one Phase 1, two Phase 2 and two Phase 3 trials
☑ Exposure-Efficacy		
☑ Exposure-Safety		

Total Number of Studies	**In Vitro**	10	**In Vivo**	5
Total Number of Studies to be Reviewed		10		5

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☑No ☐N/A	Bio-waiver request for in-vivo bioequivalence (BE) study between the AMG 416 (b) (4) parenteral drug product used in n phase 3 clinical studies and the AMG 416 ready-to-use (RTU) liquid drug product intended for commercial use.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2	☑Yes ☐No ☐N/A	

summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?		
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic	☑Yes ☐No ☐N/A	

requirements for approvability of this product?		
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☑Yes ☐No ☐N/A	

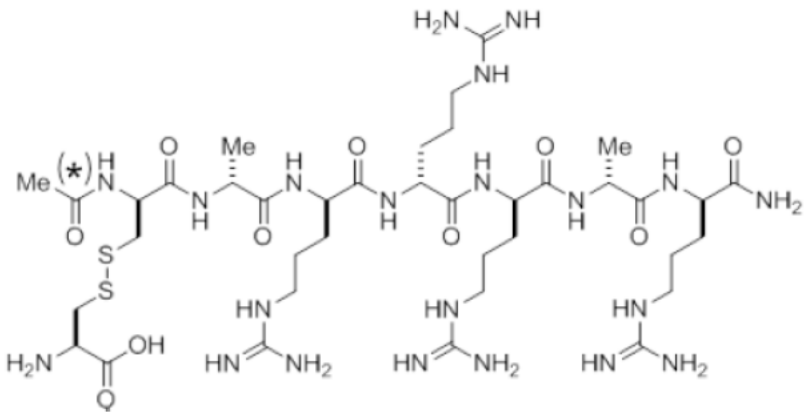
Filing Memo

Indication and Dosage Administration: Etelcalcetide (AMG416) is a calcium-sensing receptor agonist indicated for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis. Recommended starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment. Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH).

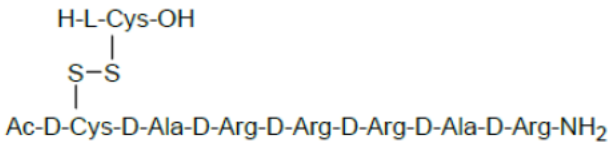
Drug Molecule and Its Mechanism of Action: AMG 416 is a synthetic peptide with a molecular weight of 1048.3 Da comprised of a 7 D-amino acid backbone and L-cysteine linked via a disulfide bond to a D-cysteine in the backbone (Figure 1). AMG 416functions as an allosteric activator of the calcium-sensing receptor (CaSR) and lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium.

Figure 1. (A) Molecular Structure and (B) Amino Acid Sequence of AMG 416 (Free Base)

(A)



