CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

RESUBMISSION CLINICAL REVIEW

Application Type	505 (b) (1)
Application Number(s)	NDA 208325
Priority or Standard	Class 1 resubmission
Submit Date(s)	December 9, 2016
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PDUFA Goal Date	February 9, 2017
Division/Office	DMEP/ODEII/OND
Reviewer Name(s)	Shannon Sullivan, MD, PhD
Review Completion Date	January 30, 2017
Established Name	Etelcalcetide
(Proposed) Trade Name	Parsabiv
Applicant	Amgen
Formulation(s)	Solution in single use vial
Dosing Regimen	5 to 15 mg by bolus intravenous injection three times per week into the dialysis circuit at the end of hemodialysis treatment
Applicant Proposed Indication(s)/Population(s)	Secondary hyperparathyroidism in patients with chronic kidney disease requiring hemodialysis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of secondary hyperparathyroidism due to chronic kidney disease in patients on hemodialysis

Clinical Review
Shannon Sullivan, MD, PhD
NDA 208325/505 (b) (1)
Parsabiv (Etelcalcetide)

INTRODUCTION

Etelcalcitide (Parsabiv) is a synthetic peptide calcium-sensing receptor agonist ('calcimimetic') under development for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis. This drug is administered intravenously three times weekly (TIW) after hemodialysis in doses of 2.5 mg to 15 mg.

The original NDA 208325 for etelcalcetide for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis was submitted on August 24, 2015. The Division denied the approval of etelcalcetide and issued a Complete Response (CR) on August 24, 2016 because an agreement between the Sponsor and the Division on the proposed labeling had not been reached. This resubmission of NDA 208325 provides a Complete Response (CR) to the Division's CR decision. (b) (4) (b) (4) (b) (4) In addition, the Agency required agreement from the Sponsor to a Post-Marketing Requirement (PMR) to assess the risk of fatal and non-fatal upper gastrointestinal bleed (UGIB) events associated with use of etelcalcetide for approval. This resubmission of NDA 208325 provides a Complete Response (CR) to the Division's CR decision

To address the above deficiency, the Sponsor was asked to (b) (4) (b) (4) (b) (4) in treating secondary hyperparathyroidism in patients with CKD on HD.

The Sponsor submitted a Complete Response to the outlined deficiency on December 9, 2016 in a Class 1 Resubmission. The Sponsor accepted all US Prescribing Information (USPI) changes proposed by the Agency, which were outlined in the CR letter to the Sponsor dated August 24, 2016. (b) (4) (b) (4) In addition, the Sponsor proposed one minor numerical change to Section 5.3 (*Upper Gastrointestinal Bleeding)* of labeling after further review lead to re-classification of one event of fatal GIB from an upper GI to a lower GI source.

All data to support approval were reviewed during the previous cycles and are summarized in

previous memoranda. Refer to these memoranda for details (See Clinical Review by Dr. Lubas in DARRTS). No new pivotal data was included in this submission. However, in this resubmission, the Sponsor provided updated supportive safety information from the single ongoing long-term, open-label extension study, Study 20130213 (referred to herein as 'Study 213'), which is reviewed below.

SAFETY UPDATE

Of note, this resubmission includes only supportive safety data from the single ongoing long-term open-label extension study, Study 213, covering the period from July 18, 2015 (the date of the last 120-day safety update, see *Clinical Safety Update*, SD-6 in DARRTS) to October 6, 2016. No unique (i.e., previously unreported) types of adverse events or increased rate of known adverse events were reported that would affect benefit-risk analysis or alter USPI.

The clinical safety resubmission also contains a comprehensive report of gastrointestinal hemorrhage in the etelcalcetide development program (AEs of interest identified during the initial NDA review cycle were fatal and non-fatal upper GI hemorrhage). The report summarizes both non-clinical and clinical data regarding a potential association between etelcalcetide and GIB and evidence supporting putative mechanisms of action for such an association.

This safety assessment led to one proposed numerical change to the USPI (Section 5.3 *Upper Gastrointestinal Bleeding* of labeling) after a fatal event involving GIB was re-classified from upper to lower GIB, which is discussed in detail below.

The safety update also includes a proposed change to the *Adverse Reactions Section in Highlights* of labeling that removes the adverse reaction of *vomiting* from the most common adverse reactions, i.e., adverse reactions seen in (b) (4) % of patients exposed to etelcalcetide. Vomiting occurred in 9% of etelcalcetide-treated patients.

This Medical Officer reviewed the resubmission for the type and frequency of new AEs and deaths reported from Study 213 that occurred since July, 2015. Types and frequency of AEs in this resubmission were compared with the types and frequency of AEs reported in the original marketing application. The results are summarized below.

Study 213 is an ongoing, Phase 3, multi-center, open-label, single-arm long-term extension study of studies 20120231 (an open-label extension study, 'Study 231'), 20120334 (a Phase 2 study, 'Study 334'), and 20120360 (a Phase 3 active comparator study with cinacalcet, 'Study 360'). Patients receiving hemodialysis 3-4 times per week for at least 3 months and who participated in one of the parent studies above were eligible for Study 213. The study duration and therefore overall exposure to etelcalcetide varied with each individual subject depending on when the patient entered study 213 from his or her respective parent study.

In this safety update, an additional 884 patients who had received at least one dose of etelcalcetide were included in the safety analysis. The mean (SD; minimum, maximum) overall duration of exposure to etelcalcetide was 71.7 (29.34; 0.1, 124.1) weeks. Compared to the Phase 3 long-term open-label combined dataset from the original marketing application, the mean duration of exposure to etelcalcetide in Study 213 is much longer (71.7 vs 32.9 weeks). The mean (±SD) cumulative total etelcalcetide dose in Study 213 was 1078±918 mg.

DEATHS

In this safety update, an additional 60 subjects had fatal treatment-emergent AEs since the last 120-day safety update, for a total of 85 subjects (9.6%) with fatal TEAEs overall in the phase 3 extension trial combined database. The cumulative exposure-adjusted incidence rates and types of fatal AEs in the complete updated safety database were similar to those reported in the phase 3 open-label extension dataset in the original marketing application. The most common fatal adverse events (those occurring in ≥ 0.5% of subjects) among the new fatal TEAEs reported in this safety update were cardiac arrest (14 subjects [1.6%]), pneumonia (6 subjects [0.7%]), sepsis (5 subjects [0.6%]), septic shock (4 subjects [0.5%]), sudden death (4 subjects [0.5%]), and death of unknown cause (4 subjects [0.5%]) (**Table 1).** One of these deaths was considered treatment-related by the investigator; however, the Sponsor does not consider this death to be study drug-related. This death occurred in a 59 year-old white male (Subject 36066041005) with multiple co-morbidities, including severe heart failure requiring supplemental oxygen, poorly-controlled hypertension, and type 2 diabetes who died at home after multiple syncopal episodes on study day 527. Prior to his death, pertinent laboratory testing showed a normal serum calcium (8.5 mg/dL), severe hypokalemia (K^+ 2.0 mg/dL), and hyperglycemia (glucose 245 mg/dL).

Table 1. Exposure-Adjusted and Crude Incidence Rates of Fatal Treatment-emergent Adverse Events for Events Occurring in More Than 1 Subject (Full Analysis Set) (Study 213 Safety Update Analysis)

System Organ Class Preferred Term	Total (N = 884) n/e (r)[a]	 (%)[b]
All fatal treatment-emergent adverse events	85/1279.4 (6.6)	9.6
Cardiac arrest	14/1281.1 (1.1)	1.6
Pneumonia	6/1281.1 (0.5)	0.7
Sepsis	5/1281.1 (0.4)	0.6
Death	4/1281.2 (0.3)	0.5
Septic shock	4/1281.1 (0.3)	0.5
Sudden death	4/1281.2 (0.3)	0.5
Cardio-respiratory arrest	3/1281.1 (0.2)	0.3
Myocardial infarction	3/1281.2 (0.2)	0.3
Acute myocardial infarction	2/1281.2 (0.2)	0.2
Aortic dissection	2/1281.1 (0.2)	0.2
Brain injury	2/1281.1 (0.2)	0.2
Cardiogenic shock	2/1281.2 (0.2)	0.2
Cerebral haemorrhage	2/1281.1 (0.2)	0.2
Cerebrovascular accident	2/1281.1 (0.2)	0.2
General physical health deterioration	2/1281.0 (0.2)	0.2
Respiratory failure	2/1281.1 (0.2)	0.2

N = number of subjects in the full analysis set; n = total number of subjects with the event;
exposure-adjusted incidence rate per 100 subject-years = 100 • n/ Total subject-year at risk.
[a] n/e = n/Total subject-year at risk (years); r = Exposure-adjusted incidence rate per 100 subject-years.
[b] % = Crude subject incidence. Crude subject incidence = 100 • n/N.

Reviewer Comment: All narratives for new death cases included in this submission were reviewed by this Medical Officer.

I agree with the Sponsor's assessment that the death of Subject 36066041005 is unlikely to be study drug-related given that this patient had multiple co-morbid conditions and serum calcium was normal on testing prior to his death. Arrhythmia due to hypokalemia in a patient with severe heart disease is a more likely cause of death in this case.

Overall, the reported causes of death in this interim analysis are not unexpected in a population of patients with CKD requiring HD, who are at high risk for cardiovascular disease and infection. Fatal AEs in this interim analysis are overall similar to those reported in the original NDA.

SERIOUS AEs (SAEs)

There was no increase in incidence rate of SAEs since July, 2015. Serious AEs were reported for an additional 221 subjects in the updated open-label extension trial dataset, for a cumulative total of 436 subjects (49.3%) experiencing SAEs. In the complete updated database (including new and previously reported SAEs), the most frequent (≥5% of subjects) SAEs reported were in the System Organ Classes (SOC) of infections and infestations (20.4%); injury, poisoning, and procedural complications (11.5%); cardiac disorders (10.9%); gastrointestinal disorders (8.3%); nervous system disorders (7.7%); vascular disorders (7.7%); respiratory, thoracic and mediastinal disorders (6.0%); and general disorders and administration site conditions (5.4%) (

Table 2).

Since the last 120-safety update, one additional patient had an SAE considered by investigators to be drug-related: ventricular tachycardia in Subject 36012003004. Subject 36012003004 was a 53 year-old white female with a history of atrial fibrillation and depression/anxiety (on SSRI) who experienced V-Tach on study day 372 in the setting of severe hyperkalemia (K^+ 7.6 mmol/L, reference range 3.6-5.2), hypermagnesemia (magnesium 4.9 mmol/L, reference range 0.7-1.0), and mild hypocalcemia (calcium 2.0 mmol/L (reference range 2.1-2.55). Of note, the V-Tach resolved after correction of the patient's hyperkalemia with hemodialysis and while continuing on etelcalcetide, making the relationship to etelcalcetide unlikely.

Table 2. Exposure-Adjusted and Crude Incidence Rates of Serious Treatment-emergent Adverse Events Occurring in ≥ 1% of Subjects (Full Analysis Set) (Study 213 Safety Update Analysis)

	Total (N = 884)	
Preferred Term	n/e (r)[a]	(%)[b]
All serious treatment-emergent adverse events	436/915.3 (47.6)	49.3
Pneumonia	40/1248.4 (3.2)	4.5
Arteriovenous fistula thrombosis	24/1261.5 (1.9)	2.7
Sepsis	24/1267.6 (1.9)	2.7
Anaemia	19/1268.0 (1.5)	2.1
Cardiac arrest	19/1278.4 (1.5)	2.1
Fluid overload	16/1270.0 (1.3)	1.8
Hyperkalaemia	16/1269.8 (1.3)	1.8
Atrial fibrillation	15/1269.7 (1.2)	1.7
Septic shock	13/1278.1 (1.0)	1.5
Syncope	13/1269.2 (1.0)	1.5
Acute myocardial infarction	12/1276.0 (0.9)	1.4
Arteriovenous fistula site complication	12/1272.0 (0.9)	1.4
Dyspnoea	12/1273.4 (0.9)	1.4
Pulmonary oedema	12/1274.5 (0.9)	1.4
Pyrexia	12/1269.8 (0.9)	1.4
Non-cardiac chest pain	11/1268.4 (0.9)	1.2
Angina pectoris	10/1273.0 (0.8)	1.1
Bronchitis	10/1272.2 (0.8)	1.1
Osteomyelitis	10/1276.4 (0.8)	1.1
Arteriovenous graft thrombosis	9/1273.8 (0.7)	1.0
Cellulitis	9/1273.6 (0.7)	1.0

N = number of subjects in the full analysis set; n = total number of subjects with the event;
exposure-adjusted incidence rate per 100 subject-years = 100 • n/ Total subject-year at risk.
[a] n/e = n/Total subject-year at risk (years); r = Exposure-adjusted incidence rate per 100 subject-years.
[b] % = Crude subject incidence. Crude subject incidence = 100 • n/N.
Coded using MedDRA version 19.0.

Reviewer Comment: Overall, the updated SAE profile in Study 213 was similar to that seen in the Phase 3 program submitted in the original marketing application.

DISCONTINUATIONS DUE TO AEs

An additional 24 patients in the updated safety database had AEs leading to withdrawal of study drug, for a total of 37 subjects (4.2%) with AEs leading to drug withdrawal in Study 213. In the updated cumulative safety database for Study 213 (including new and previously reported AEs), the most common adverse events leading to withdrawal of etelcalcetide were nausea, vomiting, septic shock, and general physical health deterioration, all of which occurred in 4 subjects (0.5%) (**Table 3**).

Reviewer Comment: In the cumulative updated safety database, AEs leading to withdrawal of study drug were similar in type and frequency to the AEs leading to withdrawal in the phase 3 long-term open-label extension combined dataset submitted with the original NDA.

Table 3. Exposure-Adjusted and Crude Incidence Rates of Treatment-emergent Adverse Events Leading to Withdrawal Occurring in ≥ 2 Subjects (Full Analysis Set) (Study 213 Safety Update Analysis)

	Total (N = 884)	
Preferred Term	n/e (r)[a]	(%)[b]
All treatment-emergent adverse events leading to discontinuation of investigational product	37/1278.0 (2.9)	4.2
General physical health deterioration	4/1280.7 (0.3)	0.5
Nausea	4/1280.8 (0.3)	0.5
Vomiting	4/1280.7 (0.3)	0.5
Septic shock	4/1281.1 (0.3)	0.5
Sepsis	3/1281.1 (0.2)	0.3
Blood parathyroid hormone decreased	2/1280.5 (0.2)	0.2
Blood parathyroid hormone increased	2/1280.8 (0.2)	0.2
Abdominal pain upper	2/1281.0 (0.2)	0.2
Cardiac arrest	2/1281.2 (0.2)	0.2

N = number of subjects in the full analysis set; n = total number of subjects with the event; exposure-adjusted incidence rate per 100 subject-years = 100 • n/ Total subject-year at risk.
[a] n/e = n/Total subject-year at risk (years); r = Exposure-adjusted incidence rate per 100 subject-years.
[b] % = Crude subject incidence. Crude subject incidence = 100 • n/N.
Coded using MedDRA version 19.0.

Treatment Emergent Adverse Events (TEAEs)
In total (i.e., including previously reported TEAEs), TEAEs were reported for 761 of 884 subjects who were exposed to etelcalcetide in Study 213. With the updated safety data, this calculates to an exposure-adjusted incidence rate of TEAEs of 208.8 per 100 subject-years, compared to 300.1 per 100 subject-years in the phase 3 long-term open-label extension combined dataset submitted with the original NDA. This difference was driven primarily by a lower rate of blood calcium decreased in the update complete d safety database for Study 213 (24.5 per 100 subject years) compared to the phase 3 open-label extension dataset (60.9 per 100 subject years). Of the 761 TEAEs in Study 213, 119 (13.5%) were mild, 221 (25%) were moderate, 321 (36.3%) were severe, 98 (11.1%) were life-threatening, and 2 (0.2%) were not yet coded at the time of this resubmission. The overall updated exposure-adjusted incidence rates for fatal AEs, serious AEs, and AEs leading to discontinuation were similar or lower in this updated safety analysis compared to that reported in the original phase 3 open-label extension dataset (**Table 4**).

Table 4. Exposure-Adjusted and Crude Incidence Rates of Treatment-emergent Adverse Events (Phase 3 Long-term OLE Combined Dataset Safety Analysis Set and Study 213 Safety Update Full Analysis Set)

	Phase 3 Long-term Open-Label Combined Dataset Total (N = 1289)		Study 20130213 Total (N = 884)	
	n/e (r)[a]	(%)[b]	n/e (r)[a]	(%)[b]
All treatment-emergent adverse events	946/315.2 (300.1)	73.4	761/364.5 (208.8)	86.1
Serious adverse events	376/733.8 (51.2)	29.2	436/915.3 (47.6)	49.3
Treatment-related adverse events	433/642.4 (67.4)	33.6	281/962.5 (29.2)	31.8
Serious treatment-related adverse events	13/913.9 (1.4)	1.0	4/1277.8 (0.3)	0.5
Adverse events leading to the discontinuation of investigational product	39/915.2 (4.3)	3.0	37/1278.0 (2.9)	4.2
Fatal adverse events	47/918.7 (5.1)	3.6	85/1279.4 (6.6)	9.6

N = number of subjects in the analysis set; n = total number of subjects with the event.
Exposure-adjusted incidence rate per 100 subject-years = 100 • n/ Total subject-year at risk.
[a] n/e = n/Total subject-year at risk (years); r = Exposure-adjusted incidence rate per 100 subject-years.
[b] % = Crude subject incidence. Crude subject incidence = 100 • n/N.

The most common TEAEs in Study 213 were overall similar to the most common TEAEs among etelcalcetide-treated subjects reported in the original NDA, with the exception of hyperphosphatemia, which had an incidence rate of 6.4 per 100 subject-years in Study 213, compared with 3.9 per 100 subject-years in the original phase 3 long-term open-label extension combined dataset.

Overall, the most frequent TEAEs in Study 213 were blood calcium decreased (27.6% of subjects), diarrhea (9.5%), hyperphosphatemia (8.7%), muscle spasms (8.1%), hypertension (7.4%), hypotension (7.1%), pain in extremity (7.1%), nausea (6.6%), and upper respiratory tract infection (6.6%)(

Table 5).

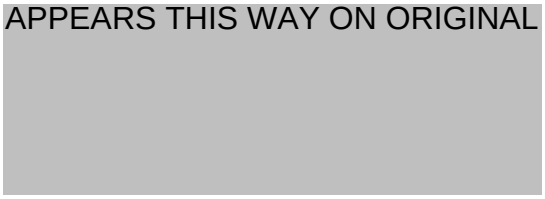


Table 5. Exposure-Adjusted and Crude Incidence Rates of Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency**.**

	Parent Study 20120360				Parent Studies 20120334 and 20120231			
	Cinacalcet (N = 211)		AMG 416 (N = 197)		AMG 416 (N = 476)		Total (N = 884)	
Preferred Term	n/e (r)*	(%)**	n/e (r)*	(%)**	n/e (r)*	(%)**	n/e (r)*	(%)**
All treatment-emergent adverse events	185/93.1 (198.6)	87.7	163/88.3 (184.6)	82.7	413/183.1 (225.6)	86.8	761/364.5 (208.8)	86.1
Blood calcium decreased	73/236.4 (30.9)	34.6	68/224.5 (30.3)	34.5	103/533.3 (19.3)	21.6	244/994.2 (24.5)	27.6
Diarrhoea	17/321.2 (5.3)	8.1	19/275.8 (6.9)	9.6	48/597.9 (8.0)	10.1	84/1195.0 (7.0)	9.5
Hyperphosphataemia	14/323.3 (4.3)	6.6	20/277.4 (7.2)	10.2	43/604.5 (7.1)	9.0	77/1205.2 (6.4)	8.7
Muscle spasms	13/318.5 (4.1)	6.2	18/281.6 (6.4)	9.1	41/600.9 (6.8)	8.6	72/1201.0 (6.0)	8.1
Hypertension	17/317.0 (5.4)	8.1	14/282.6 (5.0)	7.1	34/610.7 (5.6)	7.1	65/1210.3 (5.4)	7.4
Hypotension	9/326.6 (2.8)	4.3	18/282.8 (6.4)	9.1	36/607.5 (5.9)	7.6	63/1216.9 (5.2)	7.1
Pain in extremity	12/325.7 (3.7)	5.7	17/282.7 (6.0)	8.6	34/604.7 (5.6)	7.1	63/1213.2 (5.2)	7.1
Nausea	21/321.1 (6.5)	10.0	18/282.2 (6.4)	9.1	19/627.0 (3.0)	4.0	58/1230.3 (4.7)	6.6
Upper respiratory tract infection	12/326.8 (3.7)	5.7	12/286.1 (4.2)	6.1	34/606.1 (5.6)	7.1	58/1219.0 (4.8)	6.6

Study 20130213 data snapshot date of 06OCT2016.
Full analysis set: all enrolled subjects who received at least 1 dose of AMG 416 in current study 20130213
N = The number of subjects in Full Analysis Set. n = Total number of subjects with the event.
Exposure-adjusted incidence rate per 100 subject years = 100* n/ Total subject-year at risk.
*n/e = n/Total subject-year at risk (yrs); r = Exposure-adjusted incidence rate per 100 subject years.
**% = Crude incidence rate. Crude incidence rate = 100*n/N.
Coded using MedDRA version 19.0

Cumulative incidence of treatment-*related* AEs were lower in this safety update (29.2 per 100 subject-years) compared with the phase 3 long-term open-label extension combined dataset in the original marketing application (67.4 per 100 subject-years). Overall, the most common treatment-related AEs in Study 213 were blood calcium decreased (23.4%), blood parathyroid hormone decreased (2.4%), nausea (1.6%), and hypophosphatemia (1.1%). All of these AEs are contained in proposed labelling for etelcalcetide.

> *Reviewer Comment: This updated safety analysis of Study 213 did not identify any new treatment-emergent or treatment-related AEs with use of etelcalcetide in the hemodialysis population. The most common TEAEs were similar to those already observed and are detailed in proposed labelling. The most common treatment-related AEs are expected given the mechanism of action (e.g., blood calcium decreased, PTH decreased, hypophosphatemia) and known safety profile (e.g., nausea) of calcimimetics. The increased incidence of hyperphosphatemia in this safety report is likely a chance finding in a population at high risk for hyperphosphatemia (e.g., hemodialysis patients) and not related to study drug, which by its mechanism of action predisposes patients to hypophosphatemia.*

LABORATORY FINDINGS

Laboratory abnormalities associated with use of etelcalcetide were previously described in the review of the original marketing application. This safety update revealed no new safety risks with regard to potential laboratory abnormalities associated with etelcalcetide.

The most common clinical laboratory abnormalities in the updated Study 213 safety database were serum calcium decreased (occurring in 92.8% of subjects) and serum phosphorous decreased (occurring in 21.6% of subjects). Neither are unexpected laboratory abnormalities associated with use of calcimimetics based on the mechanism of action or in dialysis patients. These laboratory abnormalities can be easily monitored by clinicians and rectified by appropriate dose adjustments. Further, these laboratory abnormalities are appropriately labelled in proposed USPI for etelcalcetide.

Regarding liver function tests (AST, ALT, alkaline phosphatase, and total bilirubin) in this safety update, 2.1% of subjects had ALT or AST > 3x the upper limit of normal (ULN), compared with 0.9% of subjects in the phase 3 long-term open-label extension combined dataset in the original marketing application. The Sponsor points to longer mean duration of exposure in Study 213 (71.7 weeks) compared to the original phase 3 long-term open-label extension combined dataset (32.9 weeks) to explain this difference. The prevalence of ALT or AST > 3× ULN and total bilirubin ≥ 2× ULN in Study 213 is overall low and similar to the prevalence reported in the original marketing application (

, also refer to Clinical Review by Dr. Lubas in DARRTS). No Hy's law cases were reported in the study.

Reviewer Comment: Clinical laboratory data in this Safety Update reveal no new safety risks from what was presented in the original marketing application.

VITAL SIGNS
In this interim analysis of Study 213, there were no notable changes relative to baseline in systolic blood pressure, diastolic blood pressure, heart rate, or body weight.

AEs OF INTEREST
AEs of interest for etelcalcetide were identified based on the mechanism of action of the drug and on findings from the clinical and pre-clinical programs. The AEs of interest are listed below:

- Cardiac failure
- Effects on cardiac repolarization (Torsade de pointes-QT prolongation and ventricular tachyarrhythmias)
- Convulsions
- Hypersensitivity
- Hypocalcemia
- Adynamic bone
- Hypophosphatemia

- Infusion reaction
- **Gastrointestinal hemorrhage**

Overall, updated exposure-adjusted incidence rates for AEs of interest were similar compared with the original phase 3 long-term open-label extension combined dataset (**Table 6**), with one exception: infusion reactions were *lower* in the updated safety dataset compared to the original phase 3 combined dataset (6.6% vs 16.5%, respectively). According to the Sponsor, the decreased incidence of infusion reactions is likely due to a change in the methodology for collecting these events, such that in Study 213, only infusion reaction events that coincided with investigational product infusion and resolved on the same day or the day after onset were considered events of interest, whereas in the original application, all infusion reactions regardless of timing of the event were considered AEs of interest.

Table 6. Exposure-adjusted Incidence Rate and Crude Subject Incidence of Treatment-emergent Adverse Events of Interest (Phase 3 Long-term OLE Combined Dataset Safety Analysis Set and Study 213 Safety Update Full Analysis Set)

	Phase 3 Long-term Open-Label Combined Dataset Total (N = 1289)		Study 20130213 Total (N = 884)	
Event of Interest	n/e (r)[a]	(%)[b]	n/e (r)[a]	(%)[b]
Adynamic bone (EOI)	0/919.2 (0.0)	0.0	0/1281.2 (0.0)	0.0
Cardiac failure (SMQ)	42/897.6 (4.7)	3.3	32/1262.1 (2.5)	3.6
Convulsions (SMQ)	10/916.6 (1.1)	0.8	12/1267.0 (0.9)	1.4
Gastrointestinal haemorrhage (SMQ)[c]	-	-	36/1248.6 (2.9)	4.1
Hypersensitivity (SMQ)	42/894.7 (4.7)	3.3	39/1242.4 (3.1)	4.4
Hypocalcemia (EOI)	416/647.6 (64.2)	32.3	254/982.2 (25.9)	28.7
Hypophosphatemia (EOI)	16/910.4 (1.8)	1.2	18/1261.9 (1.4)	2.0
Infusion reaction (EOI)[d]	213/806.7 (26.4)	16.5	58/1224.1 (4.7)	6.6
Torsade de pointes/QT prolongation (SMQ)	5/916.3 (0.5)	0.4	4/1279.7 (0.3)	0.5
Ventricular tachyarrhythmias (SMQ)	8/917.7 (0.9)	0.6	3/1280.2 (0.2)	0.3

EOI = events of interest; SMQ = standardized Medical Dictionary for Regulatory Activities query.
[a] n/e = n/Total subject-year at risk (years); r = Exposure-adjusted incidence rate per 100 subject-years.
[b] % = Crude subject incidence. Crude subject incidence = 100 • n/N.
[c] Gastrointestinal hemorrhage was not evaluated in the phase 3 long-term open-label combined dataset.
[d] For Study 21030213, infusion reaction as listed in the Infusion Reaction EOI (narrow search) with onset day coincident with IP infusion which were resolved on the same day or the day after onset. For the phase 3 long-term open-label combined dataset, infusion reaction EOIs did not account for the timing of the event in relationship to dose administration.
Data from the Phase 3 OLE was coded using MedDRA version 17.1. Data from the Study 20130213 interim analysis was coded using MedDRA version 19.0.

UPPER GASTROINTESTINAL HEMORRHAGE

The primary safety signal identified during review of the original NDA is an association between etelcalcetide and *fatal upper* GIB events (rather than *lower* GIB). In this safety update, the Sponsor has provided updated safety data on new cases of fatal GIB AEs, which are discussed

below.

The applicant performed an updated search of the Amgen Global Safety Database (AGSD), which contains all *serious* AEs in phase 1-3 clinical trials and all serious AEs (beyond those reported in the protocol derived study periods) for treatment-emergent GI bleeding events coincident with etelcalcetide use. The search included GIB events in pivotal trials in the etelcalcetide development program (Studies 229, 230, and 360) and in long-term extension trials (Studies 231 and 213, refer to Clinical Review in DARRTS for study details). When the bleeding site was *unknown*, the most conservative approach was taken and the event was counted as an *upper* GI bleed.

Fatal Events in Subjects with Gastrointestinal Bleeding at the Time of Death in the Etelcalcetide Development Program

In this resubmission, the applicant has updated information regarding fatal events with GI bleeding based on re-review of case reports and autopsy reports for etelcalcetide-treated patients with GIB associated with death. *No additional cases of fatal UGIB were identified in etelcalcetide-treated patients*. Overall, the exposure-adjusted rates of fatal events with some evidence of GI bleeding at the time of death were similar between the etelcalcetide and control groups (0.32 vs 0.26 per 100 patient-years of exposure, respectively); this did not change with this safety update.

Fatal Events in Subjects with Gastrointestinal Bleeding at the Time of Death Identified from the Amgen Global Safety Database (AGSD)

The applicant performed an updated search of the AGSD database for all fatal events in subjects with GIB at the time of death. A total of ten cases with evidence of upper GIB or lower GIB around the time of death were identified in etelcalcetide-treated patients (**Table 7**). Seven of the ten of the cases were previously reported either in the original marketing application, but are included again in **Table 7** (Subjects 1-7 in Table 9)**.** Of the three new cases of fatal GIB, two were cases of lower GIB (Subject 23048004009 and Subject 23065056005); narratives for these cases were reviewed by this Medical Officer. The third new case, a case of GIB with unknown bleeding source associated with a fatal outcome (Subject 23021002001), is reviewed below.

- Subject 23021002001 was a 71 year-old white female enrolled in the open-label extension Study 231 with a history of GIB due to duodenal peptic ulcer, chronic heart failure, chronic atrial fibrillation, COPD, hypertension, peripheral vascular disease, and first degree AV block requiring a pacemaker. Three days after starting etelcalcetide, she was diagnosed with a recurrent duodenal ulcer requiring endoscopic hemostasis. In the week following endoscopic treatment of the duodenal ulcer, the patient was hospitalized with a heart failure exacerbation and died due to cardiogenic shock. There was no recurrence of GI bleeding at the time of death. Concomitant medications were

not reported, however, she reportedly had a history of chronic NSAID use.

Reviewer Comment: This patient had a history of duodenal ulcer prior to starting etelcalcetide treatment, making a causal relationship between etelcalcetide and occurrence of GIB unlikely. In addition, at the time of her death, there was no recurrence of GIB, which had resolved after an endoscopic hemostasis procedure. The patient's death was caused by an exacerbation of heart failure and cardiogenic shock and not by GIB. Therefore, this case should not be included in labeling of fatal UGIB events associated with etelcalcetide use.

Table 7. Fatal Events in Subjects with Gastrointestinal Hemorrhage who received Etelcalcetide from the Amgen Global Safety Database Listing of All Fatal Events

	Adverse Event	Case Number	Study Number	Subject ID	Age	Gender	Time to Event (days)	Relatedness to IP	Dose	Use of Anti-coagulants	Primary Cause of Death	Origin of Bleeding
1	Gastrointestinal haemorrhage	USACT2012058566	20120331	0517-1547	54	M	43	Not Related	5 mg	Prasugrel, ASA	Myocardial infarction, Coronary artery disease, Gastrointestinal haemorrhage, Cardiogenic shock, Pulmonary oedema, Pneumonia	Lower GI Tract
2	Upper gastrointestinal haemorrhage	USACT2013080913	20120230	23066026008	75	M	155	Not Related	15 mg	Heparin	Upper gastrointestinal haemorrhage	Upper GI Tract
3	Death	GBRCT2013062058	20120229	22965007001	73	F	10	Related	5 mg	ASA	Unknown cause	Upper GI Tract
4	Gastritis haemorrhagic Haematemesis	USACT2014023356	20120231	35966002004	49	F	78	Not Related	10 mg	ASA	Small intestinal obstruction, Acidosis, Sepsis, Pulmonary embolism, Cardio-respiratory arrest, Brain hypoxia	Upper GI Tract
5	Rectal haemorrhage	ITACT2014028161	20120360	36033006003	81	M	55	Not Related	Not listed	Ticlodipine	Cardiac failure acute	Lower GI Tract

	Adverse Event	Case Number	Study Number	Subject ID	Age	Gender	Time to Event (days)	Relatedness to IP	Dose	Use of Anti-coagulants	Primary Cause of Death	Origin of Bleeding
6	Colitis ischaemic	USACT2015066844	20130213	36066001003	52	M	296	Not Related	2.5 mg	ASA	Colitis ischaemic	Upper and Lower GI Tract
7	Gastrointestinal haemorrhage	BELCT2016001211	20130213	23013012006	88	M	701	Not Related	10 mg	Enoxaparin	Gastrointestinal haemorrhage	Unknown
8	Cardiac failure congestive	CZECT2013087566	20120231	23021002001	71	F	10	Not Related	5 mg	h/o chronic NSAID Use	Cardiac failure congestive	Unknown
9	Pneumonia	POLCT2015020748	20130213	23048004009	62	M	25	Not Related	2.5 mg	Not provided	Pneumonia	Lower GI Tract
10	Respiratory failure	USACT2014028591	20130213	23066056005	66	M	71	Not Related	10 mg	Warfarin	Respiratory failure	Lower GI Tract

Data cut-off date 4 Aug 2016

The Sponsor also reanalyzed one of three cases of fatal GIB that were included in the original label. *As a result of this analysis, the Sponsor changed the classification of the fatal GIB event in Subject 0517-1547, who participated in a phase 2, open-label, single arm trial (Study 331), from an upper GIB in the original marketing application to a lower GIB in this resubmission*. This case is reviewed below.

- Subject 0517-1547 was a 54 year-old male patient with a history of Type 2 Diabetes Mellitus (T2DM), coronary artery disease with a prior acute myocardial infarction (MI), and congestive heart failure, who was hospitalized on study day 35 with an acute sub-endocardial MI. On study day 43, while still hospitalized and 2 days after cardiac catheterization, the patient went into cardiogenic shock and developed an acute GI bleed presenting as bright red blood per rectum (BRBPR). A full autopsy report confirmed atherosclerotic coronary artery disease with evidence of prior MI. Of note, the GI tract was normal throughout except for diverticula in the lower GI tract. No ulceration, ischemic changes, obstruction, or polyps were identified. Concomitant medications included aspirin and prasugrel (an anti-platelet agent).

Reviewer Comment: The case report and the autopsy report for Subject 0517-1547 suggest that this patient suffered a lower (not upper) GIB at the time of cardiogenic shock and death. Bleeding risk was increased by recent cardiac catheterization and concomitant use of aspirin and prasugrel. I therefore agree with the Sponsor's changes to USPI to exclude this subject from the fatal cases of upper GIB observed in the etelcalcetide development program.

In conclusion, no additional cases of fatal UGIB adverse events were reported in this safety update, and the change in location of the GIB in Subject 0517-1547 from upper GIB to lower GIB

is justified. Therefore, the proposed changes to Section 5 of labeling regarding the number of patients with fatal UGIB associated with etelcalcetide use are acceptable.

PEDIATRIC STUDY PLAN

This resubmission contains no modifications to the Initial Pediatric Study Plan (iPSP) submitted with the original NDA, which was determined to be acceptable by the Agency's Pediatric Review Committee.

PRESCRIBING INFORMATION

Section 14 Clinical Studies

In this resubmission, *the Sponsor has agreed to* (b) (4) This change was in response to the Division's Complete Response comments dated 8/24/2016, stating that approval was denied (b) (4) (b) (4)

In addition, the Statistical review team recommended modifying Table 3 in labeling, such that the primary efficacy endpoint (>30% reduction in iPTH) is analyzed and reported using a multiple imputation method that imputes missing primary endpoint measurements. With this modification, Table 3 shows missing rates for achievement of >30% reduction in iPTH for the etelcalcetide and placebo groups, as well as comparisons of respective response and non-response rates using imputed data (*see Biometrics Review dated 1/27/17 in DARRTS*).

Reviewer Comment: The sponsor accepted the proposed changes to Table 3 in labeling.

Section 5 Warnings and Precautions

Proposed labeling in this resubmission includes an update to the number of deaths with upper GIB occurring in etelcalcetide-treated patients, from 3 deaths to 2 deaths:

> **5.3 Upper Gastrointestinal Bleeding**
> "In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no

patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV."

Reviewer Comment: This labeling update was made based on further review of the autopsy report for Subject 0517-1547 (discussed above). This patient's death occurred in concurrence with a GIB for which the source was initially unknown and was therefore considered to be an upper GIB as a conservative estimate. Upon review of the full autopsy report, there is no evidence of UGIB and clinical evidence strongly suggests that this patient suffered a lower GIB. Thus, the proposed change in classification of Subjects 0517-1547's fatal GIB event from an upper to a lower GIB is appropriate.

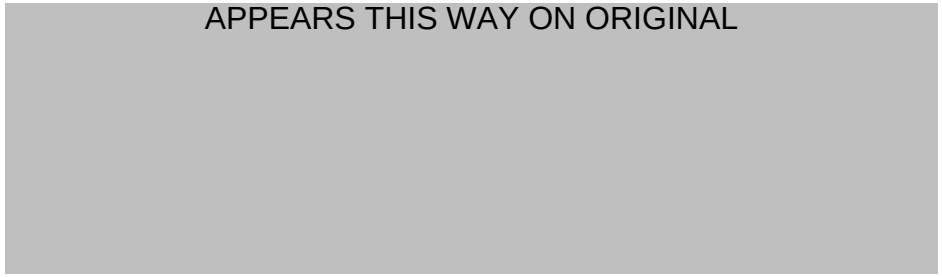
Adverse Reaction Section in *Highlights*

Proposed labeling in this resubmission also includes removal of the adverse reaction 'vomiting' from the Adverse Reactions Section in *Highlights* because the incidence of vomiting was 9%, and this section lists only adverse reactions seen in (b) (4) of patients.

Reviewer Comment: Because vomiting is known to be a common adverse reaction associated with etelcalcetide (and with calcimimetics as a drug class), this reviewer recommends including vomiting as an adverse reaction in the Adverse Reactions Section in Highlights of labeling. The original language includes adverse reactions that occurred in (b) (4) of subjects; therefore, I recommend including adverse reactions that occurred in ≥5% of subjects to capture the additional adverse reactions of vomiting, headache, hypocalcemia, and paresthesia.

The Sponsor accepted the proposed changes.

Recommendations:
I recommend approval of Parsabiv for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. The Sponsor adequately addressed all deficiencies outlined in the Complete Response letter dated 8/24/16.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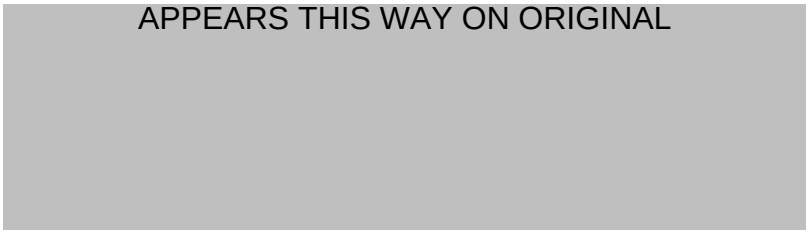
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/s/

SHANNON D SULLIVAN
01/30/2017

MARINA ZEMSKOVA
01/30/2017

Cross-Discipline Team Leader Review

Date	8/24/2016
From	Marina Zemskova, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208325
Applicant	Amgen
Date of Submission	
PDUFA Goal Date	August 24, 2016
Proprietary Name / Non-Proprietary Name	Parsabiv/etelcalcetide
Dosage form(s) / Strength(s)	Solution for injection/ 5 mg, 10 mg, (b) (4)
Applicant Proposed Indication(s)/Population(s)	Secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	Secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The applicant has proposed marketing Parsabiv, an allosteric activator of the calcium-sensing receptor (CaSR)[1], for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease on hemodialysis.

Secondary hyperparathyroidism (SHPT) refers to parathyroid gland hyper-function caused by an underlying disease that affects phosphorus, calcium or vitamin D metabolism (e.g., chronic kidney disease, Gastrointestinal, primary vitamin D metabolism disease etc.). Loss of kidney function perturbs vitamin D metabolism and mineral homeostasis and advanced chronic kidney disease (CKD) is the most common cause of secondary hyperparathyroidism.

Chronically elevated levels of circulating parathyroid hormone (PTH[2]), the biochemical hallmark of hyperparathyroidism, leads to increased bone turnover and bone resorption and in the absence of normal functioning kidneys to elevated circulating levels of calcium and phosphorus. The changes in PTH regulation that accompany progression of renal disease, along with changes in the regulation of Vitamin D and Fibroblast Growth Factor-23, contribute to the mineral and bone disorders associated with CKD (i.e., CKD-Mineral and Bone Disorders). These disorders have been associated with vascular calcification (media of vessel walls and heart valves) and with defects in bone turnover and mineralization and are believed to contribute to both the cardiovascular (i.e., hypertension, left ventricular hypertrophy, calcific uremic arteriolopathy) and skeletal (i.e., fracture, bone pain) complications of chronic kidney disease. Therapies to treat CKD-Mineral and Bone

[1] The term "calcimimetic" will be used to refer to allosteric activators of the calcium-sensing receptor for simplicity
[2] PTH in this review refers to intact PTH or the full length, 84 amino acid, protein.

Disorders, including those indicated for the treatment of secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis, aim to prevent skeletal and cardiovascular complications of CKD.

Documentation of a drug-induced decrease in serum PTH has been used as a surrogate to establish the efficacy, and support the full approval, of several marketed therapies indicated for the treatment of secondary hyperparathyroidism in adult patients with CKD on hemodialysis (i.e., vitamin D analogs and an oral allosteric activator of calcium sensing receptors). In the regulatory context, it is assumed that a significant reduction in levels of PTH from baseline (i.e., at least 30%) correlates with a reduction in adverse skeletal outcomes (e.g., fracture, bone pain) and establishes the benefit of these drugs for that indication. It must be said, however, that there is some uncertainty around the validity of this assumption because of an absence of prospective, controlled, data establishing that interventions that reduce PTH levels reduce the risk of skeletal complications in this population. Absent these data, it is not possible to verify whether the assumption is valid or to determine the exact relationship between drug induced PTH changes and risk of skeletal complication.

The most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines recognize this uncertainty and state that the optimal PTH in adult dialysis patients with secondary hyperparathyroidism is not known but recommend maintaining PTH levels in the range of 2 to 9 times the upper limit of normal (e.g., 130-600 pg/mL). While some observational data suggest an association between very highly elevated PTH levels (>600 pg/mL) and the risk of death and cardiovascular event in this population, the only prospectively planned, randomized, controlled trial designed to examine the relationship between PTH lowering and CV-risk reduction (i.e., the EVOLVE trial[3]) did not clearly and definitively establish that PTH lowering with an oral allosteric activator of calcium sensing receptors co-administered with standard of care therapies for CKD-Mineral and Bone Disorders reduces the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism on dialysis.

Benefits

The applicant demonstrated, in two adequate and well-controlled trials carried out in adults with secondary hyperparathyroidism due to CKD on hemodialysis, that Parsabiv significantly reduced baseline PTH levels compared to placebo at the end of 6 months. In these two trials a greater proportion of individuals randomized to Parsabiv experienced a 30% reduction in PTH levels from baseline compared to placebo (i.e., 75% versus 9% respectively). PTH levels decreased, on average, by 56% from baseline in the Parsabiv group and rose by 13% from baseline in the placebo group [PBO-adjusted difference (95% CI); -71.3% (-75.8, 66.8)]. Directional changes in mineral (calcium, phosphorus) and bone-turnover biomarkers (CTX and BASP) were consistent with expectations and suggest that Parsabiv use is associated with a net decrease in bone resorption. The overall data in these two trials establish the benefit of Parsabiv. Notwithstanding the uncertainty noted above, it is expected that Parsabiv will have salutary effects on bone disease associated with CKD and will reduce the risk of skeletal complications (i.e., fracture, bone pain) in these patients.

Vitamin D analogs are considered first line therapy in the treatment of SHPT in patients with CKD on hemodialysis but these drugs can cause hypercalcemia and hyperphosphatemia. This side effect that can limit their usefulness. Treatment with a calcium sensing receptor (CaSR) agonist is recommended when adequate control of PTH cannot be achieved with a vitamin D analog as these drugs lower PTH without raising circulating levels of calcium and phosphorus. The only Calimimetic approved for the treatment of SHPT in patients on dialysis is the oral tablet Sensipar (cinacalcet). Parsabiv would be the second Calimimetic to be marketed and would be administered intravenously at the end of the dialysis. Compared to a once daily oral drug, Parsabiv would reduce the high daily pill burden in this population and may facilitate management of

[3] N Engl J Med 2012; 367:2482-2494

SHPT.

The applicant submitted a comparative efficacy study which compares PTH lowering achieved at the end of 6 months between Parsabiv and Sensipar and seeks to show data that would suggest Parsabiv has superior efficacy than Sensipar. The superiority claim was not found to be substantiated because it is derived from a single trial and because the drugs were not compared at each of their maximally effective doses. Although a slightly higher proportion of patients on etelcalcetide were observed to have a greater than 30% and greater than 50% decrease in PTH by trial end, review of these data suggest that this was, at least in part, attributable to suboptimal dosing of Sensipar in the trial. Even without the fairness of comparison issue, the absolute numerical difference in PTH lowering was small between the two groups and ultimately of unknown clinical relevance. Finally, no clear differences in tolerability were observed between the two drugs to suggest one is superior to the other on these grounds.

Risks

The risks associated with the use of Parsabiv are generally consistent with risks expected for the calcimimetic class of drugs. Gastrointestinal adverse reactions (i.e., nausea, vomiting), hypocalcemia, hypophosphatemia and oversuppression of PTH (that increase the risk for adynamic bone disease) are adverse reactions associated with this class and Parsabiv. Overall, incident nausea and vomiting was one of the most common reaction associated with Parsabiv use and occurred at a rate similar to that reported for Sensipar. The incidence of mineral abnormalities (hypocalcemia and hypophosphatemia) was slightly higher with Parsabiv compared to Sensipar. This may have been due to dose differences between the two groups (see above). These mineral abnormalities improved in the majority of patients with changes to concomitant therapies or with Parsabiv dose adjustment. These risks will be mitigated through product labeling which will include recommendations on the appropriate patient selection, on monitoring for occurrence of these reactions and on interventions to address these reactions including but not limited to Parsabiv dose adjustment.

Congestive heart failure (CHF) is an adverse reaction associated with the use of calcimimetics. The exact mechanism for this adverse reaction is not known but may be due to changes in circulating calcium levels caused by the drug or to a direct drug effect involving calcium-sensing receptors in cardiac tissue. A Warning and Precaution section discussing this safety concern will be included in labeling to ensure prescribers recognize Parsabiv may be associated with this risk and can take appropriate precautions in patients with this condition.

A small imbalance in fatalities due to upper gastrointestinal (GI) bleeding the Parsabiv clinical program. Three patients died due to an upper GI bleed versus zero across all comparators while on-treatment. Although this may represent a chance finding in a population known to be at high baseline risk, we could not completely exclude the possibility that the drug may have contributed to increasing this risk. Several factors were considered in recommending that this risk be labeled as a Warning and Precautions. First the risk was interpreted in the light of the fact that efficacy was based on a surrogate measure and some uncertainty around the exact benefit(s) of these drugs remain. Second, all cases resulted in death (arguably the most serious outcome), third a relationship between Parsabiv and gastro-intestinal toxicity was found to biologically plausible and fourth it was felt to be important to mitigate this potential risk by including instructions on patient selection, monitoring and interventions in labeling. With regard to biological plausibility the CaSR is known to be expressed in the gastric mucosa and to play a role in nutrient sensing and gastric secretion. Furthermore, data from non-clinical studies in rodents appeared to demonstrate a Parsabiv-related toxic effect on the gastro-intestinal mucosa. Finally, gastro-intestinal reactions are common Parsabiv-related reactions suggesting the drug may have an effect in the GI tract in humans.

The clinical trial data show that anti-drug antibody (ADA) formation is low with Parsabiv. The clinical data did not suggest an effect of ADA on safety or efficacy. There are no data on neutralizing antibodies. Hypersensitivity reactions are a concern with all peptide products including Parsabiv. Incident allergic reactions were rare and all allergic reactions were mild and no events of anaphylaxis were reported in the clinical development program.

Overall, the benefits of using Parsabiv for the treatment of SHPT in patients with CKD on hemodialysis outweigh the identified risks. Parsabiv resulted in a large and significant decrease in PTH levels in most patients. These changes should improve bone health and decrease bone-related morbidities (bone pain and fractures). The safety profile was found to be generally consistent with the safety profile of the other approved calcimimetic. In the data, a 3 to 0 imbalance in fatal events of upper GI bleed was observed. It is unclear whether this is real or due to chance. However, in light of the seriousness of the event this will be reported in labeling to ensure prescribers consider this a potential risk in their therapeutic decision making. To gain additional insights on the potential association between Parsabiv and events of upper GI bleeding, the applicant will be required to carry out an observational study as a post-marketing requirement. All other safety concerns will be mitigated by communicating risks in the product label and recommending appropriate patient selection, monitoring and dose adjustment if required.

During the labeling negotiations the Division was not able to reach agreement on the content of the full prescribing information for Parsabiv (b) (4)

(b) (4)

I have discussed the details of my review and recommendation at length with Dr. Jean-Marc Guettier, Division Director for the Division of Metabolism and Endocrinology products, and he concurs with my assessment of the benefits and risks for Parsabiv and with my decision to recommend Complete Response of this product for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease on hemodialysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	1. Chronically high levels of PTH in patients with CKD on dialysis increase bone turnover and cause excessive loss of calcium and phosphorus from bone contributing to metabolic bone disease (i.e., renal osteodystrophy) and calcification of extra-osseous tissues (e.g., cardiovascular tissues). 2. Prospective, controlled, data establishing that interventions that reduce PTH levels reduce the risk of skeletal or cardiovascular complications in this population are not available. 3. The 2009 KDIGO guidelines, recommend treating elevated PTH levels in subjects with CKD on dialysis as a means to prevent bone and CV-risk complications. The PTH level associated with a reduced risk of bone and CV	1. Chronically high levels of PTH could lead to bone pain, fractures, arrhythmias, coronary artery disease or other CV complications (i.e., hypertension). 2. Treatments to lower chronically high PTH levels in this population aim to prevent the skeletal and cardiovascular complications. Establishing that a drug reduces PTH by a large amount has been used as a surrogate to support full approval of drugs to treat secondary hyperparathyroidism (SHPT) in the setting of renal disease. 3. The optimal PTH level to prevent skeletal and cardiovascular complications is not known.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	complications in these patients is not known. The current recommendations is to maintain PTH levels between two and nine times the upper limit of normal (UNL) for the assay.	
Current Treatment Options	1. Oral and injectable active vitamin D analogs (e.g.., calcitriol, doxercalciferol and paricalcitol) 2. Oral calcimimetic (e.g., cinacalcet) 3. Treatment of SHPT occurs in parallel with correction of mineral abnormalities (hyperphosphatemia and hypocalcemia) which are also implicated in the bone disease and mineral metabolism disorders associated with chronic kidney disease.	1. Vitamin D analogs are first line in the treatment of SHPT in patients with CKD on hemodialysis but this class of drugs can be associated with hyperphosphatemia and hypercalcemia. 2. Calcimimetics can lower PTH levels without increasing calcium and phosphorus levels which may be desirable for some patients. There is no intravenous (IV) calcimimetic and Parsabiv would be the first IV CaSR to be approved. 3. Parsabiv will used with standard of care drugs to treat CKD-Mineral and Bone disorders.
Benefit	1. Parsabiv reduced PTH levels by > 30% in the majority (75%) of patients with SHPT and CKD on hemodialysis compared to placebo (9%) in two adequate and well controlled studies. 2. The mean placebo-adjusted percent change from baseline to final visit in serum PTH levels was a decrease of 69% across the two placebo controlled trial. Bone turnover marker revealed a trend towards decrease bone resorption. Calcium and phosphorus levels decreased with use of Parsabiv. 3. An active comparator trial against cinacalcet reported slightly greater PTH lowering efficacy of Parsabiv over cinacalcet. However, in this study dosing of cinacalcet was not optimal and the comparison was biased in favor of Parsabiv. 4. The magnitude of the observed difference in PTH between the two arms is small and of unknown clinical significance.	1. Treatment with Parsabiv should reduce the risk of skeletal complications in CKD patients with SHPT receiving hemodialysis. 2. Treatment with parsabiv should reduce the risk of skeletal complications in CKD patients with SHPT receiving hemodialysis and help in the management of mineral metabolism in these patients. 3. The claim that Parsabiv has a superior PTH lowering effect than cinacalcet is not substantiated because it is derived from a single trial and the dosing between groups favored Parsabiv and was not fair. The comparative PTH lowering efficacy of the two drugs when both are used at maximally effective doses remains unknown. 4. Even if the comparison was fair, it is unclear that observed between group differences are large enough to have a clinically meaningful effect on outcomes (bone pain, fractures, end-organ damage, etc.).
Risk	1. The safety profile of Parsabiv has been generally well characterized and is generally consistent with the class. 2. The incidence of mineral abnormalities observed (hypocalcemia and hypophosphatemia) was slightly higher with Parsabiv compared to cinacalcet. 3. Over-suppression of PTH levels may predispose patients to adynamic bone disease.	1. Treatment with Parsabiv is associated with nausea/vomiting. Risks of hypocalcemia and hypophosphatemia are monitorable risks. 2. Differential use of maximally effective doses between groups may account for this difference. Monitoring and dose adjustment will be recommended to mitigate these risks. 3. Over-suppression of PTH is a monitorable risk. The risk of adynamic bone disease will

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Incidence of PTH suppression to < 100 pg/ml observed with Parsabiv was slightly higher compared to cinacalcet; however, no other clinical evidence of adynamic bone disease was seen. 4. Congestive heart failure is a known adverse reaction that has been associated with use of calcimimetic drugs, including Parsabiv. The mechanism in unclear. 5. More fatal GI bleeding events (3 versus 0) were seen in the Parsabiv clinical program. While the exact etiology for these events is not clear, the clinical and nonclinical data raise the possibility that these events could potentially be drug-related. 6. The ADA data did not raise any particular immunogenicity concerns. The pre-marketing clinical safety data did not raise concerns related to severe allergic reactions with this peptide.	be mitigated through labeling. 4. The risk of CHF will be mitigated by proper patient selection, monitoring and dose adjustment if required. 5. The potential risk for fatal upper GI bleeds will be communicated through labeling and mitigated through proper patient selection and monitoring. The signal will be further characterized and followed in a post-marketing requirement (i.e., an observational study).
Risk Management	1. A post-marketing requirement for an observational study to further characterize the potential relationship between Parsabiv use and upper GI bleeding will be issued. 2. Labeling will be used to mitigate against the real or potential serious risks of hypocalcemia, CHF, and upper GI bleeding. 3. No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).	1. There are insufficient data to conclude whether an association between Parsabiv and GI bleeding is real or the product of chance. More data are needed to reduce the uncertainty around this risk. Several study options (i.e., spontaneous reports, Sentinel) were considered and an observational study was determined to be best suited to address the question. 2. Patient selection, monitoring and interventions will be recommended in labeling to address these risks. 3. No REMS will be issued.