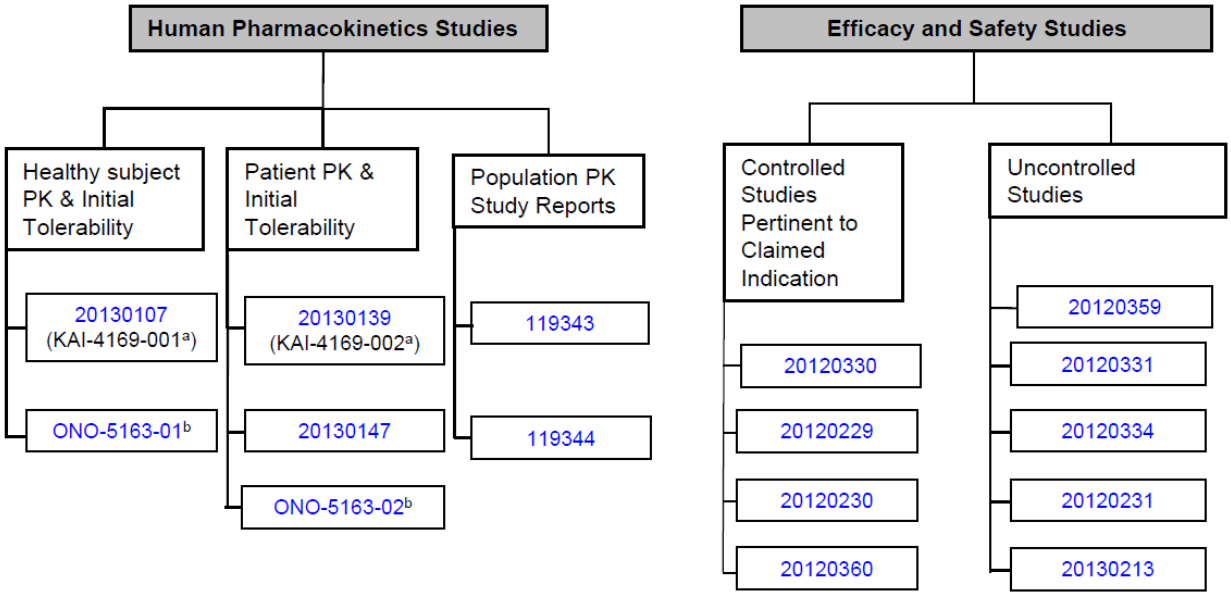
(B)



Clinical Program: The clinical program in this NDA consists of 10 vitro studies. These studies were conducted using human biomaterial to evaluate permeability, plasma protein binding, potential metabolic drug-drug interactions, transporter interactions, biotransformation, red blood cell partition, dialysis clearance, and conjugation-deconjugation kinetics.

Clinical studies in this application include 5 Phase 1 studies, 3 Phase 2 dose studies and 8 Phase 3 trials. Figure below shows the listing of clinical studies conducted in this program.

Figure 1. Organization of AMG 416 Clinical Studies



PK = pharmacokinetics
[a] These studies were conducted by KAI Pharmaceuticals before its acquisition by Amgen.
[b] These studies were conducted in Japan by an Amgen business partner.

Summary: This NDA is file able from Office of Clinical Pharmacology standpoint. No inspection is needed for Clinical Pharmacology Studies. The Clinical Pharmacology Review for this NDA will focus on the following key review questions

1. What are the PK and PD features of AMG416?
2. What is the exposure/Dose relationship for safety and efficacy?
    a. Is the starting dose and dosing frequency adequate?
    b. Is the proposed titration scheme adequate?
    c. Is there any dose/exposure relationship to Hypocalcemia?
3. Does population PK or PK/PD analysis suggests any need for dose adjustment based on covariates?

Filing Meeting Slides:

Filing Meeting
NDA 208325
AMG416 (Etelcalcetide)

Amgen

Clinical Pharmacology Review Team

Ritesh Jain
Jaya Vaidyanathan
Nitin Mehrotra

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Background: AMG416

Indication:

- AMG416 is a calcium-sensing receptor agonist indicated for Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

Dosage and Administration:

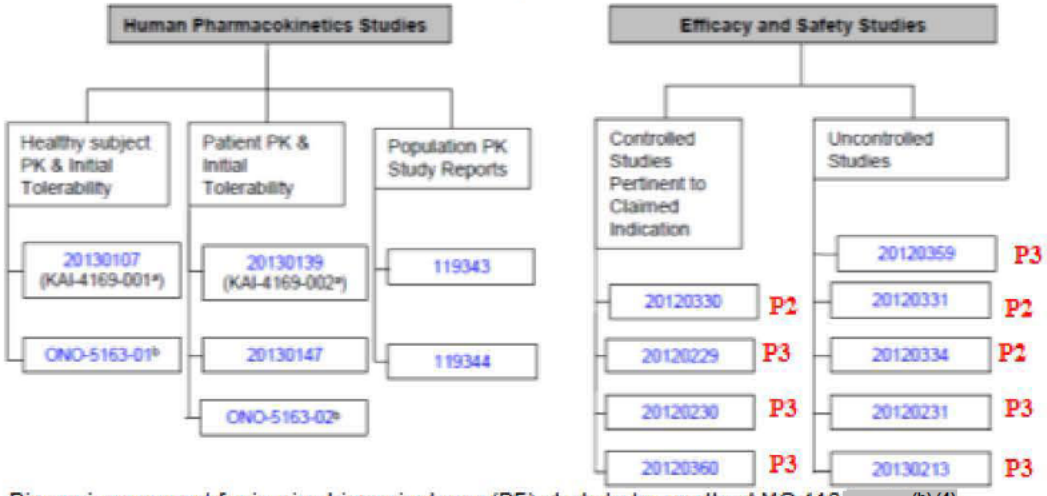
- Starting dose is 5 mg administered by bolus injection 3 times per week into the venous line of the dialysis circuit at the end of the hemodialysis treatment during rinse back or intravenously after rinse back
- Dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve a target parathyroid hormone (PTH)