2. Background

On August 24, 2015 Amgen submitted a New Drug Application (NDA) for Parsabiv (etelcalcetide) under Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act in support of the following indication:

> *Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.*

Parsabiv is a novel injectable a calcimimetic that, in the presence of extracellular calcium, enhances the activation of calcium-sensing receptors (CaSR) in parathyroid tissues and suppress the secretion of parathyroid hormone (PTH).

Therapeutic context

Secondary hyperparathyroidism (SHPT) and mineral metabolism abnormalities (e.g., calcium and phosphorus) that occur as a result of chronic kidney disease (CKD) may lead to bone disease (abnormalities in bone turnover, mineralization, and strength) and to extra-osseous calcifications (deposition of calcium in the kidneys and cardiovascular system). Poor bone health could lead to increased fracture risk and bone pain. Calcification of cardiovascular tissues such as the myocardium, conduction system, valves, arterioles and arteries could result in arrhythmias, coronary artery disease, valve disorders, hypertension or other cardiac complications.

To prevent skeletal and cardiovascular complications in patients with secondary hyperparathyroidism (SHPT) and chronic kidney disease, the 2009 Kidney Disease Improving Global Outcomes therapeutic guidelines[4] recommend that subjects with CKD stage 5D (on dialysis) who have elevated or rising PTH levels be treated with calcitriol, vitamin D analogs, a calcimimetic, or a combination of these with the goal of maintaining PTH levels between two to nine times the upper normal limit (UNL) for the assay. Treatment of SHPT with Vitamin D analogs and/or calcimimetics occurs alongside treatment of other prevalent mineral abnormalities (hyperphosphatemia, hypocalcemia) also implicated in bone disease and mineral metabolism disorders associated with chronic kidney disease.

Active vitamin D and vitamin D analogs are the de facto first line agents used for the treatment of SHPT in patients with CKD. The therapeutic forms of vitamin D available on US market include oral and injectable formulations of active vitamin D (calcitriol) or partially active vitamin D analogs (doxercalciferol, paricalcitol). Vitamin D products increase the absorption of calcium and phosphorus from the gastrointestinal tract and can cause hypercalcemia and hyperphosphatemia.

The approved calcimimetic (cinacalcet) is an oral, allosteric activator of the calcium sensing receptor (CaSR). The natural ligand for this receptor is extracellular calcium and cinacalcet

[4] KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

works by activating the receptor at a lower extracellular calcium concentration. Activation of the receptor on parathyroid cells triggers an intracellular second messenger cascade that ultimately results in decreased PTH secretion. Calimimetics do not enhance intestinal calcium and phosphorus absorption and can lower PTH without increasing circulating levels of these minerals. This differentiates them from vitamin D analogs and makes them useful for certain patients. The only a calcimimetic available for the treatment of SHPT in patients on dialysis is Sensipar (cinacalcet). The most common adverse reactions associated with cinacalcet are hypocalcemia, nausea, and vomiting.

Parsabiv is a novel a calcimimetic and, similar to cinacalcet, suppresses the secretion of PTH by activating the CaSR on parathyroid cells. Parsabiv is administered by the intravenous route at the end of dialysis. This may be a more convenient route than the oral route in this population given the expected high daily pill burden for these patients.

Regulatory Issues

Precedent Case Example

As stated above, Sensipar is the only calcimimetic approved for SHPT in patients with CKD on dialysis (refer to NDA 021688, approved in 2004). Sensipar is also approved for the treatment of hypercalcemia in patients with parathyroid carcinoma and for hypercalcemia in patients with primary hyperparathyroidism, however, these indications are not relevant to the current application for etelcalcetide, and thus, will not be discussed in this memo.

The efficacy of Sensipar was established using PTH reduction as a surrogate measure of benefit. Three multicenter, placebo-controlled, randomized, studies conducted in 1136 patients with SHPT and CKD on dialysis (665 patients received cinacalcet and 471 patients received placebo) were used to characterize the safety and efficacy of the product.

Data from these studies demonstrated that 35-46% of patients who received Sensipar and 4-6% of patients who received placebo achieved a PTH concentration of less than 250 pg/ml at trial end (primary endpoint). The primary endpoint for this application was selected based on the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines which, at the time, recommended that patients with CKD on hemodialysis maintain PTH levels between 150 and 300 pg/ml[5]. The proportion of individuals with PTH reduction of greater than 30% from baseline (the primary endpoint used in the etelcalcetide NDA) was a main secondary endpoint in cinacalcet studies. Results obtained with this endpoint were generally consistent with results obtained using the primary endpoint: 59-68% of cinacalcet-treated patients achieved reduction in PTH of > 30% compared to 10-11% of placebo-treated subjects.

As mentioned above, since Sensipar approval the EVOLVE trial was carried out. This trial did not establish that use of Sensipar in patients with CKD on hemodialysis reduced cardiovascular risk.

[5] K/DOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis.2003;42 (suppl3):S1-202.

Parsabiv Regulatory History

This section summarizes the major regulatory interactions for the Parsabiv development program for the SHPT indication:

IND 109773 was opened by KAI Pharmaceuticals on August 19, 2010 with a protocol for a Phase 1b clinical trial to evaluate PK, PD, and safety of KAI-4169 (etelcalcetide) in subjects with stage 5 CKD on hemodialysis and SHPT. The Sponsor was allowed to proceed with this study.

The Agency provided recommendations regarding the development plan for KAI-41649 on February 14, 2012 (refer to the Division's Meeting Preliminary Comments from 2/14/2012 in DARRTS). At this interaction discussion on the selection of a primary endpoint for the Phase 3 program were had. The Agency recommended using the proportion of individuals experiencing a PTH decrease of greater than 30% "as … a clinically relevant response". The Division also recommended comparing the proportions of patients experiencing a reduction in PTH levels to less than equal 300 pg/mL as a secondary endpoint.

Sponsorship of IND 109773 for KAI-4169 was transferred to Amgen from KAI Pharmaceuticals on July 5, 2012.

An End-of-Phase 2 meeting was held on July 9, 2012 to discuss Phase 3 development for Parasabiv. The Division agreed with the Sponsor's plan to conduct two placebo controlled studies in approximately 500 patients with SHPT and CKD on hemodialysis to support the proposed indication (SHPT). The Division agreed that the primary analysis (responder analysis) and primary endpoint (proportion a PTH decrease of greater than 30% from baseline) could be used to establish the efficacy of KAI-4169 for the treatment of SHPT in patients with CKD on hemodialysis. The Division disagreed with the Sponsor's plan to (b) (4) It was agreed that a dedicated QTc study would not be necessary and that ECG could be measured during the Phase 3 studies.

The Statistical Analysis Plan (SAP) for the integrated summary of effectiveness was submitted by the Sponsor on September 12, 2014. The biometric reviewer overall agreed with the proposed statistical plan, including number of pivotal studies to be included in the primary analysis (two pivotal Phase 3 placebo control trials) to evaluate efficacy of the drug in patients with CKD, with study design, primary analysis population (all randomized patients), with handling of missing data, etc. The biostatistician also emphasized that the results of the pooled data analysis will not replace the individual trial results when evaluating the collective evidence of efficacy.

The SAP for the Phase 3 study 20120360 (active control study) was submitted by the Sponsor on September 12, 2014. The Agency overall agreed with the Sponsor's SAP and provided several comments on the proposed SAP (on 1/6/2015).

These comments included recommendations to specify a primary statistical analysis which does not rely on LOCF, to include sensitivity analyses to evaluate the limitation of the missing data and the assumptions made about the missing data for the primary analysis and to include an explanation for what assumptions or limitations are being addressed or evaluated by a sensitivity analysis. In the response to the Agency's letter (1/30/2015), the Sponsor specified that the planned primary analysis uses an imputation under the non-inferiority null method to handle missing data which does not rely on LOCF and that this method was selected based on a previous recommendation from the Agency in the Advice/Information Request letter dated 10 July 2013. The Sponsor also included 3 additional sensitivity analyses in SAP as per the Agency's recommendations. The biometric reviewer also commented on the proposed non-inferiority margin; she found a non-inferiority margin of 12% to be acceptable, however, noted that "a 12% difference between treatment groups in PTH reduction is not considered a clinically meaningful difference" (refer to the review in DARRTS from 12/11/2014).

On October 14, 2013 the Sponsor reprioritized the sequential statistical testing of the key secondary endpoints for superiority claim in study 20120360 (Amendment # 3). The previous protocol version had 2 key secondary endpoints that were to be tested sequentially for superiority: mean number of days of vomiting/nausea per week in the first 8 weeks, followed by achievement of a > 50% reduction in mean PTH from baseline at the end of the study. However, the Sponsor stated that the original order of the testing of these endpoints was based on the results of Phase 2 studies, which were limited in sample size and duration of exposure. Thus, once the results of the Phase 3 placebo-controlled studies became available, the Sponsor decided to reorder the key secondary endpoints to be tested, so that the superiority of endpoints of PTH reduction would be tested first. The Sponsor stated that these changes were implemented before the study was completed (completion date was 1/8/2015), the data from study 20120360 remained blinded, and the changes were not suggested by DMC. However, these changes were not reviewed by the Agency.

On November 7, 2014, the Patient Reported Outcomes (PRO) tool, the Nausea Vomiting System Assessment (NVSA), for evaluating nausea and vomiting adverse reactions associated with Parsabiv and cinacalcet were submitted to the Agency's review. The basis for this request was the Sponsor's original hypothesis that an injectable formulation of a calcimimetic would be associated with less nausea and vomiting compared to oral formulation (cinacalcet). This submission was reviewed by the Clinical Outcome Assessment (COA) Staff in the Office of New Drugs. The COA reviewer determined that the NVSA PRO instrument was unable to distinguish between the concepts of nausea and vomiting and that there was insufficient evidence from 11 patients to support the content validity, understandability and interpretability of the NVSA PRO instrument. Based on review of the content validity evidence provided, the reviewer also recommended changing the language in the label to combine the two concepts into "nausea or vomiting" when describing the results of the study. The above responses and recommendations were sent to the Sponsor on 3/25/2015.

A Pre-NDA meeting was held on May 13, 2015. During this meeting, the Division and the Sponsor discussed and agreed on NDA's content and format and the completeness of the different NDA modules.

The new drug application was submitted on August 24, 2015.

3. Product Quality

The CMC reviewers recommend approval of this application (refer to Dr. Tran's executive summary). There are no recommendations for Phase 4 studies and no outstanding issue that precludes approval. All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance has determined these facilities are acceptable (refer to review in Panorama dated 8/3/2016).

The active pharmaceutical ingredient in Parsabiv, etelcalcetide, is a small synthetic peptide made up of 7D-amino acids linked to L-cysteine by a disulfide bond. The drug substance is a hydrochloride salt in the form of a powder, white to off-white in color, that is highly water-soluble, amorphous and hydroscopic. The CMC reviewer states that the data presented in this submission establishes the identity, purity, and quality of the drug substance and that the specified impurities have qualified limits; a limit of (b) (4)% on an unspecified impurity was agreed upon.

Parsabiv is manufactured as a sterile, preservative-free, ready to use solution for intravenous injection containing 5 mg/ml of etelcalcetide free-base. The Parsabiv presentation is a vial that comes in 3 sizes (2.5 mg/0.5 ml, 5 mg/1 ml, and 10 mg/2 ml). Excipients are sodium chloride, succinic acid, (b) (4), and adjusted to pH 3.3 with sodium hydroxide and/or hydrochloric acid. As per the CMC reviewer, the manufacturing process is standard for this type of dosage form and includes preparation of (b) (4) CMC reviewer concluded that all process parameters are adequately classified.

The biopharmaceutics reviewer, Dr. Hansong Chen, compared the commercial formulation and the earlier (b) (4) formulation (both used in the open-label extension phase 3 studies) and concluded that the two formulations have (b) (4) are not meaningful and would be expected to have a clinical impact. As per the reviewer, a biowaiver request for the change in formulation was granted because both formulations are for i.v. administration where "bioavailability is instant and self-evident" (CFR 320.22(b)).

The drug product specifications were found to be adequate; the three specified degradants are the same as in drug substance specification, with qualified limits.

The container closure system is a USP type 1 glass vial with an elastometric stopper and an aluminum outer seal and was found to be adequate.

A product expiry of 24 months was granted at a storage temperature between 2 and 8 ^{0}C.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues and the pharmacology/toxicology reviewers recommend approval of Parsabiv with no requirements for post-approval nonclinical studies.

The applicant conducted all the required non-clinical studies, including pharmacokinetic and toxicokinetic studies to support the chronic use of etelcalcetide in patients with CKD on hemodialysis.

Nonclinical and in-vitro studies have demonstrated that etelcalcetide specifically binds to and allosterically modulates the activity of the Calcium Sensing Receptor (CaSR). Binding of etelcalcetide on the CaSR in the presence of extracellular calcium reduces PTH secretion from the cells of the parathyroid gland that produce PTH. The reduction in PTH is associated with a concomitant decrease in serum calcium and phosphorus levels.

The toxicology profile observed with etelcalcetide in animals resulted from the expected pharmacologic effects of PTH suppression and was mainly attributable to changes in serum calcium and observed to be consistent across species. Carcinogenicity studies were negative for drug-related neoplasms.

With respect to fatal cases of gastrointestinal (GI) bleeding and GI erosions adverse events observed in the clinical program the pharmacology/toxicology memorandum dated 6/28/2016 indicates that "a weak but biologically plausible link between etelcalcetide and increased clinical bleeding exists…" As per this memo, an exposure and dose dependent signal was observed in the chronic rat toxicity study for stomach erosions with etelcalcetide exposure in the range of human exposure (0.7- and 2.7-fold human exposure). Recovery was noted in animals with the cessation of etelcalcetide dosing. Overt GI bleeding was not observed in animals. Similar findings of GI erosions in toxicity studies were observed with another calcimimetic, cinacalcet, and these findings may suggest that this mechanism of action could potentially predispose to gastric erosions (i.e., a risk factor for GI bleeds).

Local tolerance studies showed no adverse injection site reactions. There was no evidence that immunogenicity affected the validity of any studies, based on the observed plasma etelcalcetide concentrations and PD parameters (PTH and calcium) across all nonclinical studies.

Reproduction studies performed in rats and rabbits did not show impaired fertility, however these studies demonstrated some evidence of harm to the fetus at supratherapeutic etelcalcetide exposures. Thus, the review recommends use of the drug during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of note, patients with end-stage renal disease on dialysis, in general, have low fertility rates because of the effects of hormonal imbalance associated with renal insufficiency, dialysis, other comorbidities and use of concomitant medications.

In conclusion, I concur with Drs. Tsai and Elmore's assessment. There are no nonclinical issue that would preclude approval. The risk of identified toxicities (hypocalcemia and hypocalcemia-related toxicities, GI (b) (4) and bleeding, etc.) can be mitigated through product labeling, appropriate patient selection, monitoring, and timely introduction of treatment and/or discontinuation of the drug.

5. Clinical Pharmacology

The clinical pharmacology review was completed by Dr. Ritesh Jain, and Pharmacometrics review was completed by Dr. Jee E Lee. There are no outstanding clinical pharmacology issues and both reviewers recommended approval of Parsabiv. For a detailed discussion, please refer to their Clinical Pharmacology review in DARRTS dated 5/5/2016.

The drug demonstrates linear PK in healthy volunteers and in CKD patients on hemodialysis over the dose range studied (single dose 5-60 mg and multiple doses 2.5-20 mg), which includes the proposed therapeutic doses (5-15 mg).

In a single ascending dose study in patients with CKD on hemodialysis, Cmax was observed to be less than the dose proportional but the increase in AUC_{65hrs} was dose proportional over the dose range evaluated: a 12-fold increase in dose resulted in 7.86- and 14-fold increase in Cmax and AUC_{65hrs}, respectively.

In plasma, the drug is < 50% protein bound. In patients with CKD on hemodialysis 4 weeks are required to reach steady state etelcalcetide concentrations and the observed accumulation ratio was 3 to 5-fold. The effective half-life is approximately 5-7 days in this patient population. The drug undergoes biotransformation in the blood by reversible disulfide exchange and is metabolically stable. Etelcalcetide is mainly eliminated by hemodialysis. Results of Population PK analyses demonstrated that increasing the dialysis duration from 3 to 6 hours will reduce the accumulation ratio and effective half-life by 27% and 33%, respectively. Absorption and other non-i.v. routes of administration were not studied as the drug is to be administered by i.v. route only.

Data from a single dose Phase 1 study in patients with CKD on hemodialysis demonstrated dose-dependent PTH suppression with a maximum suppression at 60 minutes post-dose; serum PTH levels returned to baseline within 10-24 hours. A single dose of 5 mg decreased PTH by 36% from baseline and a dose of 20 mg decreased PTH by 73% from baseline.

Intrinsic factors (e.g. weight, age, gender) that could influence exposure and activity were evaluated using Population PK analyses. Age, gender, race, and body weight had no clinically relevant effect on the PK of etelcalcetide. Hepatic impairment was not evaluated in etelcalcetide program, since etelcalcetide is not metabolized by hepatic enzymes and is eliminated primarily by dialysis.

Drug-drug interactions studies were not conducted in etelcalcetide development. Dr. Jain concludes that based on in-vitro study results, no PK drug-drug interactions are expected with etelcalcetide.

Both reviewers recommend a starting dose of 5 mg three times a week with titration in 2.5 to 5 mg increments based on PTH response and calcium levels up to a maximum dose of 15 mg three times a week. These recommendations are based on the dose response data from a Phase 1 single ascending dose study, two multiple ascending dose studies, safety and efficacy data from two Phase 3 pivotal trials, and on the results of Population PK analyses. Dr. Jain also

notes that patients with higher baseline PTH levels will need higher doses of etelcalcetide for PTH control.

Pop PK analyses conducted by Dr. Lee demonstrated a dose-response relationship for hypocalcemia (hypocalcemia is one of the major safety concerns with etelcalcetide). Simulations based on the PK/PD analysis indicate that the proportion of subjects with a low calcium (i.e., corrected Ca< 7.5 mg/dl) following 2.5 mg, 5 mg, 10 mg, and 15 mg fixed doses increases with increasing dose. Dr. Lee concludes that the titration algorithm implemented in the Phase 3 studies (i.e., by 2.5-5 mg increments based on PTH and calcium levels) is "expected to provide reasonable calcium lowering, while maintaining an acceptable safety profile".

Oversuppression of PTH predisposing to adynamic bone disease is another safety concern with etelcalcetide, Dr. Lee also conducted analysis to assess the relationship between doses and PTH levels by examining doses in patients with PTH <100 pg/ml and in patients with PTH>100 pg/ml in the phase 3 studies. The results of her analysis demonstrated that patients with PTH<100 pg/ml tended to receive lower doses of etelcalcetide compared to patients with PTH > 100 pg/ml. Thus, she concludes that dose did not predict PTH suppression. This analysis is very limited and in my opinion provides little useful information since use of higher doses of etelcacetide in the clinical program were only used in patients who did not respond to lower doses and any analysis of these data is subject to important selection bias.

Lastly, a dosing frequency of three times weekly at the end of hemodialysis sessions is based on the fact that the drug is eliminated by hemodialysis.

The formulation used in the clinical program (b) (4) is different than the to-be-marketed formulation (ready to use liquid drug product). No bridging studies were conducted by the Sponsor; OPQ-Biopharmaceutics group granted a waiver from in-vivo BE study requirements (refer to CMC section above).

6. Clinical Microbiology

Quality microbiology data was reviewed by Dr. Peggy Kriger on April 20, 2016. No concerns were identified by Dr. Kriger and she recommended approval on the basis of sterility assurance.

7. Clinical/Statistical- Efficacy

This memorandum will focus mainly on the design and the results of three randomized controlled Phase 3 studies because these trials include the most comprehensive assessment of efficacy and safety of Parasabiv to treat secondary hyperparathyroidism in the intended population (i.e., patients with CKD on hemodialysis).

Studies 20120229 and 20120230, referred to as 229 and 230 from hereon in, are randomized, double-blind, placebo-controlled, multi-center, parallel group, 26-week studies. The data from these studies are considered pivotal to establishing the efficacy and safety of Parsabiv for the

proposed indication. Study 20120360, referred to as 360 from hereon in, was a randomized, double-blind, active-controlled, multi-center, parallel group, 26-week study comparing Parsabiv to Sensipar. The results of this study are considered supportive for the indication and were submitted to support the claim that the efficacy of Parsabiv is superior to that of cinacalcet. (b) (4)

The two pivotal studies and the supportive active-control study will be discussed separately. (b) (4) at treating complications of SHPT in patients on hemodialysis. A focus of my memorandum will address whether the sponsor's single active comparator trial provides substantial evidence to support a conclusion that the effectiveness of Parasabiv in patients with SHPT on hemodialysis is clinically superior to that of Sensipar. Other studies conducted within the etelcalcetide clinical program will not be discussed in details in this memorandum and will be referenced as needed only.

Pivotal Studies Establishing Efficacy and Safety: 229 and 230

The design of both pivotal Phase 3 placebo controlled studies was identical; thus I will focus attention on the design of study 229 only. Study 230 will be referenced as needed.

Study 229 was a randomized, double blind, placebo-controlled, multicenter, parallel-group, 26-week study that investigated the use of Parsabiv for the treatment of SHPT in adults with CKD on hemodialysis. Studies 229 and 230 were conducted at 111 and 97 sites, respectively, in the US, Canada, Israel, Europe, and Australia.

The primary objective of the study was to evaluate the efficacy of etelcalcetide versus placebo in reducing plasma PTH by ≥ 30% from a pre-treatment baseline.

The secondary objectives of the study were to evaluate the efficacy of etelcalcetide versus placebo in reducing PTH levels to < 300 pg/ml, to evaluate effect of the drug on serum calcium and phosphorus, and to evaluate the safety of etelcalcetide in the intended population.

Eligible Participants

Patients eligible to participate in the study were adults older than 18 years of age, with CKD requiring hemodialysis three times a week for at least 3 months were and with a diagnosis of SHPT. SHPT was defined by documenting a mean PTH levels of greater than or equal to 400 pg/ml obtained across 2 consecutive visits within 2 weeks prior to randomization. The enrollment of patients with PTH >1000 pg/ml was limited to 20% of subjects.

The selected lower inclusion criterion for PTH levels of (mean level of greater than or equal to 400 pg/ml) is consistent with KDIGO[6] guidelines (KDIGO guideline 4.2.4) which

[6] KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113):S1-130.

recommend maintaining PTH levels in the range of 2 to 9 times the upper normal reference range and to initiate treatment with vitamin D analogs and/or calcimimetics (based on serum calcium and phosphorus levels) to avoid progression to levels outside of this range and thereby reduce the risk of renal osteodystrophy. It should be noted that, the diagnosis of renal osteodystrophy is a histological diagnosis made on bone biopsy. None of the patients in the pivotal studies had bone biopsies performed.

In order to participate in the study, patients were also required to have a normal serum calcium levels (≥8.3 mg/dl) at two screening visits. Subjects were allowed to continue taking calcium supplements, phosphate binders, and vitamin D sterols throughout the study. Phosphate binder dose was allowed to be adjusted during the study based on 2 consecutive serum phosphorus levels to maintain phosphorus level between 3.5 and 5.5 mg/dl; the doses of vitamin D analogs and calcium supplements were allowed to be modified if serum calcium levels were outside the normal reference range. The use of cinacalcet was prohibited within 4 weeks prior screening labs and throughout the study.

Study Design

The study was comprised of a screening period, a 27-week treatment period, and a 30-day follow up period. All patients were randomized to receive Parsabiv or placebo in a 1:1 ratio, and randomization was stratified according to baseline PTH levels (i.e., <600 pg/ml, 600-1000 pg/ml, >1000 pg/ml), cinacalcet use within 8 weeks prior to randomization, and region (North America vs. Non-North America).

The starting dose was 5 mg i.v. three times a week at the end of the hemodialysis, before or during rinse-back. The dose was allowed to be increased every 4 weeks starting at week 5 (appropriately selected based on the time to achieve steady state of the drug, refer to Clinical Pharmacology section above) through week 17. The dose titration was based on single predialysis PTH and serum calcium values using dose increments of 5 mg (if PHT > 450 pg/ml and serum calcium > 7.5 mg/dl) or 2.5 mg (if PTH was in range of 300-450 pg/ml and calcium > 7.5 pg/ml). The titration goal was to achieve target PTH level < 300 pg/ml and serum calcium level > 7.5 mg/dl. The maximum dose was 15 mg three times a week. The dose was allowed to be decreased or suspended if two consecutive PTH vales were < 100 pg/ml or serum calcium was < 7.5 mg/dl or symptomatic hypocalcemia occurred.

Primary Efficacy Outcome

The primary efficacy endpoint was a responder analysis examining the number of subjects in the Full Analysis Set population (defined as all subjects who were randomized at baseline) who experienced a mean decrease of ≥ 30% in plasma PTH from baseline during the efficacy assessment period (i.e., weeks 20 to 27).

It should be noted that a required number of PTH values collected during EAP was not prespecified, thus, the patient could be considered as a responder based on a single PTH value collected during the efficacy assessment period (i.e., EAP) or on a mean PTH value calculated from up to 6 PTH measurements obtained during weeks 20 to 27. The majority of patients had

more than two PTH values (97%-98% patients) and 95% of patients had more than three PTH measurements during the EAP in both studies. The biostatistician also notes in his review that not all patients who were considered "responders" at end of trial were also "completers" of the study. The design made it possible for a subject to have one EAP measurement at week 20 and to be counted as a responder or non-responder, and then to discontinue treatment preliminary at this point due to adverse events or other reasons.

Subjects who did not have at least one PTH value during the EAP were classified as non-responders in the primary analysis. The percentage of patients missing at least one measurement in the EAP was 10-12% in both studies, distributed evenly across treatment groups. Dr. Cambon confirmed that the Sponsor's method of handling missing data (i.e., treating missing as non-response) was conservative and acceptable.

The selection of PTH reduction as a surrogate endpoint to establish clinical benefit in SHPT is briefly discussed below.

- As summarized in Dr. Lubas' review, Sensipar and currently marketed vitamin D analogs were approved for the treatment of SHPT in patients with CKD on hemodialysis based on their PTH lowering effects (mean decrease in PTH levels or decrease > 30%).

- Elevated PTH levels in patients with CKD are associated with metabolic bone disease and risk for soft tissue calcifications and, calcimimetics and vitamin D analogs improve biochemical endpoints associated with SHPT and metabolic bone disease (PTH, calcium, phosphorus, alkaline phosphatase, bone turnover markers, etc.). The improvement in PTH may translate into improved bone health and prevent soft tissue calcifications. These changes would be expected to improve clinical outcomes related to these complications (i.e. bone fractures, pain and decreased end-organ damage). Although there are no data from prospective clinical trials directly demonstrating that reduction in PTH levels with cinacalcet or vitamin D improves clinical outcomes (e.g., bone fractures, cardiovascular disease, etc.), the Division has accepted PTH reduction as a surrogate marker of benefit for this indication. The Division's approach is consistent with expert opinions described in past and current treatment guidelines for chronic kidney disease management (KDIGO 2009) which recommend treating elevated PTH and factors that contribute to secondary hyperparathyroidism (hyperphosphatemia, vitamin D insufficiency, hypocalcemia) to prevent mineral and bone complications of CKD. Large trials of long duration would be required to examine the effect of calcimimetics and vitamin D treatment on hard outcome measures and the trials may not be feasible in this population. In the absence of clinical trial data directly informing the question of clinical benefits gained by normalizing PTH, calcium, and phosphorus in the setting of CKD, the Division continues to accept PTH reduction as a surrogate to determine the efficacy of calcimimetics and vitamin D analogs.

- Lastly, as noted in Dr. Cambon's review, the Agency indicated during the EOP2 meeting that "the proposed primary endpoint [reduction in PTH of greater than 30%] is adequate to demonstrate the efficacy of KAI-4169 for the treatment of SHPTH in patients with CKD on hemodialysis".

Baseline Demographics and Disposition

A total of 1023 patients with CKD on hemodialysis were enrolled in the two pivotal studies and received etelcalcetide (509 patients) or placebo (514 patients). Of these, 508 subjects were randomized in Study 229 to receive placebo (N=254) or etelcalcetide (N=254), and 515 subjects were randomized in study 230 to receive placebo (N=260) or etelcalcetide (N=255). Completion rate was approximately 82% in each study.

In both studies main demographic and disease characteristics were balanced between groups. Approximately 50-55% of patients were enrolled in US centers (refer to Dr. Cambon review). The mean age of patients was ~58 years; the primary cause of CKD was diabetes mellitus, followed by hypertension. Patients had been on hemodialysis for an average of ~ 5 years. The mean PTH level was ~ 845 pg/ml and about 20% of subjects had PTH levels exceeding 1000 pg/ml in each treatment group at baseline. Mean calcium and phosphorus levels were ~9.6 mg/dl and 5.9 mg/dl at baseline respectively.

Primary Analysis Results

Dr. Alexander Cambon reviewed the primary statistical analysis methods used to support the establishment of efficacy. Efficacy findings are also reviewed and discussed in Dr. William Lubas' review. For detailed discussions of the efficacy findings, see both of these reviews. My memorandum provides a summary of the main efficacy findings.

Dr. Cambon independently verified the Sponsor's results for the primary analysis and concludes that both pivotal studies establish the superiority of etelcalcetide over placebo in terms of significant (i.e., >30%) reduction in PTH from baseline (Table 1).

Table 1: Number and percentage of patients with PTH reduction > 30% at EAP in the Full Analysis Set (FAS) population in Study 229 and Study 230[b].

	Etecalcetide	Placebo	p value[a]
Study 229 Responders, n (%)	N=254 **188 (74)**	N=254 **21 (8)**	<0.001
Study 230 Responders, n (%)	N=255 **192 (75)**	N=260 **25 (10)**	<0.001
Combined Responders, n (%)	N=509 **380 (74.7)**	N=514 **46 (8.9)**	<0.001

[a]Based on the Cochran-Mantel-Haenszel test,
[b] Subjects with missing data during EAP are counted as non-responders
FAS defined as all randomized subjects. Source: Adapted from Dr.Cambon's review.

The primary efficacy analysis was repeated under different scenarios and imputations including a Completer Analysis Set wherein only subjects with at least one PTH value during the EAP were included. The difference between treatments arms remained statistically significant. Similarly, using a Modified Last values Carried Forward Set analysis wherein subjects with at least 8 weeks of drug exposure and missing an EAP value had the last previous value carried forward, the difference was still statistically significant (refer to Dr. Lubas' review).

Dr. Cambon and Dr. Lubas confirmed that the efficacy results were consistent across all prespecified subgroups examined, including subgroups defined based on baseline PTH categories, geographic region, and prior history of cinacalcet use (indicating response was not driven by selection based on previously established sensitivity to calcimimetics). Dr. Lubas also noted that there was no consistent difference in efficacy with respect to baseline screening PTH levels. However, responders tended to have PTH levels of less than 1000 pg/ml at baseline. It is likely that this threshold selects patients with less severe/advanced parathyroid hyperplasia at baseline and patients who are more likely to respond to medical therapy with a calcimimetic.

The biostatistician also repeated the primary analysis excluding patients who had an increase in vitamin D and calcium doses during the trials from baseline, since the treatment protocols permitted the modification of doses of these PTH-lowering medications during the trial and these medications may confound the primary efficacy results. The results of this analysis demonstrated that even though the effect size was slightly lower in both groups (as expected), there were still significantly more responders in the etelcalcetide group compared to placebo group when this confounder was removed.

Lastly, Dr. Lubas also analyzed those patients who had protocol violations and used another PTH-lowering drug, cinacalcet, during the study. He concluded, that that this protocol violation occurred in a small number of subjects only and was evenly distributed with ≤2% difference between treatment group, thus, it is unlikely that the small % of subjects treated concomitantly with cinacalcet during the study would have changed the overall efficacy results.

Secondary Analyses

Dr. Cambon and Dr. Lubas verified that the analysis carried out on secondary endpoints were statistically rigorous (including multiplicity adjustment using a hierarchical testing procedure) and were supportive of the primary analysis.

Briefly, the proportion of subjects achieving a predialysis PTH level of less than 300 pg/ml during the EAP in the FAS population was much higher in the etelcalcetide group than in placebo. Approximately 50% of subjects who received etelcalcetide (versus ~ 5% on placebo) in each study had a decrease in PTH levels below 300 pg/ml during EAP.

It should be noted however that the selection of PTH level < 300 pg/ml as an important clinical threshold was derived from earlier KDOQI guidelines (2003), which recommended maintaining PTH levels in the range of 150 to 300 pg/ml in patients with SHPT due to CKD on hemodialysis. However, these recommendations have since changed and the 2009 KDIGO guidelines do not recommend aiming for a specific PTH target and recognize either the absence of data or limitation around the available existing data to make an informed and firm recommendation on an ideal treatment threshold. The current KDIGO guidelines (2009) now recommend maintaining PTH within two to nine times the upper normal limit for the assay

(i.e. ~ 144-648 pg/ml depending on the assay). Thus, this endpoint provides little additional useful information over the primary endpoint.

As per Dr. Lubas' review, statistically significant differences between groups were noted for mean changes in PTH, Calcium, Calcium Phosphorus product (Ca x P product) and phosphorus from baseline in both studies (Table 5). It also should be noted that the 2009 KDIGO guidelines recommend using individual serum calcium and phosphorus values rather than the mathematical construct of Ca X P, since it is largely driven by serum phosphorus (3.1.5). Thus, changes in Ca X P product are not included in the table below and will not be discussed in this memorandum (refer to Dr. Lubas' review for details). I also recommend

(b) (4)

Table 5: Percent Change from Baseline to EAP in mean PTH, corrected calcium, and phosphorous (Full Analysis Set)

	PTH		Calcium		Phosphorus	
	n	Mean (SE),%	n	Mean (SE),%	n	Mean (SE),%
Study 229						
Placebo (n=254)	219	13 (2.8)	219	1.18 (0.29)	214	-1.31 (1.42)
Etecalcetide (n=254)	229	-55.1 (1.94)	229	-7.29 (0.53)	227	-7.7 (2.16)
Treatment difference [a]						
Estimate[b] (SE), %	-71.1 (3.39)		-8.38 (0.58)		-7.45 (2.47)	
(95%CI),%	(-77.77, 64.46)		(-9.52, -7.23)		(-12.31, -2.59)	
p-value	<0.001		<0.001		0.003	
Study 230						
Placebo (n=260)	237	13.7 (2.5)	237	0.6 (0.29)	234	-1.6 (1.42)
Etecalcetide (n=255)	227	-57.4 (1.9)	227	-6.7 (0.55)	223	-9.6 (1.6)
Treatment difference [a],						
Estimate[b] (SE), %	-71.3 (3.1)		-7.2 (0.6)		-8.04 (2.1)	
(95%CI),%	(-77.5, 65.1)		(-8.4, -6.3)		(-12.1, -3.9)	
p-value	<0.001		<0.001		<0.001	
Combined						
Placebo (n=514)	456	13.4 (1.9)	456	0.9 (0.2)	448	-1.5 (1)
Etecalcetide (n=509)	456	-56.2 (1.4)	456	-7 (0.4)	450	-8.7 (1.3)
Treatment difference [a],						
Estimate[b] (SE), %	-71.3 (2.3)		-7.8 (0.4)		-7.6 (1.6)	
(95%CI),%	(-75.8, 66.8)		(-8.6, -6.9)		(-10.8, -4.4)	
p-value	<0.001		<0.001		<0.001	

n= number of subjects with observed data in the analysis set;
[a] adjusted analysis: mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates, [b] Estimated difference in mean percent change during the EAP for corresponding lab parameter between the treatment groups (AMG416-placebo)
Source: Dr. Lubas' review, Table 14, page 57 and Table 18, page 69

Exploratory Endpoints

Both trials also included evaluation of changes to a bone specific hormone involved in the regulation of phosphorus levels (i.e., FGF-23) and to bone turnover markers [bone-specific

alkaline phosphatase (biomarker of bone formation), and type 1 collagen C-telopeptide (biomarker of bone resorption)] as exploratory endpoints. These markers are not qualified clinical surrogates but the direction of change in these markers appear to suggest that the effect on PTH was temporally associated with reduction in FGF-23 (consistent with the direction of change noted for phosphorus) and reduction in net bone resorption.

It should be noted however that even though descriptive analysis of mean changes in these biomarkers demonstrated some between-group differences, interpretability of the clinical meaningfulness of the difference is difficult since it is unknown what magnitude of the observed change could reasonably be expected to translate to clinical benefit (i.e. improvement in fracture rates) or on the contrary could signal an increased risk for adynamic bone disease. Overall, data from the pivotal trials are not designed to allow a rigorous direct assessment of the effect of etelcalcetide on bone structure or morphology and the biomarker findings are considered exploratory.

Supportive Comparative Effectiveness Study: Study 360

Although Study 360 was not a pivotal study, it warrants additional discussion (b) (4)

(b) (4)

This was a Phase 3, multicenter (164 centers in US, Europe, Canada, New Zeeland and Turkey), active-control, double blind, double dummy study to compare the therapeutic efficacy and safety of oral doses of cinacalcet with intravenous doses of etelcalcetide in patients with SHPT and CKD on hemodialysis.

This study was designed as a non-inferiority trial to demonstrate that the treatment with etelcalcetide is not clinically worse than treatment with cinacalcet for lowering PTH in patients with SHPT on dialysis. Establishing that etelcalcetide was superior to cinacalcet in reducing PTH from baseline by 50% and 30% was a secondary objective of the trial. Other secondary objectives were to demonstrate that etelcalcetide is superior to cinacalcet based on changes to serum calcium, phosphorus, and severity of nausea and vomiting (assessed as number of episodes of vomiting per week by PRO instruments).

The design of the study was similar to the design of pivotal trials 229 and 230. Thus, I will discuss the design of study 360 only briefly, focusing mainly on how it differs from the pivotal studies.

Eligible Participants

The inclusion and exclusion criteria in Study 360 were generally similar to criteria in the pivotal studies. Study 360 however, allowed enrollment of patients with higher PTH levels, and thus, with more severe parathyroid disease. Patients were eligible to participate in the study if their PTH was > 500 pg/ml (compared to PTH> 400 pg/ml in the pivotal studies) and a 20% cap on enrollment for patients with PTH >1000 pg/ml was not used. Additionally,

enrollment in the Study 360 required that patients undergo longer washout from cinacalcet (3 months) compared to washout period implemented in studies 229 and 230 (2 weeks) allowing PTH to rise to higher levels and to stay elevated for a longer period of time prior to randomization. Similar to the pivotal studies, patients were allowed to continue taking calcium supplements, phosphate binders, and vitamin D sterols throughout the study.

Study Design

The study design and duration were similar to those of the pivotal studies. The total duration of treatment was 27 weeks, with dose titration occurring in the first 17 weeks and the efficacy assessment phase (i.e., EAP) from week 20 to week 27. All patients were randomized to receive Parsabiv or cinacalcet in a 1:1 ratio. Randomization was stratified by region (similarly to the patients in pivotal studies), and by baseline PTH values (<900 pg/ml, or >900 pg/ml).

The etelcalcetide starting and maximum doses (5 and 15 mg), titration schedule (i.e., every 4 weeks based on PTH and calcium levels), dose increments (2.5 mg or 5 mg) and titration period (17 weeks) were the same as those used in the two placebo-controlled trials.

Patients randomized to cinacalcet followed the same titration schedule as for etelcalcetide (every 4 weeks until week 17, based on PTH and calcium levels). The starting dose for cinacalcet was 30 mg oral daily and the maximum dose was 180 mg oral daily.

Doses of each product could be titrated up at weeks 5, 9, 13, and 17 to achieve predialysis serum PTH between 100 and 300 pg/mL while maintaining serum calcium of greater than or equal to 8.3 mg/dL. Doses or dose increase could be held for safety reasons (refer to Dr. Lubas' review for specific criteria).

Figure 1: Titration Instructions

PTH (pg/mL)	IV Investigational Product Dose	Oral Investigational Product Dose*
PTH > 450	Increase dose by 5 mg	Increase dose by 30 mg
300 < PTH ≤ 450	Increase dose by 2.5 mg	Increase dose by 30 mg
PTH ≤ 300	Maintain dose	Maintain dose

*Note that the oral investigational product dose increases from 120 mg to 180 mg

Differences between the two treatment groups in the titration regimen favored the etelcalcetide group for the following reasons;

1. **The starting dose favors etelcalcetide:** The starting dose of etelcalcetide represents ~30% of the maximally effective dose (i.e., 15 mg). The starting dose of cinacalcet represents 17% of the maximally effective dose (i.e., 180 mg).

2. **The dose escalation instructions favor etelcalcetide:** Etelcalcetide could be increased in 2.5 or 5 mg increments up to 15 mg at the discretion of the investigator. Maximally effective doses could be reached in 5 or 3 dose escalation steps respectively. Each

etelcalcetide dose escalation allows for a dose increase representing 30% of the maximally recommended dose. Cinacalcet was increased in 30 mg increments up to 180 mg (30, 60, 90, 120, 180 mg). At least 4 dose escalation steps or 17 weeks were required to reach the maximum cinacalcet dose. Each cinacalcet dose escalation allows for a dose increase representing 17% of the maximally recommended cinacalcet dose. Patients in the etelcalcetide group had the opportunity to reach a maximally recommended dose in in less time (i.e., 12 weeks) than patients in the cinacalcet arm and had on average the opportunity for larger relative dose increases with each dose escalation step.

3. **The time allowed for titration favors etelcalcetide:** The time allotted to reach maximally effective doses was limited to 17 weeks and this handicapped the cinacalcet arm disproportionally as discussed above. This bias may have been made worse by other elements of the trial design. For example, doses were not allowed to be increased in patients who had their dose reduced within last 3 weeks. Thus, if a patient in the cinacalcet group required a single dose reduction (e.g., to decrease dose from 60 mg to 30 mg), the time to the next dose increase was at minimum 7 weeks, and in these patients greater than 17 weeks was required to reach a maximally effective dose.

As shown on page 86 of Dr. Lubas' review, subjects randomized to etelcalcetide were using doses of etelcalcetide that were on average closer to the maximally recommended doses for the product at the efficacy assessment phase. There were no differences in disposition or adverse events that were found to explain these findings.

Pre-specified Primary and Secondary Analyses

The primary efficacy endpoint in study 360 was the same as in the pivotal studies, 229 and 230 [i.e., the proportion of individuals in the Full Analysis Set population who experienced a mean decrease of greater than 30% in plasma PTH from baseline in the efficacy assessment period (EAP)].

A non-inferiority margin of 12% was selected based on data from the EVOLVE study (5-year Sponsor's trial evaluating the effect of cinacalcet on cardiovascular disease in patients with CKD on hemodialysis)[7]. In this trial, 60 and 25% of patients in the cinacalcet and placebo arm had a 30% reduction in PTH from baseline, respectively. The 2-sided 95% CI for the treatment difference was 31% and 39%. The biostatistics reviewers confirmed that the proposed non-inferiority margin of 12% would preserve at least 50% of the minimum cinacalcet effect and meet applicable standards and FDA guidance and would be acceptable. In the initial SAP review for study 360 submitted on 9/12/2014 it was noted that a 12% difference in response between treatment groups would not be considered a clinically meaningful loss of efficacy (refer to Dr. Sinks's review in DARRTS from 12/10/2014).

Subjects who did not have at least one PTH value during the EAP were classified as non-responders in the primary analysis. The percentage of patients missing at least one measurement in the EAP was 11% and distributed evenly across the two treatment groups. Dr.

[7] Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R et al. N Engl J Med. 2012 Dec 7;367(26):2482-94.

Cambon confirmed that the Sponsor's method for handling missing data was acceptable. The majority of patients who were evaluated during EAP had more than two PTH values (99%) and 97% of patients had at least three PTH measurements during EAP in both studies.

The following three key secondary endpoints were to be tested in the FAS population sequentially in order to evaluate the superiority of etelcalcetide compared to cinacalcet:

- the proportion of individuals in the Full Analysis Set population who experienced a mean decrease of greater than 50% reduction from baseline in PTH during the EAP
- the proportion of individuals in the Full Analysis Set population who experienced a mean decrease of greater than 30% reduction from baseline in PTH during the EAP
- the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment.

Baseline Demographics and Disposition

A total of 683 patients with CKD on hemodialysis were enrolled in this trial and received etelcalcetide (343 patients) or cinacalcet (340 patients). Completion rate was approximately 85% in each arm.

The two groups were well balanced at baseline with respect to main demographic and disease characteristics. Approximately 26% of patients were enrolled in US centers (refer to Dr. Cambon review). The mean age of patients was 55 years. The primary cause of CKD was diabetes mellitus, followed by hypertension. Patients had more parathyroid disease in study 360 compared to patients enrolled in the two pivotal placebo-control studies. The mean PTH levels were ~1100 pg/mL compared to 820 pg/ml in the pivotal studies. The mean calcium and phosphorus levels were 9.7mg/dl and 5.8 mg/dl respectively.

Primary Analysis Results

The efficacy results of the study 360 will be briefly summarized below; for detailed discussion of the results refer to Dr. Cambon's and Dr. Lubas' reviews.

The results of the primary efficacy analysis conducted in the full analysis set, using non-responder imputation (i.e. all subjects with missing data during EAS were considered as non-responders), suggest that a numerically higher proportion of patients in the etelcalcetide group had reduction in PTH levels from baseline of at least 30% [68.2% for etelcalcetide (232/340) vs. 57.7% for cinacalcet (198/343); p-values=0.004)]. The treatment difference was estimated to be 10.5% [95% CI (-17.45, -3.51)] and the upper bound of the 95% CI of the treatment difference excludes the pre-specified non-inferiority margin (12%). This suggests that at the doses used in the trial etelcalcetide was not unacceptably worse than cinacalcet at controlling PTH. However, this estimate of the difference is likely biased since the two products were not compared at maximally effective doses and titration scheme favored etelcalcetide over cinacalcet. Ultimately the exact difference in efficacy between etelcalcetide and cinacalcet is unknown.

Drs. Cambon and Lubas confirmed that the primary analysis results were consistent across prespecified subgroups tested including baseline PTH categories and geographic regions.

Analyses of Secondary Endpoints

As discussed above, superiority hypotheses were tested for the key secondary endpoints. These analyses were conducted in the FAS population assuming that patients in the FAS who did not have at least one PTH value during the EAP were non responders. As stated in Dr. Cambon's review, the null hypothesis was rejected for the first two key secondary endpoints. However, differences between groups for the third endpoint (the reduction in mean number of days of vomiting or nausea per week in the first 8 weeks) did not reach statistical significance and endpoints in the hierarchy beyond this endpoint were not tested for statistical significance (mean serum calcium levels, mean serum phosphorus level, severity of nausea and number of episodes of vomiting).

Since the applicant seeks to claim that etelcalcetide is clinically superior to cinacalcet based on the observation of a differential PTH lowering response, I will focus my review on analyses of these secondary endpoints and on the merit of the superiority claim. Other findings were summarized in details in Dr. Lubas' review.

The analysis of the first two key secondary endpoints demonstrated numerical differences between groups that were found to be statistically significant. In these analyses, a higher proportion of patients in the etelcalcetide group had a reduction in PTH levels of greater than 50% and 30%, respectively compared to cinacalcet group (refer to Table 7 in Dr. Cambon's review). In the first of the two secondary analysis, 52% of subjects in the etelcalcetide group and 40% of subjects in the cinacalcet group had a PTH reduction of greater than 50% (p-value=0.0015). Differences in response rate for PTH reduction of greater than 30% are discussed as part of the primary analysis above. These analyses suggest that at doses of etelcalcetide and cinacalcet achieved in the trial more subjects in the etelcalcetide group met pre-specified target PTH reduction thresholds.

Even though statistical differences in response rates between treatment groups were observed in these secondary analyses it is unclear whether the estimate of the between group efficacy difference is free of bias as discussed above. Notwithstanding the issue of bias in the estimate of the treatment difference, it is uncertain whether a difference (95% CI) in response of 10.5% (17.45, 3.51) is clinically important (recall that a difference of 12% was not considered clinically relevant for the purpose of establishing a non-inferiority margin).

The two major issues which affect the overall interpretability of the comparative efficacy results and claim are summarized below.

1. **The first issue is related to the fact that cinacalcet dosing in the trial was suboptimal and in the majority of patients cinacalcet was not used at the highest recommended dose. The trial data did not reveal obvious reasons to explain differential suboptimal dosing (e.g., more dose limiting tolerability issues in one arm versus another).**

The ICH E10 guidance recommends that the control, in an active comparator trial, be used at "an appropriate dose and regimen, generally the highest recommended dose[8]". The average daily doses achieved in Study 360 were lower than the maximum recommended doses for either product. In the etelcalcetide group an average dose of 6 mg was achieved (40% of the maximally recommended dose) and in the cinacalcet group an average dose of 48 mg was achieved (30% of the maximally recommended dose). Refer to the applicant's response to an Agency information request dated 7/12/2016 and page 85-86 in Dr. Lubas' review. The efficacy comparison was therefore not performed at maximally recommended doses.

At the end of the study, disproportionally more responders in the etelcalcetide group than responders in the cinacalcet group were on maximally recommended doses of each respective product [30/210 patients (14.3%) vs. 10/184 patients (5%), respectively]. In contrast, at the end of the study disproportionally less nonresponders in the etelcalcetide group than nonresponders in the cinacalcet group were on the lowest recommended dose of each respective product [11/106 (17%) versus 28/143 (29%), respectively]. These data highlight dosing discrepancies between treatment groups and suggest dosing was not optimized. These factors rather than intrinsic differences between products could have explained the observed efficacy differences.