Dosage Form and Strengths:

- 2.5 mg etelcalcetide in 0.5 mL solution in a single-use vial
- 5 mg etelcalcetide in 1 mL solution in a single-use vial
- 10 mg etelcalcetide in 2 mL solution in a single-use vial

Overview: Clinical Program

Total 16 Clinical Trials: 5 Phase 1 Trials, 3 Phase 2 Trials, 8 Phase 3 Trials

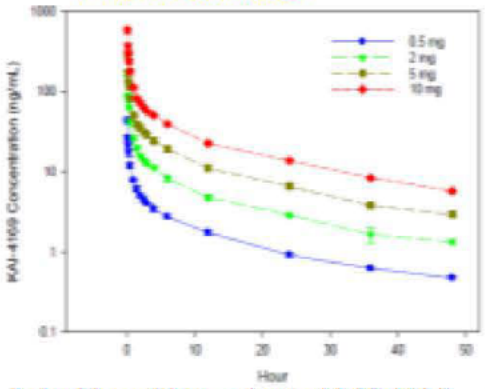


Bio-waiver request for in-vivo bioequivalence (BE) study between the AMG 416 (b) (4) parenteral drug product used in phase 3 clinical studies and the AMG 416 ready-to-use (RTU) liquid drug product intended for commercial use.

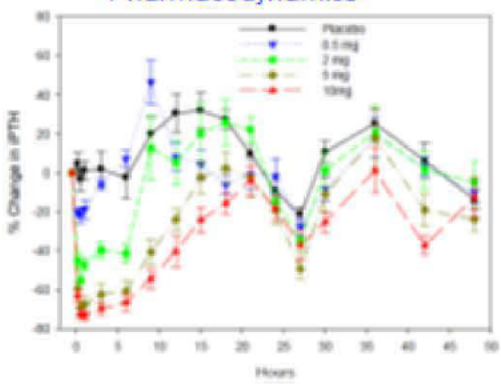
U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Overview: PK/PD Healthy Subjects