The reasons for the lack of dose optimization in the trial are unclear. One contributor alluded to earlier may have been a differential, and biased, dose escalation schedule between etelcalcetide and cinacalcet (refer to the discussion in the study design section above). More patients in the cinacalcet group (20%) required the dose to be increased during the last week of the titration period (week 17) compared to patients in the etelcalcetide group (8.6%) suggesting the dose escalation regimens were not comparable (i.e., time to reach optimal dosing was not comparable). A longer titration time in the cinacalcet arm may have negated any difference in efficacy between products.

Another reason may be related to tolerability issues preventing dose increase more in one group than another. The Sponsor indicated that the major reasons for not maximizing the doses were drug-related and due to intolerability, adverse events and/or hypocalcemia in the overall trial. However, as noted in Dr. Lubas' review, the incidence of nausea and vomiting was the same in both treatment groups and etelcalcetide groups had more events of hypocalcemia. This should have placed etelcalcetide at a disadvantage for dose increase. Additionally, as per Sponsor's analyses, the incidence of the adverse event that led to treatment interruption was the same in both groups: 41% in the cinacalcet group and 43% in the etelcalcetide group. Tolerability issues do not explain the inadequate dosing in the cinacalcet group.

2. **The second interpretability issue relates to the meaningfulness of the magnitude of the treatment difference observed at 26 weeks.**

[8] International Conference on Harmonization (ICH) guidance E10 (Choice of Control Group and Related Issues in Clinical Trials).

The superiority claim is based on a short term, small, between group difference on a surrogate endpoint. The estimated between group difference in response rate is small (~ 11%) and of unknown clinical significance. Recall that for the purpose of establishing a non-inferiority margin, a difference of 12% was not considered a clinically important difference. In addition, absolute differences in mean PTH changes from baseline to week 22, 24, and 26 between etelcalcetide and cinacalcet groups were small (389-525 pg/ml vs. 417- 515 pg/ml, respectively). As alluded to earlier the strength of the relationship between 26-week PTH differences and longterm clinical outcomes has not been robustly defined.

Overall, the comparative efficacy claim is based on a single trial. As per FDA guidance, "reliance on only a single study (to form the basis for a claim) will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible[9]". These "situations" are not applicable to Study 360. Conducting a second confirmatory trial in patients with CKD and SHPT would be ethically and practically possible and, in light of the dosing issues in this trial, desirable. The comparative PTH lowering effect of both drugs used at the maximum recommended dose remains unknown.

To conclude, I disagree that Study 360 establishes that etelcalcetide has a superior PTH lowering efficacy than cinacalcet. The superiority claim is based on the results of a single short term study comparing the effect of two sub-optimally dosed drugs on a surrogate measure. This level of evidence would not qualify as substantial evidence per 21 CFR 201.57(c)(2)(iii). The problem of suboptimal dosing appeared to affect the cinacalcet group disproportionally and raises concerns about the fairness of the comparison. Notwithstanding this major issue, the difference between groups is relatively small in magnitude and is unlikely to be clinically important. Finally the safety data in the application do not suggest the safety profile of etelcalcetide is superior to cinacalcet. (b) (4)

(b) (4)

Other Secondary Endpoints

The third key secondary endpoint, (mean number of days of vomiting or nausea during the first 8 weeks of treatment) difference between etelcalcetide and cinacalcet groups; the mean number of days of vomiting or nausea in both groups was similar [mean = 1 day, (95% CI; 0.9, 1.2) vs. mean =1 day, (95% CI; 0.8, 1.2), respectively). No difference was observed in severity or number of episodes of vomiting between groups either. Dr. Lubas also noted that treatment with etelcalcetide resulted in lower calcium and phosphorus levels compared to cinacalcet. Thus, the safety profile of etelcalcetide is not superior to cinacalcet and might even be slightly

[9] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998.

worse than the cinacalcet safety profile, since the greater decrease in calcium and phosphorus level with etelcalcetide treatment might be associated with greater frequency of hypocalcemia and hypophosphatemia that is symptomatic and/or requiring treatment as compared to cinacalcet.

Extension Data

During open-label single-arm extension trials, 20130213 and 20120231, the treatment effect observed with etelcalcetide in studies 229, 230 and 360 was observed to be maintained up to 52 weeks. Although data from extension trials provide some evidence of persistence of the etelcalcetide effect for up to 1 year, the quantitative efficacy data obtained from such open-label, uncontrolled trials should not be used for labeling because by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, and a control group is lacking.

8. Safety

Dr. Lubas has summarized the main safety findings in the clinical program and appropriately focused on safety information collected in the controlled periods (6-month) of studies 229 and 230. The controlled periods provide the most informative and rich data on common product-related safety issues because they allow side by side comparisons of etelcalcetide to placebo, were obtained in randomized groups in a blinded fashion with frequent assessments. Supportive safety information is obtained from study 360 comparing safety profiles across the specific calcimimetics (etelcalcetide and cinacalcet). Lastly, information on long-term safety and infrequent safety issues were obtained from two extension studies (20120231 and 20130213). The data from study 360 and long-term studies will be referenced as needed.

Exposure in the Controlled Phase of Study 229 and 230

In the 6-month phase 3 placebo-controlled studies, 503 subjects received at least 1 dose of etelcalcetide. The mean (SD) duration of exposure was 23.6 (5.9) weeks. During the efficacy assessment phase (Weeks 20-27), the most frequent dose per administration (i.e., the dose level at which the subject spent the most time) was 5 mg for 15.5% of subjects, 0 mg for 15.3% of subjects, 15 mg for 14.9% of subjects, 10 mg for 14.5% of subjects, 2.5 mg for 12.7% of subjects, 7.5 mg for 9.7% of subjects, and 12.5 mg for 5.8% of subjects. Subjects could have received 0 mg of AMG 416 for multiple reasons, including corrected calcium < 7.5 mg/dL, symptomatic hypocalcemia, 2 consecutive PTH concentrations < 100 pg/mL, and adverse events.

The dropout rate in pivotal studies 229 and 230 was approximately 18% in both studies; however more subjects in the placebo group as compared to the etelcalcetide group dropped out. The difference in subject discontinuation rate between treatment groups was mainly due to the fact that more patients in the placebo group met the criteria for discontinuation of the study after week 12 because of rising PTH (0.4% (1 subject) in etelcalcetide group and approximately 11 % of subjects in placebo group). The other most frequent reasons for the

study discontinuation were withdrawal of consent, lost to follow up, and death; these reasons for the study discontinuation were well balanced between the treatment groups.

The dropout rate in study 360 was 14%; reasons for the dropouts were similar to the drop out reasons observed in the pivotal studies and were balanced between treatment groups.

Death

In the two pivotal studies there were a total of 26 deaths. There was no imbalance in the number of fatal cases between treatment groups in both studies: 15 - in placebo group and 11 - in etelcalcetide group. Fatal events that occurred in more than one patient were: sepsis (3 patients in etelcalcetide group (considered as non-drug related) and 4 patients in placebo group) and death due to cardiac event (3 patients in etelcalcetide group (cardiac arrest, CHF and myocardial infarction) and 4 patients in placebo group). All other causes of death in the etelcalcetide group occurred in one patient each (sudden death (due to aspiration and GI bleed, as per Dr. Lubas' review), postoperative respiratory failure, death, graft hemorrhage, road traffic accident, metastatic biliary cancer). Three additional subjects treated with etelcalcetide and one subject treated with placebo in these studies died > 30 days after the last dose of the study drug: the causes of death in the etelcalcetide group were chronic renal failure, sudden death, and upper gastrointestinal hemorrhage; subject treated with placebo died of cardiac valve disease. In conclusion, there was slight imbalance in fatal events due to GI bleeding across treatment groups during 6- month treatment in pivotal studies (2 in etelcalcetide group vs.0 in placebo group).

In study 360, 15 subjects died during the study: 9 subjects in the etelcalcetide group and 6 subjects in the cinacalcet group. The cause of death that occurred in more than one patient was cardiac disorder; 6 subjects in the etelcalcetide group and 3 subjects in the cinacalcet group. All other causes of death in the etelcalcetide group occurred in 1 patient each (sepsis, graft hemorrhage, sudden death, cerebral hemorrhage). Two additional subjects died > 30 days after the last dose of the study drug: one subject treated with etelcalcetide died of renal failure and one patient treated with cinacalcet died of MI.

There were additional 47 deaths during the uncontrolled open label extension studies 20120231 and 20130213 (all patients were treated with etelcalcetide): cardiac events, including cardiac arrest, arrhythmias and CHF (38), sepsis (5), cerebral hemorrhage (1) and sudden death (3). However, no firm conclusion regarding causal relationship of the events of death with the drug can be drawn in the absence of controlled group and presence of multiple confounding factors in this population (use of other concomitant medications, vitamin D analogs and calcium, age, underlying serious medical conditions, etc.).

It should be noted that an additional case of fatal GI hemorrhage was reported in the Phase 2 study evaluating PK/PD of etelcalcetide in patients with CKD on hemodialysis. Thus, a total of 3 fatal events due to GI bleeding in patients treated with etelcalcetide were reported in the etelcalcetide clinical program.

In conclusion, I agree with Dr. Lubas that, most deaths (with the exception to deaths due to GI bleeding) are unlikely to be related to the study drug and more likely to be due to complications of chronic renal failure and other underlying serious conditions (diabetes, hypertension, dyslipidemia, cardiovascular disease, immunosuppression, etc.). The contribution of a drug effect for the three deaths attributed to GI hemorrhage in patients treated with etelcalcetide cannot be readily dismissed and the reason for this will be discussed in the dedicated section below.

Serious Adverse Events (SAE)

The event rate for SAEs was similar across treatment groups in pivotal studies and in study 360. In pivotal studies, 130 subjects (25.8%) in the etelcalcetide group and 149 subjects (29%) in the placebo group developed an SAE and in study 360, 85 subjects (25.1%) in the etelcalcetide group and 93 (27.3%) subjects in the cinacalcet group developed an SAE. The most frequent SAEs that occurred in patients treated with etelcalcetide were hyperkalemia, followed by pneumonia, angina pectoris, fluid overload, atrial fibrillation, CHF, sepsis, vascular graft and fistula thrombosis, gangrene, and anemia.

The only SAEs that occurred more frequently in patients treated with etelcalcetide compared to patients treated with placebo in pivotal studies was hyperkalemia (10 patients in etelcalcetide group and 2 patients in placebo group); in the active-control study 1 patient in the etelcalcetide group and 5 patients in the cinacalcet group had SAE of hyperkalemia, respectively. All case narratives were reviewed by Dr. Lubas who concluded that all SAEs (including hyperkalemia) are common and expected events in the hemodialysis population and are most likely not drug-related. I agree with Dr. Lubas' conclusion that no drug-related safety concerns that were identified from SAE review. The observed imbalance in events of hyperkalemia was attributed to factors other than the interventional agent and to the play of chance.

Adverse Events Leading to Discontinuation

In placebo-controlled trials, a total of 9 etelcalcetide-treated and 13 placebo-treated patients discontinued studies prematurely due to the adverse events. The most frequent AE that led to study discontinuation in the etelcalcetide group was decreased calcium (n=5); all other AEs occurred in one patient each (i.e., nausea, vomiting, drug hypersensitivity, chest discomfort, GI malformation, hemiparesis, and hyperhidrosis). In the active-control trial, similar numbers of patients in both treatment groups (19 patients in etelcalcetide group and 16 patients in cinacalcet group) discontinued the study prematurely due to AEs; these AEs were distributed evenly across the both treatment groups. The most frequent AEs that led to study discontinuation in the etelcalcetide group was vomiting (n=3), followed by dermatitis (n=2); all other AEs occurred in one patient each (i.e., nausea, esophageal hemorrhage, hepatic enzyme increased, muscular weakness, myocardial ischemia, cardiac arrest, calciphylaxis, bronchospasm).

Common Adverse Reactions

A total of 91.7% of etelcalcetide-treated subjects and 79.9% % of the placebo-treated subjects reported at least one treatment-emergent adverse event (Table 5).

The table below summarizes the common treatment emergent adverse reactions noted in the 26-week Placebo-Controlled Studies that occurred in more than 5% of etelcalcetide-treated subjects and more than in placebo-treated subjects. The highlighted reactions had the largest between group differences.

Table 5: Parsabiv Related Adverse Reactions Occurring in more than 5% of Individuals

Adverse events	Placebo, n=513 N (%)	Etelcalcetide, n=503, N (%)
Blood calcium decreased	52 (10.1)	321 (63.8)
Muscle spasms	34 (6.6)	58 (11.5)
Diarrhea	44 (8.6)	54 (10.7)
Nausea	32 (6.2)	54 (10.7)
Vomiting	26 (5.1)	45 (8.9)
Headache	31 (6)	38 (7.6)
Hypocalcemia	1 (0.2)	35 (7)
Hypertension	29 (5.7)	31 (6.2)
Hypotension	26 (5.1)	30 (6)
Arteriovenous fistula site complications	26 (5.1)	29 (5.8)

Source: Dr. Lubas' review, table 37.

The safety findings in active control study 360 were consistent overall with safety findings from placebo-control trials; no new safety signals were identified in this study. Frequency of nausea and vomiting observed during treatment with etelcalcetide and cinacalcet were comparable across the treatment groups: nausea was observed in 18% and 23% of patients, respectively; vomiting in 13% and 14% of patients, respectively. Hypocalcemia was observed more frequently in the etelcalcetide group as compared to the cinacalcet group (5% of patients vs. 2% of patients), most likely related to the larger effect of etelcalcetide on PTH levels noted in the trial (refer also to the discussion of secondary endpoints in study 360 in Efficacy section above).

GI hemorrhage

As noted above, there was an imbalance in fatal cases due to GI bleeding between treatment groups: 3 patients treated with etelcalcetide (two patients in placebo-control trials, and one patient in Phase 2 study) died from GI bleeding vs. 0 patients treated with placebo.

As per Dr. Lubas review, one of these patients developed GI bleeding during the first 2 weeks of the study and 2 other patients died 1 and 6 weeks after the drug discontinuation; the patient

who died 6 weeks after the drug discontinuation also had an earlier report of "coffee ground vomit".

The applicant conducted an additional analysis of the entire clinical program specifically for cases where GI bleeding was reported at the time of the death. Four additional cases (Refer to the Sponsor's Response to the 29 July 2016 PMR Document). In two of these cases, GI bleeding occurred 2 and 10 months after the drug discontinuation, in another patient had GI bleed was due to diverticulosis (not upper GI bleeding). Finally, one of the four patients identified in the Sponsor's analysis had a GI-bleed associated death 10 days after drug discontinuation.

This last case identified in the Sponsor's analysis and two other cases identified earlier in Dr. Lubas's review (patient who died while treated with etelcalcetide and patient who died within 1 week after the drug disconsolation) are concerning as a causal relationship between the event of GI bleeding (which may have precipitated the death) and the drug cannot be altogether excluded even though some confounding factors were presented in all cases (underlying serious medical conditions, concomitant medications, age, etc.). Perhaps even more concerning is the fact that two of the three cases occurred in patients treated with drugs to treat gastric acid secretion (one patient - with proton pump inhibitor and one patient - with an H2 blocker) which should have decreased the risk of erosions and bleeding from gastric ulcers.

The three cases are briefly summarized below:

1. ***Subject 0517-1547 (Case USACT2012058566):*** A 54-year old male in study 20120331 with a history of diabetes type 2, coronary artery disease and ESRD developed GI bleeding, became hypotensive and died from cardiac arrest 10 days after drug discontinuation. Confounding factors include use of aspirin, heparin, recent, within last week, MI (and possible use of anticoagulants during cardiac catheterization?), gastro-intestinal reflux disease and intermittent nausea and vomiting.

2. ***Subject 35966002004 (Case USACT201402335649):*** A 49-year old female participated in the extension of study 20120231 and developed hematemesis and hemorrhagic gastritis and was diagnosed with stomach and duodenal ulcers (by endoscopy) 11 days after the drug discontinuation. Within next 2 days, the subject developed abdominal distention, confusion and tachycardia and died due to cardiopulmonary arrest. No underlying medical conditions and concomitant medications reported. The results of autopsy revealed pulmonary embolus, gastric ulcer and ischemic colitis.

3. ***Subject 22965007001 (Case GBRCT2013062058):*** A 73-year old female with renal cell carcinoma and ESRD initiated treatment with etelcalcetide in placebo-controlled study 229. The patient developed vomiting of "coffee ground material", aspirated and died during the second week of the study. Autopsy demonstrated multiple mucosal ulcers in the gastrointestinal tract and pulmonary edema.

The observed imbalance in fatal cases due to GI bleeding in etelcalcetide-treated patients is concerning because a contribution of etelcalcetide to these events cannot be completely excluded. A putative relationship between CaSR activation and gastric related adverse reactions exist. As I have mentioned above, the most common reactions associated with these products are adverse GI reactions (i.e., nausea and vomiting) suggesting these drug could exert direct or indirect effects on the GI tract.

In the review of NDA 21688 for cinacalcet, another calcimimetic, the clinical reviewer for the application noted an increased incidence of reported events of gastritis and esophagitis in patients exposed to cinacalcet and stated that; "the increase in esophagitis and gastritis noted in the cinacalcet-treated group compared to placebo in this study raise concern that cinacalcet may have the unintended side effect of increased gastric acid secretion" (refer to the clinical review by Dr. Kehoe in DARRTS dated 2/2004). In addition, the cinacalcet label describes a [redacted] (b) (4)

The non-clinical reviewers for this application, Drs. Elmore and Tsai, noted a signal of stomach erosions in chronic rodent toxicity studies. The signal was dose-dependent, reversed with dosing cessation and was associated with etelcalcetide exposure comparable to human exposure (0.7- and 2.7-fold human exposure). Similar findings were observed in the cinacalcet nonclinical program. The non-clinical reviewers concluded that "a weak but biologically plausible link between etelcalcetide and increased clinical bleeding exists…"

Etelcalcetide and cinacalcet are calcimimetics. The literature[10] reports that the CaSR is expressed in antral cells of the stomach and has a role in nutrient sensing and regulation of gastric secretion. It is postulated that CaSR may be involved in the regulation of gastrin secretion. Gastrin stimulates the production of gastric acid, and, thus, may predispose to erosions and GI bleeding. Additionally, the common adverse reactions of nausea and vomiting with these drugs could also predispose patients to bleeding through mechanisms other than gastric acid secretion (i.e., Mallory Weiss tears, chronic esophagitis etc.).

There are several factors that make a causality assessment particularly challenging. First CKD patients may be at heightened baseline risk for bleeding due to multiple factors including concomitant medications (NSAIDs, heparin, etc.), renal disease or a host of other underlying serious medical conditions that could predispose to bleeding complications (CKD, coronary artery disease, hypertension, preexisting GI erosions/ulcers, etc.). Presence of confounders was noted in all cases. The numerical imbalance in fatal bleeding events is ultimately small and could still be due to a play of chance.

The applicant is of the opinion that these findings are attributable to play of chance. The applicant conducted an additional analysis specifically on adverse events for terms related to GI bleeding and/or GI erosions reported by investigators in Phase 3 studies (the Division's information request from 6/16/2016). In the two placebo control trials, no imbalance between etelcalcetide and placebo groups for incident GI bleeding [10/503 patients (2%) and 11/513

[10] Buchan AM, Squires PE, et al,. Mechanism of action of the calcium-sensing receptor in human antral gastrin cells. Gastroenterology. 2001 Apr;120(5):1128-39

patients (2.1%), respectively] was observed. However, a slightly higher proportion of patients in the etelcalcetide group developed GI ulcerations compared to placebo [6 patients (1.2%) vs. 4 patients (0.8%), respectively]. In the active-control study, the incidence of GI bleeding was 2.7% vs. 1.5% for etelcalcetide versus cinacalcet and the incidence of ulcerations was 0.3% vs. 0.3% for etelcalcetide versus cinacalcet; the Sponsor concluded that the rates of AEs were comparable between treatment groups and to the incidences observed in placebo controlled trials.

Of all the AEs related to bleeding/ ulcerations reported in the etelcalcetide group, 11 AEs of GI bleeding and 2 AEs of ulcerations were considered serious adverse events. Dr. Lubas reviewed all narratives of SAEs of GI bleeding/ ulcerations and concluded again that multiple factors including concomitant medications (NSAIDs, heparin, etc.), underlying serious medical conditions predisposing to bleeding complications (CKD, coronary artery disease, hypertension, low platelet count, preexisting GI erosions/ulcers, etc.) confound the causality assessment.

Lastly, the Sponsor also compared the incidence of these AEs observed in the etelcalcetide program with a "historical" control, i.e. safety data obtained from the EVOLVE study, and concluded that the rate of these AEs of concern did not exceed the rate of these events observed in the EVOLVE study. However, I do not agree that the data from the EVOLVE study can make the imbalance in the control trials completely go away. Historical controls have limitations because of differences in study design, study duration, and baseline demographic and disease characteristics (duration of dialysis, presence of other comorbidities, severity of hypocalcemia/SHPT, etc.), and study conduct different drop-out rate, etc.

In conclusion, based on the severity of the events (death), identified common adverse reactions in clinical trials, presence of a weak nonclinical signal, similar findings for another member of the class, and a putative biological mechanism, I cannot exclude a role for etelcalcetide in augmenting the risk of GI bleed and recommend including the event of fatal GI bleeding in the WARNING and PRECAUTION section of the etelcalcetide label. This will allow prescribers to recognize this risk as potentially drug-relate and take appropriate measures to monitor for and treat this risk should it occur. We also recommend conducting a PMR study to evaluate the rate of GI bleeding and

Congestive heart failure (CHF)

The Sponsor proposed an inclusion of the adverse event of congestive heart failure in the WARNING and PRECAUTION of the label.

I agree that the event of CHF should be included in the WARNING and PRECAUTION section of the label and under the separate subsection (and not under *Hypocalcemia* subsection) due to the following reasons;

1. There was a slight imbalance in the rate and severity of CHF observed in patients treated with etelcalcetide compared to placebo. In the placebo controlled trials, slightly more patients treated with etelcalcetide (n=16) developed CHF than placebo (n=13).

Patients in the etelcalcetide group also had more serious adverse events of CHF compared to patients treated with cinacalcet (7 vs. 3 respectively). As per the Sponsor's analysis, twice as many patients treated with etelcalcetide in pivotal placebo-control trials had CHF requiring hospitalization compared to placebo-treated patients (11 vs. 6 respectively). Lastly, more patients in the Phase 3 clinical program treated with etelcalcetide died from CHF as the cause: 3 patients in active control trial treated with etelcalcetide vs. one patient treated with placebo in study 229 vs. 0 patients on cinacalcet (study 360).

2. Acknowledging that many of the cases are confounded, a causal relationship between the event and etelcalcetide cannot be completely ruled out due to the drug's mechanism of action. Dr. Lubas speculates that a higher rate of hypocalcemia seen with use of etelcalcetide might cause decreased cardiac contractility and increase the risk for CHF. However, preceding problems with hypocalcemia were not identified in the majority CHF cases and did not appear to explain these cases. CaSR are found in cardiac tissue and may play a role in cardiac contractility, it is therefore unlikely that hypocalcemia is the only plausible biological mechanism to explain a potentially heightened risk of this event in this population at high baseline risk. In conclusion, I believe CHF should be listed as a separate WARNING under a different subsection of the WARNING and PRECAUTION section of the label, and not as part of the "Hypocalcemia" subsection of the WARNING and PRECAUTION section.

3. CHF is a labeled adverse reaction for cinacalcet (another calcimimetic) and included in the WARNING and PRECUATION section of the cinacalcet label.

Hypersensitivity:

I agree that the drug has to be contraindicated in patients with known hypersensitivity to the active ingredients. Etelcalcetide is a therapeutic peptide, thus, hypersensitivity reactions are not unexpected events and were observed across all three Phase 3 trials. No 22 in placebo controlled trials and 19 patients in active control trial). The majority of reactions reported were rash, facial edema, and rhinitis. No serious adverse events of hypersensitivity, Stevens-Jonson syndrome, or toxic epidermal necrolysis were reported in any of the trials.

Immunogenicity

The immunogenicity data obtained from the clinical program was reviewed by Dr. Bruce Huang from the Division of Biotechnology Research and Review II, Office of Biotechnology Products (OBP) (refer to the review in DARRTS from 4/8/2016). The OBP reviewer concludes that the immunogenicity assay is properly validated and suitable for the evaluation of the presence of etelcalcetide anti-drug antibodies. He also confirmed that the proposed claim on etelcalcetide immunogenicity in Section 6.2 of the labeling is supported by the results from the assay and no further edits for Section 6.2 were suggested.

As per OPBP review, binding antibodies to etelcalcetide were detected in 7.1% of patients (71/995 patients) overall (i.e. pre-existing and emergent). 71 patients (1.5%) developed anti-

drug antibodies during 6-month treatment with etelcalcetide (all other patients had pre-existing anti-drug antibodies). No neutralizing antibody data was submitted in this NDA. The reviewer agreed with the Sponsor's conclusion that the neutralizing antibody assay was impractical since the results of the in-vitro evaluation demonstrated the absence of anti-drug antibodies blocking ability (with regards to the drug activity) even at high titers.

Lastly, the reviewer concluded that the presence of the anti-drug antibodies did not affect the PK of the drug, PTH levels, overall efficacy or safety of etelcalcetide. No subjects with emergent anti-drug antibodies development in the 6-month trials had hypersensitivity reactions, and only 2.3% of patients with pre-existing antibodies developed hypersensitivity (vs. 4.7% antibody-negative subjects).

Laboratory Parameters

Hypocalcemia and hypophosphatemia

There is a known risk of hypocalcemia and hypophosphatemia associated with use of calcimimetics. Thus, the Clinical Reviewer paid special attention to the occurrence of out-of-range calcium and phosphorus values and adverse events related to these biochemical changes. Main analyses conducted to characterize the frequency and severity of these adverse reactions are summarized below.