Pharmacokinetics

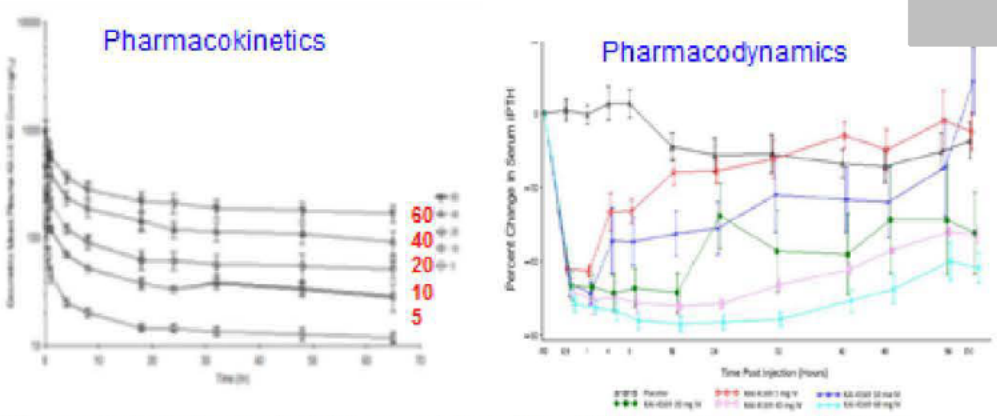


Pharmacodynamics



- In healthy subjects, plasma AMG 416 C_{max} and AUC_{inf} values increased approximately dose-proportionally. The terminal elimination half-life ranged from 18.4 to 20.0 hours
- Maximum decrease in PTH occurred by 30 mins. PTH levels gradually returned to baseline within 10 to 24 hours.
- The maximum serum PTH reduction from baseline at 30 minutes post-dose in the placebo, 0.5, 2, 5, and 10 mg dose groups was 3.5%, 21.7%, 55.4%, 69.0%, and 72.6%, respectively.

Overview: PK/PD CKD Patients with HPT



- The terminal elimination half-life ranged from 81 to 175 hours (data not sufficient)
- Maximum decrease in PTH occurred by 30 min.
- At 65 hours post-dose, serum PTH was suppressed -48.5%,-49.3%, and -62.6%, in the 20, 40, and 60 mg dose groups, respectively

5

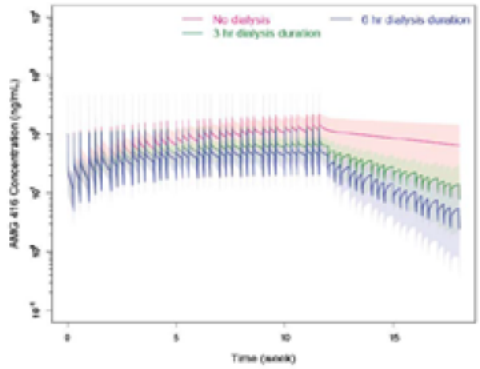
Overview: ADME

- AMG 416 is not metabolized by cytochrome P450 enzymes. AMG 416 was not a substrate of human cytochrome P450 enzymes in vitro
- AMG 416 was bio transformed upon administration in blood by disulfide exchange with endogenous thiols. It also forms covalent binding with serum proteins.
- The elimination of AMG 416 and its biotransformation products was presumed to be predominantly by renal excretion in healthy subjects.
- The elimination of AMG 416 in CKD patients receiving hemodialysis was slow, predominantly by hemodialysis and by nonspecific elimination.

6

Overview: Population PK

Figure 20. Simulation of AMG 416 PK After 5 mg TIW Dosing for 12 Weeks Followed by 6 Weeks Washout at Dialysis Duration of 0, 3 or 6 hours



- The plasma accumulation ratio of AMG 416 was 2- to 3-fold by week 4.
- The effective half-life is 3 to 5 days following a TIW dosing and dialysis schedule.
- At week 4 plasma concentration are near steady state and after 6-10 weeks of dosing steady state concentrations are reached.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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Pivotal Phase 2 Study Results (20120330)

- AMG 416 administered 3 times weekly for 2 weeks (cohort 1) or 4 weeks (cohorts 2 and 3) in subjects with secondary HPT who were receiving hemodialysis.

Table 9-1. Summary of iPTH at Endpoint (MITT Population)

	Cohort 1		Cohort 2		Cohort 3	
	Placebo	5 mg AMG 416	Placebo	10 mg AMG 416	Placebo	5 mg AMG 416
Baseline[a]						
N	4	6	21	21	13	13
Mean (SD)	636.3 (191.64)	588.3 (250.52)	601.5 (239.20)	765.1 (480.82)	619.4 (310.35)	662.1 (442.01)
Median	676.3	512.5	536.0	641.5	526.0	536.5
Minimum, maximum	369.5, 823.0	341.5, 1049.5	196.0, 1018.5	258.5, 2185.5	179.5, 1245.0	344.0, 1988.5
Percent change from baseline to endpoint						
N	4	6	21	21	13	13
Mean (SD)	0.3 (17.11)	-19.4 (20.65)	28.5 (70.39)	-49.4 (20.42)	2.3 (29.44)	-33.0 (26.28)
Median	1.0	-15.4	13.0	-54.5	0.0	-36.1
Minimum, maximum	-20.2, 19.3	-44.3, 11.6	-73.0, 293.9	-76.5, 3.8	-46.3, 47.1	-68.3, 20.7
LS mean[a]	2.2	-18.1	28.9	-48.0	1.9	-34.8
LS mean for difference[b]		-20.3		-76.9		-36.7
95% CI for difference[b]		-51.4, 10.8		-109.1, -44.8		-59.8, -13.6
P-value[b]				< 0.0001		0.0032
95% CI for difference[d]				-86.9, -50.0		
P-value[d]				< 0.0001		