Serum Calcium

In the two placebo controlled pivotal trials, mean serum calcium decreased from a baseline to EAP to a greater extent in etelcalcetide group (from 9.6 mg/dl to 8.9 mg/dl) than in the placebo group (from 9.7 mg/dl to 9.7 mg/dl) (refer to the Efficacy section above). However, the mean decrease in calcium levels was small and unlikely to be clinically meaningful. The greater changes in etelcalcetide group might be explained by the pharmacodynamics effect. Visual comparison of scatterplots in Dr. Lubas' review (Figure 29, page 143) indicate multiple values in the abnormal range in both treatment groups, but no obvious outliers at the end of the study.

Seventy-nine percent of patients treated with etelcalcetide and 19.4% of patients treated with placebo in pivotal studies had at least one episode of a calcium level below the lower normal limit (8.3 mg/dl). The majority of these patients had only a single event. In the majority of cases the decrease in calcium returned to normal levels at the next visit and without dose adjustment and/or with increase in vitamin D and calcium doses. Seven percent of subjects in the etelcalcetide group and 3% of subjects in the placebo group had an even of a calcium level of < 7 mg/dl during the study. These events resolved with dose reduction and/or increases in doses of vitamin D and or calcium supplementation.

The rate of AEs related to low calcium levels was higher in the etelcalcetide group compared to placebo: "blood calcium decreased" was observed in 64% and 10% patients respectively and "hypocalcemia" in 7% and 0.2%, respectively. These data do not allow determination of whether these represented symptomatic events or asymptomatic biochemical abnormalities. Finally the rates of adverse events suggesting symptoms consistent with hypocalcemia that

were higher in the etelcalcetide group as compared to the placebo group (paresthesis-4.8% vs. 0.6%; muscle spasm - 12% vs. 7%; myalgia -1.6% vs. 0.2%), however, no low calcium was documented in the majority of these patients.

Seizure adverse event rates, a potential complication of hypocalcemia, were similar between groups 0.8% vs. 1% for etelcalcetide and placebo respectively but data on calcium for these events were not collected. The results of the active-control study 360 were consistent with findings from placebo controlled studies: 85% in the etelcalcetide group and 74% of subjects in the cinacalcet group had at least one calcium level below 8.4 mg/d, and approximately 10% of subjects in each group had a calcium level < 7 mg/dl.

No SAEs of hypocalcemia were reported during the treatment with etelcalcetide in any of the three Phase 3 studies; 5 subjects in placebo-controlled studies and no subjects in the active-control study treated with etelcalcetide were withdrawn from the study prematurely due to hypocalcemia.

Overall, I agree with Dr. Lubas' conclusion that the risk of hypocalcemia is low in the intended patient population and can be mitigated with proper monitoring of calcium levels and intervention.

Serum phosphorus

In placebo-controlled trials, greater decreases in mean serum phosphorus levels from baseline to the final visit was observed in the etelcalcetide group (from 5.9 mg/dl to 5.2 mg/dL; net change of-0.7 mg/dl) compared to the placebo group (-0.7 mg/dl in etelcalcetide group vs. + 0.2 mg/dl in placebo group). The overall mean change is small and unlikely to be clinically meaningful. The lower phosphorus level in the etelcalcetide group is explained by the drug's mechanism of action.

Approximately 37% of patients treated with etelcalcetide and 16-20% of patients treated with placebo had decreases in phosphorus levels below the lower normal limit (2.8 mg/dl). The majority of patients were asymptomatic and had their levels normalized during the next visits without etelcalcetide dose adjustment or adjustment in doses of concomitant medications.

The results of active-control study 360 were consistent with findings from placebo controlled studies: 29% in the etelcalcetide group and 20% of subjects in the cinacalcet group had at least one phosphorus level below 2.8 mg/dL.

No SAEs of hypophosphatemia were reported during treatment with etelcalcetide and no subjects were withdrawn from the studies due to hypophosphatemia. I agree with Dr. Lubas' conclusion that the risk of hypophosphatemia is low with etelcalcetide treatment in patients with CKD on hemodialysis.

Oversuppression of PTH levels and risk of adynamic bone disease

There is a concern with all PTH-lowering drugs (calcimimetics and vitamin D analogs) that oversuppression of PTH levels may lead to adynamic bone disease, fractures and bone pain in patients with SHPT and CKD. However, the specific levels of PTH associated with this complication are unknown.

Dr. Lubas identified 64 patients in the three Phase 3 studies with at least one PTH level of < 100 pg/ml (threshold established by the applicant as the risk threshold justifying etelcalcetide dose suspension): 2 patients in the placebo group (0.4%), 52 patients (6.9%) in the etelcalcetide group and 10 patients (3.2%) in the cinacalcet group. In these patients PTH levels increased with no or some dose adjustments, and outcomes of bone pain or fractures were not reported in these patients.

It should be noted that the Sponsor's proposed PTH threshold of < 100 pg/ml for the dose suspension is based on the cinacalcet label[11], findings from clinical study evaluating bone histomorphometry in patients treated with cinacalcet for 1 year (2/77 patients with other confounding factors (age, diabetes, use of vitamin D analogs) with PTH levels < 150 pg/ml during the trial and developed "adynamic bone" on biopsy after 12 months of treatment)[12] and the European Renal Best Practice Work Group Guideline (based on the evidence of the low bone turnover on bone biopsy and experts' opinion)[13].

Overall, it is unknown whether low PTH levels in the etelcalcetide clinical program were associated with adynamic bone disease; none of these patients had bone biopsy and low PTH levels alone are not uniformly predictive of bone histology, especially when considered alone (i.e. without concomitant abnormalities in calcium, phosphorus levels, or use of medications affecting bone structure such as bisphosphonates).

Overall, I agree with inclusion of adynamic bone disease in the WARNING and PRECAUTION section due to the established causal relationship of the event with low PTH levels. While I agree that lower PTH levels increase the risk, I do not agree with the applicant's plan to include a (b) (4) in the WARNING and PRECAUTION section of the label that refers to this risk. The sponsor's (b) (4)

(b) (4)

Other laboratory parameters

[11] Sensipar (cinacalcet) tablets label. Section 5.2 Adynamic Bone Disease.
[12] Behets GJ[1], Spasovski G[2], Sterling LR[3], Goodman WG[3], Spiegel DM[3], De Broe ME[4], D'Haese PC[1]. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015 Apr;87(4):846-56.
[13] David J.A. Goldsmith, Adrian Covic, et al. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement.

There were no clinically meaningful differences between treatment groups in the change from baseline to final visit in any other laboratory parameters (hematology, clinical chemistry, urinalysis, etc.). Few subjects in each of the treatment groups (0.2-0.4%) in the placebo controlled studies had isolated ALT, AST > 3 XULN or isolated bilirubin elevation > 2 X ULN; these events were distributed evenly across the treatment groups and none of these subjects met the definition of Hy's law. In the active-control trial, no subjects treated with etelcalcetide had abnormal LFTs.

Vital signs
There were also no significant changes in vital signs between the treatment groups.

4. Advisory Committee Meeting

No issues needing input from the Advisory Committee were identified in the review of this application and no meeting was held.

5. Pediatrics

No pediatric patients were studied in the etelcalcetide development program. The Applicant has submitted a proposed pediatric study plan which was reviewed and discussed by the Pediatric Review Committee on June 15, 2016. The proposed pediatric study plan includes a waiver for patients < 1 month, and deferred pediatric studies for older pediatric patients until safety and efficacy have been established in adults. The initial pediatric study plan proposed a PK/PD modeling and simulation study to enable extrapolation of efficacy data obtained in adults to the pediatric population and to support the selection of doses of etelcalcetide in pediatric population, one PK/safety multiple dose titration study in pediatric population (Phase 3), and comparative PK/PD modeling study between adult and pediatric SHPTH patients.

As initially proposed, the Phase 3 study was planned to begin approximately 2 years after the completion of study 1(PK/PD modeling study). It was unclear why such a long period of time was required between these two studies and we are recommending initiating a Phase 3 study sooner than 2 years after the data is available from PK/PD modeling study. The list of required pediatric studies was communicated to the Sponsor via email on August 9, 2016. The Sponsor accepted the proposed pediatric plan and sent a copy of the PMR studies to the Division with proposed milestone dates via email on August 12, 2016.

6. Other Relevant Regulatory Issues

Office of Scientific Investigation Inspections

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on April 21, 2016. Six principal investigators were investigated. The audit resulted in five No Action Indicated decisions and one Voluntary Action Indicated letter due to the regulatory violations, however, the review concluded that these violations "are unlikely to significantly impact

primary safety and efficacy analyses and reliability of data from this site is acceptable for use in support of the indication for this application".

The inspection of the Sponsor also resulted in No Action Indicated decisions. Overall, the review concluded that "the inspectional findings support validity of the data as reported by the Sponsor under this NDA".

Financial Disclosure and Reportable Financial Interests

Financial disclosure documentation was reviewed by Dr. Lubas. He identified 5/500 Investigators in study 229 who received compensations and were listed on Form 3455 submitted to the Agency. However, as per Dr. Lubas, there was no clear evidence that the data contributed by their sites could have affected the study results (total of (b) (6) subjects were enrolled at these sites; and only (b) (6) subjects received etelcalcetide and were responders at the end of the study).

In study 230, 7/400 Investigators received compensations and were listed on Form 3455 submitted to the Agency. These Investigators enrolled a total of 57 patients: 33 patients in placebo group and 29 patients in etelcalcetide group. Dr. Lubas analyzed the data from these sites and concluded that only (b) (6) patients in placebo group and (b) (6) patients in etelcalcetide group, respectively, were responders and that it is unlikely that these patients influenced the results of the study.

Dr. Lubas also identified 2/500 investigators at 200 clinical sites in study 360 who had financial interests. These investigators enrolled only (b) (6) 683 subjects, thus, as per dr. Lubas, data from these subjects will not affect the study results.

Interdisciplinary Review Team (IRT) for QT Studies Consultation

As agreed during EOP2 meeting (on 7/9/2012), the dedicated QTc study was not required; however, the Division recommended to monitor ECG during the Phase 3 studies.

The IRT consultant reviewed ECG data and confirmed that thorough QT study is not required (DARRTS 1/4/16) based on the fact that a "thorough QTc study cannot be safely conducted with KAI-4169 in healthy subjects because hypocalcemia was observed following a single 10 mg dose, limiting the exposure that can be safely achieved in healthy volunteers. In addition, a thorough QTc study in either healthy volunteers or hemodialysis subjects will produce results that are confounded by the direct effect of reductions in serum calcium on QTc, making any meaningful interpretation difficult. Furthermore, a significant number of hemodialysis subjects have prolonged QTc (i.e., > 450 ms) at baseline, so the inclusion of a positive control to assess assay sensitivity may not be acceptable in this population."

The consultant reviewed the Sponsor's proposed labeling section *6.1 QTc Prolongation Secondary to Hypocalcemia* and found it to be acceptable; no additional labeling was recommended.

7. Labeling

Prescribing Information

The following sections should be changed in the label:

- INDICATIONS AND USAGE section:
  - The indication should be restricted to the adult population with CKD on hemodialysis, since the Parasabiv clinical program did not evaluate safety and efficacy of the drug in the pediatric population.
  - Limitation of use should be included in the label stating that the drug should not be used in patients with CKD not on the dialysis. The efficacy of Parasabiv has not been evaluated in this patient population and the safety profile of the drug including risk of hypocalcemia is unknown. Of note, the Sensipar label contains the following limitation of use: "Sensipar is not indicated for use in patients with CKD who are not on dialysis because of an increased risk of hypocalcemia" due to the risk of hypocalcemia in this population. As per the Medical Team Leader's review of NDA 21688 (cinacalcet), treatment with cinacalcet in predialysis patients was associated with serum calcium levels < 7.4 mg/dl in nearly 50% of patients compared to none in placebo group[14].
  - Limitations of use should be included for other Sensipar indications that are unrelated to the indications studied in the etelcalcetide applications (i.e., parathyroid carcinoma etc.)

- DOSAGE AND ADMINISTRATION section:
  - I agree with the proposed dosage regimen and titration schedule (based on PTH and calcium levels) and with using dose increments of 2.5 mg- 5 mg. The PK/PD of these doses was evaluated in dose-response studies in healthy volunteers and in patients on hemodialysis; PopPK analysis also demonstrated a clear dose response for doses 2.5 mg-15 mg (refer to the Clinical Pharmacology section above). The proposed titration algorithm was successfully implemented in the pivotal Phase 3 studies and approximately 10% of patients responded to this dose by a reduction in PTH level> 30% at the end of the trial.

- Safety information in the CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - I agree that the drug should be contraindicated in patients with known hypersensitivity to active substance etelcalcetide. The drug is a therapeutic protein and there were reports of hypersensitivity in the etelcalcetide clinical program.
  - The adverse reactions of GI bleeding should be included in the WARNINGS AND PRECAUTIONS section because it is a **potential serious risk**, there is some reason to believe the drug could contribute to this risk (refer to Safety Section) and it can fatal outcomes can be prevented and treated if recognized early.

[14] Medical Team Leader's Review of NDA 21688 in DARRTS from 2/14/2004

- I agree that the adverse reactions of congestive heart failure should be listed in the separate subsection of the WARNINGS AND PRECAUTIONS section and do not recommend including it in the "Hypocalcemia" WARNING. No link between low calcium levels and CHF has been established in the nonclinical and clinical program; CHF might be due to hypocalcemia independent effects.
- I recommend deleting the statement that (b) (4) [redacted]

- ADVERSE REACTIONS SECTION
  - I recommend deleting (b) (4) [redacted] The label was reviewed by LRT who agreed with the above recommendations and concluded that (b) (4) [redacted]
  - The description of hypocalcemia and hypophosphatemia events that occurred during the studies should include all patients with abnormal laboratory values (i.e. calcium and phosphorus), and not only the number of adverse events reported by the Investigators.

- CLINICAL STUDIES section:
  - Studies 229 and 230 are adequate placebo-controlled studies that provide substantial evidence supporting the efficacy for the proposed indications as described above (refer to the Efficacy section). Thus, I recommend including the results of 6- month treatment results from these pivotal studies in this section of the label.
  - Mean percent change from baseline in PTH for both pivotal trials (229 and 230) can be pooled into a single figure. Tabular data showing mean baseline PTH, % change in PTH from baseline and % of subjects with > 30% reduction in PTH from baseline should be also provided in this section.
  - The information regarding (b) (4) [redacted]
  - I recommend removing (b) (4) [redacted]

(b) (4)

- USE IN SPECIFIC POPULATIONS section

  The Division of Pediatric and Maternal Health (DPMH) was consulted on April 15, 2016 to assist in the labeling for this NDA. The DPMH reviewer revised subsections 8.1, 8.2, and section 17 in the Parsabiv labeling for compliance with the PLLR and found the proposed language in these sections to be acceptable (refer to review in DARRTS from 7/27/2016). However, the reviewer recommended to delete the statement that (b) (4) . I agree with the reviewer's recommendations to delete the above language in the absence of the additional information. However, I disagree with the recommendations to (b) (4) (b) (4) (refer to Postmarketing Recommendations section below).

Conclusion

During the labeling negotiations the Division was not able to reach agreement on the content of the full prescribing information for Parsabiv. (b) (4) (b) (4) (b) (4) Thus, I recommend a Complete Response of the application (b) (4)

Other Labeling

- Proprietary name

The proposed proprietary name for etelcalcetide is Parsabiv. This was reviewed and deemed acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on November 11, 2015.

- Carton and container labeling

Commercial container label and carton were reviewed by DMEPA and was found to be acceptable (refer to the review in DARRTS from 7/18/2016).

[15] Guidance for Industry "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products-Content and Format"

8. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Division of Risk Management (DRISK) evaluated whether REMS for Parasabiv is necessary (refer to the review in DARRTS from 5/5/2016) to ensure the benefit of this product outweighs its risk. The reviewers concluded that REMS is not required for this product and that the risk seen with this drug (i.e. hypocalcemia, worsening of heart failure, adynamic bone disease) should be communicated through the labeling.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

- The following post marketing requirements were requested and communicated to the Sponsor by the etelcalcetide review team:

  - To assess the risk of upper GI bleeding observed during the Parsabiv nonclinical and clinical program in postmarketing settings

    The review team requested the Sponsor to conduct a hypothesis-testing observational study to provide data regarding the potential association between etelcalcetide and fatal and non-fatal gastrointestinal bleeding. The study should have a comparator group, be powered to detect the outcomes of interest, with justification for the proposed detectable differences in incidence rates. Special attention should be given to complete data availability in dialysis patients with secondary hyperparathyroidism above and below the age of 65 years (since the risk of fatal outcome increases in patients > 65 years old), the ability to ascertain cause of death in a timely manner, and a statistical consideration of competing risks. Secondary analyses should aim to quantify the exposure-risk window, including periods after exposure discontinuation. The choice of study design, data source(s), and sample size should be supported by a feasibility analysis and reviewed by FDA prior to final protocol submission.

    The Division also requests that for a period of two years, the Sponsor submit all cases of gastrointestinal bleeding events reported with Parsabiv (etelcalcetide) injection as 15-day alert reports, and that the Sponsor provides detailed analyses of clinical study and post-marketing reports of gastrointestinal bleeding events as adverse events of special interest in the Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of Parsabiv (etelcalcetide) injection as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of s gastrointestinal bleeding events reported with Parsabiv (etelcalcetide) injection should also be provided in the PBRER.

  - Pediatric studies

    A PK/PD modeling and simulation study to enable extrapolation of efficacy data obtained in adults to the pediatric population and to support the selection of doses of etelcalcetide in pediatric population.

A Phase 3 PK/safety multiple dose titration study in pediatric population (Phase 3) to evaluate safety of the selected doses in patients 1 month-18 years old.

A comparative PK/PD modeling study between adult and pediatric SHPT patients to extrapolate adult efficacy data to the pediatric population.

- The Division does not recommend [redacted] (b) (4) (refer to the Labeling section above).

DPMH recommendations are based on the Sponsor's comment during the label revision regarding [redacted] (b) (4)

(b) (4)

9. Recommended Comments to the Applicant

The action letter will communicate the deficiencies that need to be resolved in order to achieve the agreement on the content of the full prescribing information.

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

/s/

MARINA ZEMSKOVA
08/24/2016

CLINICAL REVIEW

Application Type	505 (b) (1)
Application Number(s)	208325
Priority or Standard	Standard
Submit Date(s)	August 24, 2015
Received Date(s)	August 24, 2015
PDUFA Goal Date	August 24, 2016
Division/Office	DMEP/ODEII/OND
Reviewer Name(s)	William Lubas M.D., Ph.D.
Review Completion Date	August 19, 2016
Established Name	etelcalcetide
(Proposed) Trade Name	Parsabiv
Applicant	Amgen
Formulation(s)	Solution in single use vial
Dosing Regimen	The recommended dose is 5 to 15mg by bolus injection three 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
Applicant Proposed Indication(s)/Population(s)	Secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of secondary hyperparathyroidism due to chronic kidney disease in hemodialysis patients

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Glossary

AC	advisory committee
AE	adverse event
AMG 416	etelcalcetide
ARF	acute renal failure
BFR	bone formation rate
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSAP	bone specific alkaline phsophatase
BUN	blood urea nitrogen
Ca	Serum Calcium
CBER	Center for Biologics Evaluation and Research
cCa	Corrected Serum Calcium
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EEAS	Efficacy Evaluable Analysis Set
EOP2	end of phase 2
EOT	end of treatment
EAP	efficacy assessment phase

ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GE	gastroesophageal
GI	gastrointestinal
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
iPTH	Intact Parathyroid Hormone
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LLN	lower limit of normal
LOCF	last observation carried forward
MAED	MedDRA-Based Adverse Event Diagnostic
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NKF	National Kidney Foundation
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	Periodic Safety Update report
PT	Preferred Term
PTH	Parathyroid Hormone
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGE	special government employee
SOC	standard of care or System Organ Class
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
TIW	three times a week dosing
ULN	upper limit of normal
WK	week
YR	year

Executive Summary

1.1. Product Introduction

Etelcalcetide is a calcium-sensing receptor agonist indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis.

Etelcalcetide is a synthetic peptide calcimimetic that is a new molecular entity (NME).

The recommended starting dose is 5 mg administered by bolus injection three times a week into the venous line of the dialysis circuit at the end of hemodialysis treatment during the rinse back or intravenously after rinse back. The dose can be increased in 2.5mg to 5 mg increments no more frequently than every 4 weeks to a maximum of 15 mg three times per week. It is available in single use vials containing 2.5mg, 5mg and 10mg doses.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application contains substantial evidence to support the efficacy of etelcalcetide in decreasing elevated iPTH levels by at least 30% from baseline in adult hemodialysis patients with secondary hyperparathyroidism. The clinical program did not study other conditions associated with hyperparathyroidism and approval for such conditions is not indicated:

- predialysis subjects with secondary hyperparathyroidism due to Stage 3 or 4 chronic kidney disease,
- patients with hypercalcemia due to hyperparathyroidism from a parathyroid carcinoma,
- patients with primary hyperparathyroidism for whom thyroidectomy would be indicated on the basis of serum calcium but who are unable to undergo parathyroidectomy and
- renal transplant patients with tertiary hyperparathyroidism that has not yet responded adequately following transplant surgery.

Given that etelcalcetide must be given three times a week by intravenous therapy and is likely to be less effective in subjects with normal or only partial loss of renal function, off-label use for these other conditions is unlikely.

Benefit-Risk Summary and Assessment

Etelcalcetide is a calcium-sensing receptor agonist indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis. Overall the risk benefit profile supports approval of etelcalcetide for the proposed indication.

Secondary hyperparathyroidism is a condition in which there is excessive secretion of parathyroid hormone (PTH) in response to low levels of active vitamin D and serum calcium. In subjects with worsening chronic kidney disease (CKD) this is triggered by the kidney's inability to adequately excrete phosphorous and reabsorb sufficient calcium, and by the inability of the kidney to adequately 1-hydroxylate 25-hydroxyvitamin D to make the maximally active 1,25-dihydroxyvitamin D analog. Prolonged elevation of PTH causes excessive calcium and phosphorus to be released from bone, leading to the metabolic bone disease referred to as renal osteodystrophy which can result in bone pain and an increased risk of fracture. In addition, excess calcium and phosphorus release from the bone can lead to unintended calcification of the vasculature in skin causing calciphylaxis or soft-tissues such as the heart and kidney resulting in increased morbidity and mortality in this population. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines from 2009 state that the optimal iPTH in adult dialysis patients with secondary hyperparathyroidism due to Stage 5D CKD is not known, but suggest maintaining iPTH levels in the range of 2 to 9 times the upper limit of normal (e.g. 130-600pg/mL). Vitamin D analogs have been shown to decrease PTH levels by inhibiting PTH synthesis and secretion and are typically used as a first line treatment especially as these patients need to replenish their total body stores of calcium. However, as vitamin D analogs increase calcium absorption from the intestines patients can develop hypercalcemia which limits the utility of vitamin D analogs to treat hyperparathyroidism. In such cases adding a calcimimetic, which acts as an allosteric activator of the calcium sensing receptor in the parathyroid increasing its sensitivity to extracellular calcium and directly lowers serum PTH levels, can be a useful treatment approach. There is currently available only one approved calcimimetic, cinacalcet, so there is need for additional drugs in this class in patients who may not tolerate cinacalcet or in whom use of cinacalcet is not optimal.

The applicant has completed two randomized, placebo-controlled studies 20120229 and 20120230 in hemodialysis patients with secondary hyperparathyroidism which showed statistically significant differences in the primary endpoint, the proportion of subjects in the Intent to Treat (ITT) population attaining a mean decrease of 30% in serum iPTH from the pretreatment baseline to the efficacy assessment phase (EAP, weeks 20 to 27) relative to placebo (i.e. 74% vs. 8.2 %, and 75% vs. 9.6%, for studies 20120229 and 20120230, respectively). Excluding data from subjects with an increase in active vitamin D analog dose or serum calcium supplements during the pivotal studies, which may have confounded the PTH results, lowered the effect size slightly but did not affect the statistical significance of the study results (e.g. 64.3% vs. 8.1%, and 61.4% vs. 8.6%, for studies 20120229 and 20120230, respectively). Results were also statistically significant for the first secondary

endpoint of "treatment to iPTH goal of ≤ 300pg/mL", which was similar to the primary endpoint "treatment to iPTH goal of ≤ 250pg/mL" used for the approval of the first calcimimetic Sensipar (cinacalcet) (see Study Endpoints under Section 6.1.1 for a further discussion of the use of iPTH as a surrogate for clinical benefit). The mean decrease in iPTH from baseline to the efficacy assessment period was -55% vs. +13% and -57% vs. +14%, for studies 20120229 and 20120230, respectively, well above the > 30% decrease in iPTH used for the primary endpoint. Changes in bone biomarkers, which were exploratory endpoints, were consistent with a net decrease in high bone turnover associated with renal osteodystrophy, adding further support for clinical benefit. The randomized, double-blind, double-dummy, active-controlled study 20120360 showed that etelcalcetide had greater efficacy with respect to the proportion of subjects having a > 50% or > 30% reduction in iPTH from baseline compared to cinacalcet, (52% vs. 40% and 68% vs. 58%, respectively). Mean iPTH levels during the EAP were 581 pg/mL (SE=36 pg/mL) for etelcalcetide compared to 743 pg/mL (SE=45 pg/mL) for cinacalcet. Therefore, etelcalcetide may provide a potential benefit to subjects who need a greater level of PTH lowering as demonstrated by the fact that the iPTH mean in this study reached the recommended KDIGO guideline range of 130 to 600pg/mL only in the etelcalcetide treatment group. In addition, given that the product is to be given three times a week (TIW) intravenously following routine hemodialysis at the dialysis unit, compliance is likely to be less of a problem than with cinacalcet; which has to be given as a daily oral medication to hemodialysis patients who may already be overburdened with a large number of other oral medications. Another potential benefit with etelcalcetide is that it has no known risk for pharmacokinetic drug-drug interactions due to the lack of interaction with CYP450 enzymes; unlike cinacalcet which is a strong inhibitor of CYP2D6 and is partially metabolized by CPY3A4. In addition, while nausea and vomiting which are among the most common adverse reactions associated with calcimimetics were not statistically significantly less common with etelcalcetide compared to cinacalcet, the point estimate was slightly in favor of etelcalcetide so it is possible that for certain patients who may not tolerate cinacalcet because of these symptoms etelcalcetide may provide a useful alternative.