Dose Selection Rationale for Phase 3 Trials

- **The starting dose of 5 mg AMG 416 is supported by:**
  - The phase 1 and 2 studies, which showed clinically relevant reductions in PTH in the patient population
  - In addition, the phase 3 studies (Studies 20120230 and 20120229) confirmed that the 5 mg starting dose is reasonable because at the first titration step (Week 4), 35 to 37% of patients stayed at 5 mg and 53% titrated upward to achieve desired PTH control.
  - Approximately 18% to 23% of subjects required titration to the highest dose of 15 mg by week 17 in an effort to achieve target PTH levels of ≤ 300 pg/mL
  - The remainder of patients (approximately 10%) either had their dose withheld (5 to 6%), missed a dose (1 to 2%), or titrated down (3 to 4%).

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Phase 3 Efficacy Results

Table 15. Percent Change in PTH During the Efficacy Assessment Phase - Mixed-effects Model Repeated Measures (Studies 20120229 and 20120230 and 6-month Placebo-controlled Combined Dataset – Full Analysis Set)

	20120229		20120230		Total placebo-controlled studies	
	Placebo (N = 254)	AMG 416 (N = 254)	Placebo (N = 260)	AMG 416 (N = 255)	Placebo (N = 514)	AMG 416 (N = 509)
Baseline PTH (pg/mL)						
n	254	254	260	255	514	509
Mean	819.74	848.70	851.67	845.03	835.89	846.86
SE	24.22	32.65	34.23	29.08	21.04	21.83
Mean PTH (pg/mL) during the EAP						
n	219	229	237	227	456	456
Mean	897.39	383.57	960.28	383.35	930.07	373.51
SE	32.21	25.40	48.09	26.26	29.40	18.25
Percent change from baseline in PTH during the EAP (%)						
n	219	229	237	227	456	456
Mean	13.00	-55.11	13.72	-57.39	13.37	-56.25
SE	2.81	1.94	2.50	1.91	1.87	1.36
Treatment difference (AMG 416 - Placebo) from adjusted analysis*						
Estimate		-71.11		-71.34		-71.30
SE		3.39		3.15		2.31
(95% CI)		(-77.77, -64.46)		(-77.53, -65.14)		(-75.84, -66.76)
p-value		< 0.001		< 0.001		< 0.001

CI = confidence interval; EAP = efficacy assessment phase; PTH = parathyroid hormone; SE = standard error
Full analysis set: all randomized subjects in the dataset
*Mixed-effects model includes treatment and stratification factors as covariates. For individual study, stratification factors were screening PTH level, prior cinacalcet use, and region; for integrated studies, stratification factors were screening PTH level, prior cinacalcet use, region, and study.
Source: ISE Table 4.5

Clinical Pharmacology Review Focus

- What are the PK and PD features of AMG416?
- What is the exposure/Dose relationship for safety and efficacy?
  - Is the starting dose and dosing frequency adequate?
  - Is the proposed titration scheme adequate?
  - Is there any dose/exposure relationship to Hypocalcemia?
- Does population PK or PK/PD analysis suggests any need for dose adjustment based on covariates?

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Conclusions

- This NDA is filable from Office of Clinical Pharmacology standpoint.
- No inspection is needed for Clinical Pharmacology Studies.
- No comments for the 74 Day letter.

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/s/

RITESH JAIN
10/19/2015

JAYABHARATHI VAIDYANATHAN
10/19/2015