Toxicity associated with the use of calcimimetics is primarily related to the risk of hypocalcemia, which can result in symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, cardiac arrhythmias (torsades de pointes & ventricular tachycardia) and worsening heart failure. Other concerns include hypophosphatemia, which is less likely to result in serious adverse reactions as renal failure patients typically have high phosphorous levels and difficulty excreting phosphorous, and adynamic bone disease which occurs due to long term chronic over suppression of PTH. In the pivotal placebo-controlled trials etelcalcetide significantly lowered mean corrected serum calcium levels from a baseline of 9.6mg/dL to about 8.6mg/dL by week 10 of treatment in contrast to no change from baseline in the placebo group (see Figure 26). Most of the cases of low serum calcium were asymptomatic and of CTCAE grades 1 & 2 (7.0 to 8.3mg/dL) with only about 4% of the difference between treatment groups at serum calcium levels below 7.0 (CTCAE grade 3) (see Table 46). Consistent with this most of the AEs of blood calcium decreased or hypocalcemia seen in the etelcalcetide treatment group in the

placebo-controlled studies were graded as mild or moderate (99%), only 2 cases (0.4%) were considered severe and non were reported as serious. In the 6-month placebo-controlled dataset only 5 subjects (1%) discontinued etelcalcetide treatment due to an event of hypocalcemia, and 1 subject (0.2%) discontinued due to nausea, while no subjects discontinued due to other symptoms potentially associated with hypocalcemia such as muscle spasms, myalgias, paresthesias, convulsions or hypotension. That said a MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the data from the pivotal placebo-controlled studies confirmed much higher event rates for blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), hypocalcemia (7% vs. 0.2), paresthesias (5% vs. 1%) and myalgias (2% vs. 0.2%) in the etelcalcetide treatment group compared to placebo, all with p-values < 0.05. Of note "convulsions" which can also be related to hypocalcemia were seen at an equal rate in both treatment groups at 0.8%, and hypotension (6% vs. 5%) and "ECG QT prolonged" (0.8% vs. 0.6%) were only slightly higher in the etelcalcetide group. The analysis also showed the point estimates of the AEs of nausea (11% vs. 6%) and vomiting (9% vs. 5%) which are likely to be drug related were also more common in the etelcalcetide treatment group compared to placebo although not statistically significant. In conclusion low blood serum calcium levels and hypocalcemia are known risks associated with the use of calcimimetics. Most cases were mild or moderate in severity and did not lead to discontinuation of treatment, although they did result in increased dosing with vitamin D sterols (31% vs. 10% placebo) and calcium supplements (50% vs. 9% placebo). Other AEs that may be related to hypocalcemia and occurring infrequently including muscle symptoms, paresthesias, and possibly hypotension and QT prolongation are potentially monitorable events. Labeling to recommend against dosing in subjects with serum calcium levels below the lower limit of normal and including information on symptoms of hypocalcemia to aid healthcare professionals to identify cases of concern should provide adequate risk management. With respect to hypophosphatemia etelcalcetide significantly lowered mean serum phosphorous levels from a baseline of 5.9mg/dL to about 5.0mg/dL by week 10 of treatment in the placebo-controlled pivotal trials, compared to a slight decrease of 0.2mg/dL from baseline to end of treatment in the placebo group (see Figure 27). However, given that renal failure patients typically have elevated serum phosphorous levels these changes resulted in few patients with AEs of hypophosphatemia: 7 patients (1.4%) with etelcalcetide compared to only 1 patient (0.2%) in the placebo group in the placebo-controlled trials. Of the 7 cases in patients treated with etelcalcetide, 4 were mild, 3 were considered moderate but none were serious. In conclusion, low blood serum phosphorous levels are a known risk associated with the use of calcimimetics which lower serum PTH but in general they are unlikely to result in severe or serious AEs. Hypophosphatemia can typically be controlled with routine monitoring and appropriate changes to diet or concomitant medications without need for interrupting the dose of the calcimimetic. With respect to the AE of adynamic bone disease (low bone turnover) associated with the decreased ability to repair microdamage in bone which places subjects at higher risk of fracture and which is associated with vascular calcifications due to the decreased calcium buffering capacity of the abnormal bone, no cases were identified in the current clinical program. However, given the clinical program was limited in duration (e.g. 6-month placebo-controlled trials) and did not include bone biopsies which would be necessary to identify adynamic bone disease the risk for adynamic bone disease was not clearly assessed. An analysis of the data showed that a small but significant

proportion of subjects in the etelcalcetide treatment group had low serum iPTH and low bone specific alkaline phosphatase (BSAP) levels at the efficacy assessment period (EAP) compared to cinacalcet or placebo, placing them at a higher risk of developing adynamic bone disease despite study protocols designed to maintain PTH at recommended levels. Labeling should emphasize the risk for adynamic bone disease with chronic over suppression of iPTH levels. Regular monitoring should be emphasized to maintain iPTH levels (b) (4)

Etelcalcetide provides a clear benefit in lowering iPTH levels in adult patients with chronic kidney disease on hemodialysis with secondary hyperparathyroidism. Treatment with etelcalcetide is associated with lowering of serum calcium which can be helpful in patients already on active vitamin D who may have elevated serum calcium levels which would limit further increase in their vitamin D dose. However all patients especially those with low serum calcium levels need to be monitored for the risk of hypocalcemia and hypocalcemia related symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, cardiac arrhythmias (torsades de pointes & ventricular tachycardia) and worsening heart failure. Additional risks include hypophosphatemia and adynamic bone disease which can be handled with appropriate labeling and monitoring. In a single active-controlled study etelcalcetide provided slightly more efficacy at lowering iPTH levels than the only currently approved calcimimetic, cinacalcet, but appeared to be associated with a greater risk for hypocalcemia and a greater risk of progression to adynamic bone disease, both risks which could be adequately addressed with appropriate monitoring. However, given concern that the study design in the active-controlled study may not have been optimized for maximal cinacalcet response, it is recommended that these results be confirmed by a second study before etelcalcetide can be allowed to claim superiority with respect to lowering iPTH in hemodialysis patients with secondary hyperparathyroidism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Secondary hyperparathyroidism in subjects with chronic kidney disease is a condition in which there is excessive secretion of parathyroid hormone (PTH) in response to low levels of active vitamin D and serum calcium. • Prolonged elevation of PTH causes excessive calcium and phosphorus to be released from bone, leading to metabolic bone disease referred to as renal osteodystrophy resulting in bone pain and fracture, and vascular calcification in skin (calciphylaxis) and cardiovascular and renal soft-tissues	• Prolonged elevation of PTH in secondary hyperparathyroidism is believed to be responsible for renal osteodystrophy and vascular calcification in skin and soft-tissues. • Optimal PTH guidelines to prevent these conditions are not known.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	responsible for increased morbidity and mortality in this population. • The Kidney Disease Improving Global Outcomes (KDIGO) guidelines from 2009 state that the optimal iPTH in dialysis adult patients with secondary hyperparathyroidism due to Stage 5D CKD is not known, but suggest maintaining iPTH levels in the range of 2 to 9 times the upper limit of normal (e.g. 130-600pg/mL).	
Current Treatment Options	• Activated vitamin D analogs: calcitriol, doxercalciferol and paricalcitol which are all available in oral capsules and IV injection formulations • Calcium-sensing receptor agonist: cinacalcet tablets requiring daily oral dosing	• Etelcalcetide is a useful treatment option for hemodialysis patients with secondary hyperparathyroidism that is not adequately treated with activated vitamin D analogs alone or in subjects who cannot tolerate cinacalcet tablets
Benefit	• Efficacy was established in two pivotal, placebo-controlled, 26wk studies, using a responder analysis looking at the number of subjects in the ITT population attaining a mean decrease of >30% in serum iPTH from the pre-treatment baseline during the EAP • The results were statistically significant even after excluding patients who had an increase in active vitamin D analog dose or serum calcium supplements during the pivotal studies, which may have confounded the PTH results. • The exploratory endpoints of serum bone biomarkers gave results which were consistent with etelcalcetide being responsible for a decrease in the excessive bone turnover seen in renal osteodystrophy. • In an double-blind, double-dummy, active-controlled 26 wk study etelcalcetide showed greater efficacy compared to cinacalcet with	• A 30% reduction in iPTH is a surrogate for bone turnover which had been previously used to approve active vitamin D analogs for the treatment of secondary hyperparathyroidism in subjects with chronic kidney disease. • The bone biomarker data support the use of the 30% change in PTH as a surrogate for efficacy. • Using iPTH as a surrogate for efficacy, etelcalcetide showed greater efficacy with respect to cinacalcet in the treatment of hemodialysis subjects with secondary hyperparathyroidism. A

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	respect to the proportion of subjects having > 50% or > 30% reduction in iPTH from baseline. However there were concerns with the study results that suggested the efficacy of the cinacalcet comparator may not have been optimized to justify a direct superiority claim.	second study confirming these results is recommended to confirm a superiority claim.
Risk	• Hypocalcemia is a known risk associated with the use of calcimimetics. Most of the AEs of blood calcium decreased or hypocalcemia seen in the etelcalcetide treatment group in the 6-month, placebo-controlled studies were graded as mild or moderate (99%), only 2 cases (0.4%) were considered severe and non were reported as serious. Only 5 subjects (1%) discontinued etelcalcetide treatment due to an event of hypocalcemia, and 1 subject (0.2%) discontinued due to nausea, while no subjects discontinued due to other symptoms potentially associated with hypocalcemia such as muscle spasms, myalgias, paresthesias, convulsions or hypotension. In the active-controlled, double-blind, double-dummy study hypocalcemia was more common in the etelcalcetide treatment group compared to cinacalcet. • Hypophosphatemia, was uncommon in the placebo-controlled trials with few patients with AEs of hypophosphatemia: 7 patients (1.4%) with etelcalcetide compared to only 1 patient (0.2%) in the placebo group. Of the 7 cases in patients treated with etelcalcetide, 4 were of mild and 3 were of moderate severity but none were considered serious. • While actual adynamic bone disease which occurs due to long term chronic over suppression of PTH, was not identified in these clinical trials with limited duration of treatment, which did not include bone	• Toxicity associated with the use of calcimimetics is primarily related to the risk of hypocalcemia, which can result in symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, cardiac arrhythmias (torsades de pointes & ventricular tachycardia) and worsening heart failure. Labeling to recommend against dosing in subjects with serum calcium levels below the lower limit of normal and including information on symptoms of hypocalcemia should provide adequate risk management. • Hypophosphatemia can typically be controlled with routine monitoring and appropriate changes to diet or concomitant medications without need for interrupting the dose of the calcimimetic. • Labeling should emphasize the risk for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	biopsy data, a small but significant proportion of subjects in the etelcalcetide treatment group had very low serum iPTH and low bone specific alkaline phosphatase (BSAP) levels at the efficacy assessment period compared to cinacalcet or placebo, placing them at a higher risk of developing adynamic bone disease despite study protocols designed to maintain iPTH at recommended levels.	adynamic bone disease with chronic over suppression of iPTH levels and the need for routine regular monitoring.
Risk Management		

2 Therapeutic Context

2.1. Analysis of Condition

Secondary hyperparathyroidism is a condition in which there is excessive secretion of parathyroid hormone (PTH) in response to low levels of active vitamin D and serum calcium. In subjects with worsening chronic kidney disease (CKD) this is triggered by the kidney's inability to adequately excrete phosphorous and reabsorb sufficient calcium, and by the inability of the kidney to adequately 1-hydroxylate 25-hydroxyvitamin D to make the maximally active 1,25-dihydroxyvitamin D analog. Prolonged elevation of PTH causes excessive calcium and phosphorus to be released from bone, leading to the metabolic bone disease referred to as renal osteodystrophy which can result in bone pain and an increased risk of fracture. In addition, excess calcium and phosphorus release from the bone can lead to calcification of the vasculature in skin causing calciphylaxis or soft-tissues such as the heart and kidney resulting in increased morbidity and mortality in this population. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines from 2009 state that the optimal iPTH in adult dialysis patients with secondary hyperparathyroidism due to Stage 5D CKD is not known, but suggest maintaining iPTH levels in the range of 2 to 9 times the upper limit of normal (e.g. 130-600pg/mL).

2.2. Analysis of Current Treatment Options

Three different activated vitamin D analogs are currently available for the treatment of secondary hyperparathyroidism in hemodialysis patients with CKD stage 5D: calcitriol, doxercalciferol and paricalcitol which are all available as oral capsules and IV injection formulations. Vitamin D analogs have been shown to decrease PTH levels by inhibiting PTH synthesis and secretion and are typically used as a first line treatment if dietary adjustments are not effective. However, vitamin D analogs also increase calcium absorption from the GI tract and so can be limited in their use due to the development of hypercalcemia. Other drug-related AEs associated with the use of vitamin D analogs include hypophosphatemia and adynamic bone disease.

Cinacalcet in a calcium-sensing receptor agonist currently also approved for the treatment of secondary hyperparathyroidism in hemodialysis patients. It is an oral tablet that has to be given daily. It directly lowers serum PTH levels by increasing the sensitivity of the calcium-sensing receptor in the parathyroid gland to extracellular calcium. The reduction in PTH levels is then associated with a decrease in serum calcium and phosphorous levels. Cinacalcet is therefore useful in the treatment of subjects who still have elevated PTH levels on active vitamin D therapy but who are limited in further increasing the vitamin D analog dose due to the risk for

hypercalcemia. It has also been shown to be effective in subjects not currently on vitamin D analogs as long as serum calcium and phosphorous levels are adequate. Drug related AEs associated with the use of cinacalcet are hypocalcemia, adynamic bone disease, nausea and vomiting. Special precautions are recommended in subjects with hepatic impairment as the drug is typically metabolized in the liver and cinacalcet exposure can become elevated in patients with moderate to severe hepatic impairment. Also cinacalcet is a strong inhibitor of CYP2D6 and is partially metabolized by CYP3A4 so serum levels may be elevated with co-administration of a strong CYP3A4 inhibitor.

An intravenous calcium-sensing receptor agonist would potentially be beneficial in subjects who could not tolerate cinacalcet because of GI discomfort, active liver disease or treatment with multiple concomitant medications that are metabolized by relevant CYP enzymes. Three times a week intravenous dosing after hemodialysis sessions could potentially also provide improved compliance in certain patients who have difficulty keeping track of their daily oral medications.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Etelcalcetide is an NME and not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 109773 was opened by KAI Pharmaceuticals in August 19, 2010 for the use of etelcalcetide (KAI-4169) in the treatment of secondary hyperparathyroidism in end stage renal disease patients. On July 5, 2012 KAI Pharmaceuticals including KAI-4169 were acquired by Amgen.

At the EOP2 meeting in July 9, 2012, the Division agreed that two randomized, double-blind, 26-week, placebo-controlled clinical studies to be conducted in hemodialysis subjects with secondary hyperparathyroidism and an extension study allowing for open label treatment of subjects from the 2 pivotal phase 3 studies for at least an additional 52 weeks were adequate to support the proposed indication. We agreed that the primary endpoint, proportion of subjects with > 30% reduction from baseline in predialysis PTH, was appropriate for the 2 pivotal phase 3 placebo-controlled studies. We agreed to a waiver for the thorough QTc study and instead recommended ECG assessments during the course of the pivotal studies. We did not agree that the sponsor's proposed indication (b) (4) in this patient population was appropriate for this drug class. We recommended that if the sponsor was planning to do a comparator study vs. cinacalcet that it be performed as a double-blind, double-dummy study to help maintain the study blind.

Neither the pivotal placebo-controlled nor the active-controlled study vs. cinacalcet were performed under a Special Protocol Agreement (SPA). However, the carcinogenicity studies in Sprague Dawley rats and transgenic rasH2 mice were performed under SPA agreements.

In November 2014 the applicant requested advice from the agency about the possible use of a (b) (4) (b) (4)

In May 2015 at the Type B Pre-NDA meeting general agreements regarding the NDA filing package were obtained.

3.3. Foreign Regulatory Actions and Marketing History

Etelcalcetide is not currently marketed in any foreign jurisdiction.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Study site inspections were performed at two sites each for studies 20120229, 20120230 and 20120360. Domestic sites were chosen based on the OSI site selection tool.

Name Address Site#	Protocol # and # of Subjects	Reason for inspection	Classification
Geoffrey A. Block, M.D. 130 Rampart Way, Suite 175 Denver, CO 80230 Site 66004	20120230 23 subjects	ranked #3 for Study 230 and had reported financial interest	No Action Indicated (NAI)

Raffi R. Minasian, M.D. 1427 South Glendale Avenue Glendale, CA 91205 Site 66006	20120230 23 subjects	ranked #1 for Study 230 and had a previous inspection in February 2015 with OAI, downgraded to VAI	No Action Indicated (NAI)
Lakhi H. Sakhrani, M.D. 801 South San Gabriel Boulevard San Gabriel, CA 91776 Site 66059	20120360 18 subjects	ranked #4 for Study 360 and was a high US enroller	Voluntary Action Indicated (VAI)
Kwabena Ntoso, M.D. 150 South Independence Mall Suite 100, Public Ledger Building Philadelphia, PA 19106 Site 66009 Site 66086	20120229 18 subjects 20120360 2 subjects	ranked #3 for Study 229 and was the highest enroller site was also involved with Study 360; ranked #131 with two subjects enrolled	No Action Indicated (NAI)
Prince J. Sidhu, M.D. 521 East Michigan Avenue Kalamazoo, MI 49007 Site 66089	20120229 7 subjects	ranked #6 for Study 229 with many adverse events reported	No Action Indicated (NAI)
Douglas C. Lanier, Jr., M.D. South Mississippi Medical Research 4300 B West Railroad Street Gulfport, MS 39501	20120360 9 subjects	ranked #22 for Study 360, but site had never been inspected	No Action Indicated (NAI)

The clinical sites, from Drs. Block (#66004), Minasian (#66006), Ntoso (#66009, #66086), Sidhu (#66089), and Lanier (#66013) were classified as No Action Indicated (NAI) as they revealed no regulatory violations. One site from Dr. Sakhrani (#66059), which was the high US enroller for Study 20120360 was classified as Voluntary Action Needed (VAI) because of problems with strictly following study protocols and with transferring all information to the eCRF. The investigator also came under review for GCP issues related to (b) (6) (b) (6) (b) (6). Although regulatory violations were noted the audit did not indicate serious deviations/findings that would have impacted on the validity or reliability of the submitted data for study 20120360 relevant to this NDA. Therefore data from this site were also considered acceptable.

In conclusion, the overall integrity and submission quality of the data from these six sites that were inspected were found to be adequate to support the current NDA.

4.2. Product Quality

The primary quality review of the drug substance was performed by John Leginus, Ph.D. and recommended approval. Etelcalcetide is supplied for intravenous administration as a sterile, single-use, preservative-free liquid solution in a 3-cc Type I glass vial with 13 mm stopper. It is formulated at a 5 mg/mL concentration 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. All the excipients used adhere to compendial standards. The deliverable volume and over the proposed dose range of 2.5 to 15mg would be 0.5 to 3mL.

The Biopharmaceuticals Review performed by Chen Hansong compared the (b) (4) formulation to the liquid formulation which is the to-be-marketed product and found the minor differences would not affect in vivo performance and a biowaiver was granted.

4.3. Clinical Microbiology

The product quality microbiology review was performed by Peggy Kriger, PhD and recommended approval on the basis of sterility assurance. (b) (4) drug solution is (b) (4) Endotoxin specifications at the maximal proposed dose were within the USP recommendation of (b) EU/kg/hr.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical/Pharmacology studies demonstrated that etelcalcetide was a selective allosteric activator of the calcium sensing receptor in the parathyroid. All adverse effects were attributable to low serum calcium levels. No clear off-target toxicities were identified. No clinically relevant safety signals were observed in cardiovascular, neurologic or respiratory safety pharmacology studies.

Repeat IV dose toxicity studies were conducted in rats at doses up to 5 mg/kg every day for durations up to 6 months and in dogs at doses up to 1.5 mg/kg every other day for durations up to 9 months. The increased dosing frequency in the rats was to account for the shorter half-life of etelcalcetide in that species. Toxicities observed in rats and dogs resulted from the expected pharmacologic effects of PTH suppression in healthy animals, predominantly decreased serum calcium and were reversible once the study drug was discontinued. The No Observed Adverse Effect Levels (NOAEL) for hypocalcemia in animals with normal kidney function and without secondary hyperparathyroidism represented 0.7-fold and 0.15-fold the maximum clinical dose of 15 mg, based on AUC comparisons according to the Non Clinical Review.

Etelcalcetide was not genotoxic in standard assays.

Etelcalcetide was not carcinogenic in Tg rasH2 transgenic mice at up to 3.0 mg/kg/day or in rats at up to 1.6 mg/kg/day. The 1.6 mg/kg/day dose in rats represents 0.4-fold the maximum clinical dose of 15 mg administered three times per week based on AUC.

Etelcalcetide was detected in breast milk in rats at concentrations similar to plasma.
Low placental transfer of etelcalcetide was observed in rats, with fetal levels measuring 2.4 to 3.0% that of maternal levels. Maternal toxicity occurred in rats at 3.0 mg/kg/day during the perinatal period. This dose produced etelcalcetide exposures 1.8-fold the clinical exposures at 15 mg administered 3 times per week based on AUC, which was associated with marked reductions in serum calcium, decreased body weight/body weight gain and food consumption, delayed estrous cycle, and increased follicular cysts. Lower mean fetal body weight, small delays in time to parturition, increased pup mortality, and transient decreases in pup growth rates were also observed at this maternally toxic dose. However, etelcalcetide resulted in no reproductive or development toxicity in rats and rabbits in the absence of maternal toxicity.

Local tolerance studies with etelcalcetide showed no adverse injection site reactions when administered by the IV route in dogs.

In conclusion the Pharmacology/Toxicology review recommended approval of etelcalcetide for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.

Medical officer's comments-

The major toxicities seen in the animal studies were related to low serum calcium levels. Given that serum calcium levels are regularly monitored during standard of care in the treatment of subjects with secondary hyperparathyroidism on hemodialysis, the risk of hypocalcemia will be adequately addressed in this study population.

There were no clear off target toxicities seen in the healthy animal studies. But when asked specifically about emesis and stomach erosion to go along with the nausea, vomiting and GI bleed seen in some patients there was some evidence for these in the mid and high doses:

- *emesis was seen in a few dogs (at mid and high doses; 6 month dog and 7 day dog studies – Study No 119036 and Study No 4169-NC-101) and*

- *glandular stomach (erosion) was seen in a few rats (at mid and high doses; 6 month rat studies – Study No 119037 and Study No 4169-NC-133 and 7 day rat study – Study No 2082-NC-100)*

Even though etelcalcetide can be detected in breast milk in rats at concentrations similar to plasma, given that it is a peptide and likely to be degraded following oral ingestion it is likely that only limited amounts if any would be expected to be absorbed intact into the circulation following oral feeding, mitigating the potential risk associated with breast feeding.

The abnormal findings in the reproductive or development toxicity studies in rats and rabbits were related to severe hypocalcemia and thereby probably over represent the human risk due to etelcalcetide as pregnant women would be closely monitored for the risk of hypocalcemia during their pregnancy. However, given that small levels of etelcalcetide due pass through the placental barrier in animal studies, it is still unknown whether this low level of exposure would pose potential risk for the developing fetus. Therefore use in this population should be avoided unless adequate control of secondary hyperparathyroidism is not possible without this medication, as secondary hyperparathyroidism is likely to pose a risk to the developing fetus as well.

4.5. Clinical Pharmacology

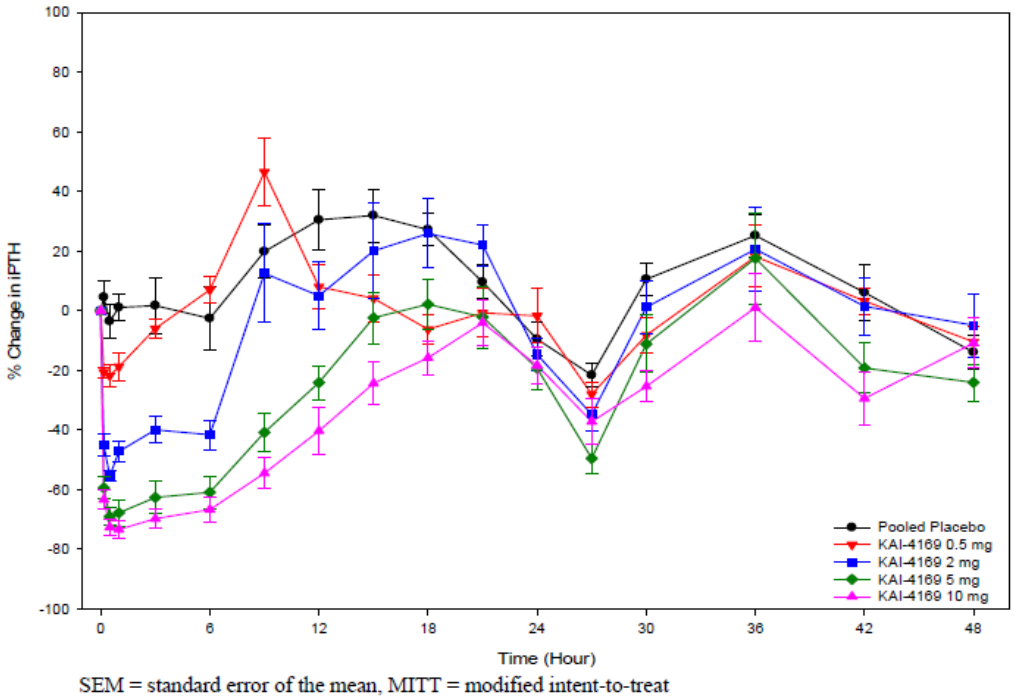
4.5.1. Mechanism of Action

Etelcalcetide is an allosteric activator of the calcium sensing receptor in the parathyroid, binding directly to the extracellular domain and activating the receptor at a site which is distinct from the calcium activating site. Since serum calcium levels are regulated by PTH, lowering of PTH levels by etelcalcetide leads to a corresponding decrease in calcium levels. In a study with isolated rat parathyroid glands, etelcalcetide suppressed secretion of PTH across a range of physiologically relevant calcium concentrations. In normal rats and dogs, etelcalcetide administration suppressed PTH secretion within an hour in a dose-dependent and reversible manner. In rat models of uremia and secondary hyperparathyroidism, etelcalcetide was also effective at reducing circulating levels of PTH.

4.5.2. Pharmacodynamics

In healthy volunteers the maximum serum PTH reduction from baseline was rapid and occurred within 30 minutes after a single IV dose. Maximum reductions at 30 minutes post dose in placebo, 0.5, 2, 5, and 10 mg dose groups were dose-dependent at 3.5%, 21.7%, 55.4%, 69.0%, and 72.6%, respectively.

Figure 1 Mean (SEM) % change in Serum iPTH Over Time in Healthy Volunteers (Study 20130107)

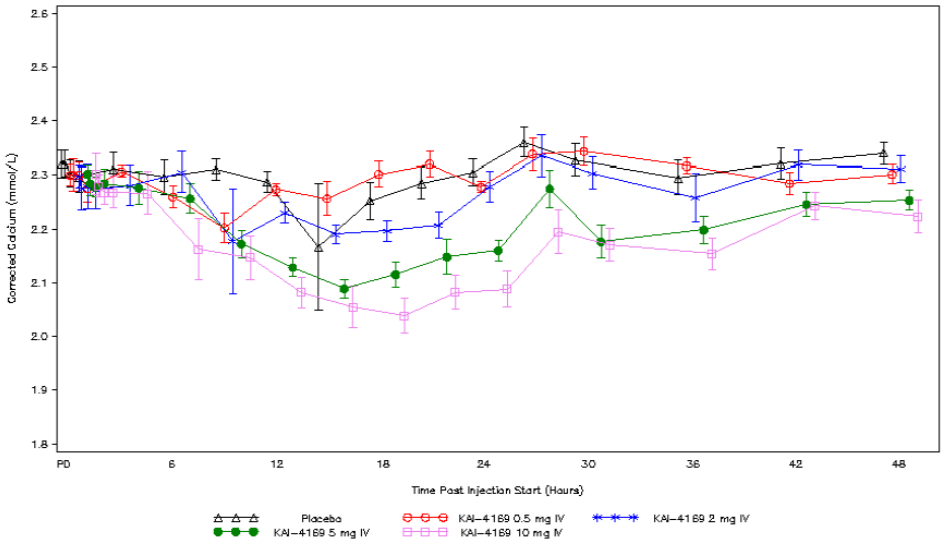


SEM = standard error of the mean, MITT = modified intent-to-treat

Source Fig. 12 CSR Study 20130107

Reduction of calcium, secondary to the reduction in PTH, was maximal at 12 to 18 hours post dose and returned to baseline within 24 to 48 hours after dosing.

Figure 2 Mean (SEM) Serum Corrected Calcium over Time in Healthy Volunteers (Study 20130107)



SEM = standard error of the mean, MITT = modified intent-to-treat, PD = pre-dose assessment
Note: Treatments are offset for ease of interpretation.
Source Fig. 13 CSR Study 20130107

4.5.3. Pharmacokinetics

The PK of AMG 416 is linear over the dose range of 0.5 to 10mg in healthy subjects and over the dose range of 5 to 60mg in CKD patients with secondary hyperparathyroidism receiving hemodialysis.

Figure 3 PK for Etelcalcetide in Healthy Volunteers

Cohort (dose)	n	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL (L/h)	Vss (L)
1 (2 mg/person)	6	164 (28)	20 (1)	315 (38)	361 (43)	5.60 (0.61)	164 (26)
2 (5 mg/person)	6	405 (40)	20 (3)	724 (80)	828 (104)	6.11 (0.70)	171 (26)

AUC_{last} = area under the concentration-time curve from time 0 to last time point with quantifiable concentration before the next hemodialysis; AUC_{inf} = area under the concentration-time curve time 0 to last time point with quantifiable concentration before the next hemodialysis; C_{max} = maximum observed concentration; CL = systemic clearance; PK = pharmacokinetics; $t_{1/2}$ = terminal half-life; Vss = volume of distribution at steady state
Source: Modified from Table 11.4.1-2 in Study ONO-5163-01 CSR

Biotransformation products are primarily formed by reversible disulfide exchange with serum albumin. Intact etelcalcetide accounted for approximately 17% of the total radioactive $AUC_{0\text{-}68hr}$ in plasma before the first dialysis after dose administration. The most abundant biotransformation products in plasma were the covalent protein disulfide bound adducts which represented 73% of the total radioactivity in the AUC pooled plasma.

After IV bolus administration in end stage renal disease patients, plasma etelcalcetide quickly declined from its peak concentration and remained detectable over a sampling period of approximately 65 hours. The disposition of etelcalcetide exhibited a multiple exponential decay. When available, the terminal elimination half-life ranged from approximately 83.7 to 183 hours, or 3.5 to 7.6 days. Clearance and volume of distribution at steady state values appeared to be dose-independent over the dose range evaluated. The hemodialysis clearance was estimated at 47.4 L/hr, more than 18 times higher than the population mean clearance estimated at 2.58 L/hr. Therefore etelcalcetide is eliminated primarily by hemodialysis in CKD patients and consequently, should not be administered during hemodialysis. The plasma accumulation ratio of etelcalcetide was 2 to 3-fold by week 4 and 3 to 5-fold by month 6.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this submission.

4.7. Consumer Study Reviews

Not applicable to this submission.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled	Subject Diagnosis and Key Entry Criteria	Study Duration[a]	Study Status, Report Type, and Location
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)							
Efficacy/Safety 20120330 (formerly KAI-4169-003)	Change from baseline in PTH, PK, safety, and tolerability	Phase 2a, multicenter, randomized, double-blind, placebo-controlled, multiple-dose, dose escalation	5 or 10 mg AMG 416 or placebo TIW for 2 or 4 weeks	AMG 416: 45 Placebo: 42	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD	41 to 55 days	Completed; full CSR/ 5.3.5.1 (20120330)
Efficacy/Safety 20120229 (formerly KAI-4169-006)	Reduction from baseline of predialysis PTH by > 30%, PK, safety, and tolerability	Phase 3, multicenter, randomized, double-blind, placebo-controlled	5-mg AMG 416 starting dose (maximum dose of 15 mg) or placebo TIW for 26 weeks	AMG 416: 254 Placebo: 254	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD	30 weeks	Completed; full CSR/ 5.3.5.1 (20120229)
Efficacy/Safety 20120230 (formerly KAI-4169-007)	Reduction from baseline of predialysis PTH by > 30%, PK, safety, and tolerability	Phase 3, multicenter, randomized, double-blind, placebo-controlled	5-mg AMG 416 starting dose (maximum dose of 15 mg) or placebo TIW for 26 weeks	AMG 416: 255 Placebo: 260	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD	30 weeks	Completed; full CSR/ 5.3.5.1 (20120230)
Efficacy/Safety 20120360	Reduction from baseline of predialysis PTH by > 30%, safety, and tolerability	Phase 3, multicenter, active-controlled, double-blind, double-dummy, multiple dose	5-mg IV AMG 416 TIW starting dose (titrated between 2.5 and 15 mg) and oral placebo daily for 26 weeks; or 30-mg oral cinacalcet daily starting dose (maximum dose of 180 mg) and IV placebo TIW for 26 weeks	AMG 416: 340 Cinacalcet: 343	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD	30 weeks	Completed; full CSR/ 5.3.5.1 (20120360)
Study Reports of Uncontrolled Clinical Studies (Module 5.3.5.2)							
Efficacy/Safety 20120331 (formerly KAI-4169-005)	Change from baseline in PTH, PK, safety, and tolerability	Phase 2, multicenter, open-label, single-arm, multiple-dose, dose titration	5-mg AMG 416 TIW starting dose (maximum dose of 20 mg) for 12 weeks	AMG 416: 37	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD	16 weeks	Completed; full CSR/ 5.3.5.2 (20120331)
Efficacy/Safety 20120359	Incidence of serum corrected calcium values < 7.5 mg/dL and safety	Phase 3, multicenter, open-label, single-arm, multiple-dose, switch study from oral cinacalcet HCl to IV AMG 416	5 mg AMG 416 TIW for 4 weeks (minimum dose of 2.5 mg)	AMG 416: 158	Male and female subjects ≥ 18 years of age with CKD and secondary HPT receiving HD on a stable dose of cinacalcet	8 weeks	Completed; full CSR/ 5.3.5.2 (20120359)
Safety 20120334 (formerly KAI-4169-005-01)	Safety, tolerability, and efficacy	Phase 2, multicenter, open-label, single-arm extension of Study 20120331	2.5 to 15 mg AMG 416 TIW for 40 weeks with an additional 2 years of open-label treatment	AMG 416: 30	Male and female subjects with CKD and secondary HPT receiving HD who completed treatment in Study 20120331	Approx. 156 weeks[c]	Terminated; full CSR/ 5.3.5.2 (20120334)
Safety 20120231 (formerly KAI-4169-008)	Safety, tolerability, and efficacy	Phase 3, multicenter, open-label, single-arm extension of Studies 20120229, 20120230, and 20120359	5-mg AMG 416 TIW starting dose (maximum dose of 15 mg) for 52 weeks	AMG 416: 891	Male and female subjects with CKD and secondary HPT receiving HD who completed Studies 20120229, 20120230, or 20120359 or were discontinued for rising PTH from Studies 20120229, or 20120230	56 weeks	Ongoing; interim full CSR/5.3.5.2 (20120231)
Safety 20130213	Long-term safety, tolerability, and efficacy	Phase 3, multicenter, open-label, single-arm long-term extension of Studies 20120231, 20120334, and 20120360	2.5 to 15 mg AMG 416 TIW for approximately 2.5 years after the first subject was enrolled	AMG 416: 559[d]	Male and female subjects with CKD and secondary HPT receiving HD who completed treatment in Studies 20120231 or 20120360 or participated in Study 20120334	Approx. 2.5 years	Ongoing; interim full CSR/5.3.5.2 (20130213)

5.2. Review Strategy

The two 6-month, pivotal, placebo-controlled studies 20120229 and 20120230 and one 6-month active-controlled study 20120360 comparing etelcalcetide to cinacalcet are the focus of the efficacy review. This review includes the applicant's analyses for efficacy with this medical reviewer's commentary. A separate analysis and review was performed but the FDA Statistician Dr. Alexander Cambon and confirmed the sponsor's findings of efficacy.

The safety data analyzed included data from both the controlled trials described above and open-label extensions 20120331, 20120334 and 20130213. This review includes the sponsor's analyses with this medical reviewer's commentary, as well as analyses generated by this medical reviewer using the JMP and MAED software, which pooled data from the two pivotal studies, 20120229 and 20120230 to compare etelcalcetide to placebo and which analyzed data from the active controlled study 20120360 separately.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 20120229-A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects with Chronic Kidney Disease on Hemodialysis

6.1.1. Study Design

Overview and Objective

Study 20120229 was a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of AMG 416 in the treatment of secondary hyperparathyroidism in subjects with chronic kidney disease who were receiving hemodialysis.

Trial Design

Studies 20120229 and 20120230 were designed as identical 26 week, double-blind, randomized, multi-center, placebo-controlled, Phase 3 studies to evaluate the efficacy and safety of etelcalcetide in the treatment of secondary hyperparathyroidism in hemodialysis subjects with CKD, except for additional assessments of post-hemodialysis electrocardiograms and post-hemodialysis lab and PK sampling in Study 20120229. All subjects, regardless of treatment assignment, were to receive standard of care with calcium supplements, active vitamin D sterols, and phosphate binders, as prescribed by their individual Investigator. Subjects were randomized 1:1 to etelcalcetide or placebo. Randomization was stratified by

baseline serum iPTH (< 600 pg/mL, between 600 and 1000 pg/mL, or > 1000 pg/mL) obtained within 2 weeks prior to randomization, recent cinacalcet use within 8 weeks prior to randomization, and region: North America vs. non-North America.

Table 1 Randomization by Stratification Categories in the Pivotal Studies

Stratification Factor Category	20120229 Placebo (N = 254) n (%)	20120229 AMG 416 (N = 254) n (%)	20120230 Placebo (N = 260) n (%)	20120230 AMG 416 (N = 255) n (%)	Total placebo-controlled studies Placebo (N = 514) n (%)	Total placebo-controlled studies AMG 416 (N = 509) n (%)
Mean screening serum iPTH (pg/mL)						
<600	84 (33.1)	87 (34.3)	84 (32.3)	84 (32.9)	168 (32.7)	171 (33.6)
≥600 to ≤1000	114 (44.9)	115 (45.3)	121 (46.5)	118 (46.3)	235 (45.7)	233 (45.8)
>1000	56 (22.0)	52 (20.5)	55 (21.2)	53 (20.8)	111 (21.6)	105 (20.6)
Recent cinacalcet use within 8 weeks prior to randomization						
Yes	34 (13.4)	33 (13.0)	33 (12.7)	29 (11.4)	67 (13.0)	62 (12.2)
No	220 (86.6)	221 (87.0)	227 (87.3)	226 (88.6)	447 (87.0)	447 (87.8)
Region						
North America	129 (50.8)	132 (52.0)	150 (57.7)	146 (57.3)	279 (54.3)	278 (54.6)
Non-North America	125 (49.2)	122 (48.0)	110 (42.3)	109 (42.7)	235 (45.7)	231 (45.4)

Studies 20120229 and 20120230 were conducted at 111 and 97 centers, respectively, in the United States, Canada, Europe, Israel, Russian Federation, and Australia. Enrollment of subjects with mean screening iPTH > 1000 pg/mL was to be limited to approximately 20% of subjects. Eligible subjects were adults ≥ 18 years of age receiving hemodialysis three days per week (TIW) for ≥ 3 months. Subjects had stable dialysate calcium concentration (≥ 2.25 mEq/L) and had screening predialysis PTH of > 400 pg/mL and corrected serum calcium (cCa) ≥ 8.3 mg/dL. Subjects who were receiving vitamin D sterols, phosphate binders, or calcium supplements were required to have been on stable doses.

Inclusion criteria for studies 20120229 and 20120230 (including but not limited to):

- 18 years of age or older
- Receiving hemodialysis TIW for at least 3 months
- Subjects receiving vitamin D sterols, phosphate binders or calcium supplements must be on a stable dose of the medication and expected to maintain those stable doses for the duration of the study.
- Dialysate calcium concentration must be on a stable dose of ≥2.25 mEq/L prior to randomization and expected to stay on that stable dose for the duration of the study.
- On two consecutive screening labs within 2 wks of randomization
    - Mean Serum iPTH >400 pg/mL (enrollment of iPTH >1000 pg/mL will be limited to 20% of subjects)
    - Serum cCa ≥8.3 mg/dL
- Stable medical condition based on medical history, PE, and routine labs in the judgment of the investigator

- Female subjects of childbearing potential must agree to remain abstinent or use effective contraception for the duration of the study and for 3 months after the last dose, and must have a negative serum pregnancy test within 2 weeks of the first study dose.

Exclusion criteria for studies 20120229 and 20120230 (including but not limited to):

- History of kidney transplant or parathyroidectomy or anticipated to have the procedure during the study period.
- Previously received etelcalcetide in a prior clinical trial
- Exposure to cinacalcet within 4 weeks prior to screening labs
- Pregnant or nursing female
- Abnormal screening labs including but not limited to:
    - serum albumin ≤3.0g/dL
    - serum magnesium <1.5mg/dL
    - SGOT or SGPT >2.5xULN
- History of symptomatic ventricular dysrhythmias or Torsade de Pointes
- Poorly controlled hypertension
- CHF NYHA classification III or IV, symptoms of angina pectoris at rest or with minimal activity within the past 6 months
- History of MI, coronary angioplasty, or CABG within past 6 months
- History of a seizure disorder requiring treatment in the past 12 months
- Surgery, excluding minor surgery, within the past 8 weeks prior to screening
- History of any illness that in the opinion of the investigator might confound the study results or pose an additional risk to the subject

The starting dose of etelcalcetide 5 mg or placebo was administered intravenously before or during rinse-back at the end of each hemodialysis session three times weekly (TIW) for 26 weeks. At least 150 mL of rinse-back volume was administered after the injection to ensure the entire dose reached the systemic circulation. If the rinse-back was completed without administration of the investigational product, the drug product was administered intravenously followed by a saline flush of at least 10 mL. The dose could be increased at 4-week intervals, at study weeks 5, 9, 13, and 17 by 2.5 mg or 5 mg on the basis of the predialysis PTH and cCa concentrations obtained in the prior week which corresponded to at least 3 weeks of treatment at the prior dose level.

Predialysis iPTH (pg/mL)		Serum Calcium		AEs	Etelcalcetide adjustment
>450	&	≥ 7.5mg/dL	&	No symptomatic hypocalcemia or ongoing AE	Increase by 5mg
>300 but ≤450	&	≥ 7.5mg/dL	&	No symptomatic hypocalcemia or ongoing AE	Increase by 2.5mg
≤300	&	≥ 7.5mg/dL	&	No symptomatic hypocalcemia or ongoing AE	Maintain dose
Two consecutive <100	or	< 7.5mg/dL	or	Symptomatic hypocalcemia or other ongoing AE	Dose Suspended until Criteria resolved
The lower limit of normal in the calcium assay was 8.3mg/dL.					

Serum Phosphorous	Phosphate binder dose
≥ 3.0 mg/dL and ≤5.5mg/dL	No change in dose
2 Consecutive values > 5.5mg/dL	increase permitted
2 Consecutive values < 3.0mg/dL	decrease permitted
The upper limit of normal in the phosphorous assay was 5.1mg/dL. The lower limit of normal in the phosphorous assay was 2.2mg/dL.	

Serum corrected Calcium	Active Vitamin D analogs
≤10.6 mg/dL	No change in dose
2 Consecutive values > 10.6 mg/dL	decrease permitted
2 Consecutive values > 11.0 mg/dL or symptomatic hypocalcemia	decrease or discontinuation permitted
The upper limit of normal in the calcium assay was 10.6mg/dL	

The maximum dose of etelcalcetide was 15 mg; the minimum dose was 2.5mg.

Medical Officer's comments-

A 26 week randomized, double-blind, placebo-controlled trial is considered an appropriate study design for this condition.

Table 2 Schedule of Assessments for 20120229 and 20120230

	Screening	Treatment Period[a]															
Study Week (Day)		**Day 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Investigational product administration		Three times per week with hemodialysis treatment																
Dose titration						T				T				T				T
Informed consent	X																	
Inclusion/ exclusion	X																	
Medical history & hemodialysis symptoms	X																	
Prior & concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																	
Randomization[b]		X																
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior to dialysis																		
12-Lead ECG[c]	X	X				X								X				
Pregnancy test	X												X					
Hematology	X	X				X								X				
Chemistry 1	X	X				X								X				
Albumin, Ca, and phosphorus	X		X	X	X		X	X	X	X	X	X	X		X	X	X	X
Albumin and Ca																		
PTH	X	X	X		X		X		X		X		X		X		X	
Pharmacokinetics		X			X	X							X	X				
25(OH)D		X																
BSAP		X											X					
FGF-23		X											X					
CTX		X											X					
Anti-AMG 416 antibodies		X											X					
Hepatitis B and C serology		X																
Archive plasma & serum		X											X					
After dialysis																		
12-Lead ECG[c] (10 to 30 min postdose)	X	X				X								X				
Pharmacokinetics (10 to 30 min postdose)		X				X								X				
Chemistry 2 (10 to 30 min postdose)	X	X				X								X				
PTH (10 to 30 min postdose)	X	X				X								X				
Pulse and blood pressure[d]	X	X			X				X				X				X	
Weight	X	X			X				X				X				X	

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	Treatment Period[a]							Follow-up		
Study Week (Day)	**18**	**19**	**20**	**22**	**24**	**26**	**27[e]**	**30 days after last dose ± 3 days**	**Early Term**	**Dose Suspension**
Investigational product administration	Three times per week with hemodialysis treatment									
Dose titration										
Informed consent										
Inclusion/ exclusion										
Medical history & hemodialysis symptoms										
Prior & concomitant medication	X	X	X	X	X	X	X	X	X	
Physical examination							X	X	X	
Randomization										
Adverse events[f]	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	
Prior to dialysis										
12-Lead ECG[c]						X			X	
Pregnancy test					X			X	X	
Hematology						X		X	X	
Chemistry 1						X		X	X	
Albumin, Ca, and phosphorus	X	X	X	X	X		X			
Albumin and Ca										X[g]
PTH	X		X	X	X	X	X	X	X	
Pharmacokinetics			X			X		X	X	
25(OH)D										
BSAP							X		X	
FGF-23							X		X	
CTX							X		X	
Anti-AMG 416antibodies							X	X	X	
Hepatitis B and C serology										
Archive plasma & serum							X		X	
After dialysis										
12-Lead ECG[c] (10 to 30 min postdose)						X				
Pharmacokinetics (10 to 30 min postdose)						X				
Chemistry 2 (10 to 30 min postdose)						X				
PTH (10 to 30 min postdose)						X				
Pulse and blood pressure[d]			X		X		X	X	X	
Weight			X		X		X	X	X	

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25(OH)D = 25-hydroxy vitamin D; BSAP = bone-specific alkaline phosphatase; cCa = corrected calcium; Ca = calcium; CTX = collagen type 1 cross-linked C-telopeptide; ECG = electrocardiogram; FGF-23 = fibroblast growth factor-23; PTH = parathyroid hormone.

[a] Baseline assessments were performed on the first day of dosing with investigational product (Day 1). Assessments during the treatment period were performed during the designated study week on the same hemodialysis treatment day of the week as the day dosing was started whenever possible.
[b] Randomization was performed within 1 day before the first dose of investigational product.
[c] Subjects remained supine or sitting for at least 10 minutes before recording 12-lead ECGs, and were supine during the 12-lead ECG. The screening predialysis ECG was a single recording; all other predialysis and postdialysis ECG recordings were performed in triplicate with recordings approximately 2 minutes apart. All postdialysis blood collection was performed before the ECG recordings.
[d] Subjects remained sitting for at least 5 minutes before all measurements of pulse rate and blood pressure.
[e] Week 27 assessments were performed on the day of the first hemodialysis treatment after the last dose of investigational product.
[f] Subjects were followed for both adverse events and serious adverse events for 30 days after the last dose of investigational product.
[g] When dosing with investigational product was suspended for cCa < 7.5 mg/dL, a predialysis serum sample for albumin and calcium was submitted to the central laboratory on the day dosing is suspended. Dose suspension samples did not need to be collected if a routine chemistry or albumin/calcium/phosphorus sample is obtained on the same day.

Study Endpoints

Cinacalcet the only currently approved calcimimetic was approved in 2004 for the treatment of secondary hyperparathyroidism in dialysis patients with CKD using iPTH as a surrogate for improvement in bone turnover and bone structure due to renal osteodystrophy. The three pivotal 26 wk trials consisted of 12 to 16 wk titration phases followed by 14 to 10 wk, respective maintenance phases and randomized at total of 1,136 pts. The primary endpoint was the % of subjects with a mean iPTH ≤250 pg/mL during the Efficacy Assessment Phase (EAP). Across the three trials mean baseline iPTH levels ranged between 630 and 847pg/mL, and 35 to 46% of cinacalcet treated subjects achieved the primary endpoint compared to 4 to 6% of the placebo treated subjects ($p<0.001$). Positive results were also obtained for the secondary endpoint of ≥30% reduction in iPTH with 59 to 68% of cinacalcet treated subjects achieving that endpoint compared to 10 to 11% of the placebo treated subjects ($p<0.001$).

The choice, at the time, of the primary endpoint of mean iPTH ≤250 pg/mL was consistent with the 2003 NKF/KDOQI guidelines which recommended a PTH target of 150 to 300pg/mL for subjects with Stage 5 CKD on renal dialysis. In 2009 the International Society of Nephrology issued the revised Kidney Disease: Improving Global Outcomes (KDIGO) guidelines which suggested maintaining iPTH in the range of 2 to 9-times the upper reference of the assay, typically corresponding to 130 -600pg/mL instead of the 150 to 300pg/mL range which had been previously recommended and initiation of therapy to better control PTH for "marked changes" in either direction[1]. The reasoning behind the wider acceptable range in the newer guidelines took into account the large inter assay variability of commercially available PTH assays currently in use. The reasoning for a higher acceptable dose range related to findings that show skeletal resistance to PTH in CKD patients on renal dialysis[2] so subjects may need higher PTH levels to maintain normal serum calcium, and the fact that while observational studies have linked elevated PTH with mortality there was a lack of randomized controlled trial data to support improvement in clinical outcomes with treatment based on specific PTH goals.

In addition to cinacalcet two active vitamin D analogs, Zemplar and Hectorol have also been approved for the treatment of secondary hyperparathyroidism in dialysis patients with CKD using iPTH as a surrogate endpoint. Given that the Division had used the surrogate of iPTH as a primary endpoint for the treatment of secondary hyperparathyroidism in the dialysis population in the past and without definitive evidence that this was no longer appropriate the Division recommended the use of the responder rate of > 30% decrease in iPTH as the primary

[1] https://www.kidney.org/sites/default/files/docs/kdoqi-ckd-mbd-commentary.pdf KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD) American Journal of Kidney Diseases 55: No 5 (May), 2010: pp 773-799
[2] Irfana H. Soomro and David S. Goldfarb, Dysphoria Induced in Dialysis Providers by Secondary Hyperparathyroidism, *Clin J Am Soc Nephrol* 10: 9–11, 2015

endpoint at both a type C meeting in Feb. 2012 and a type B EOP2 meeting in July 2012. The pivotal trials were not reviewed under a Special Protocol Assessment.

Statistical Analysis Plan

The Full Analysis Set was used for the primary analysis. It included all randomized patients with dose based on assigned treatment group. Subjects with no scheduled assessments during the EAP weeks 20 to 27 were considered nonresponders. Sensitivity analyses included a Completer Analysis Set (i.e. including only subjects with at least one iPTH value during EAP), and a Modified Last Values Carried Forward (Modified LVCF) Set (i.e. subjects with at least 8 wks of drug exposure and missing an EAP value had the last previous value carried forward for their endpoint measurement). The primary endpoint and each of the secondary endpoints were also to be tested at a 2-sided significance level of 0.05 using data from the 6-month placebo-controlled combined dataset.

The Safety Analyses Set consists of all subjects who received at least one dose of investigational product.

Multiplicity adjustment using a hierarchical testing procedure was performed to maintain the overall significance level for the secondary endpoints.

Primary endpoint analysis-
The proportion of subjects with > 30% reduction from baseline in predialysis PTH during the EAP was analyzed using a Cochran-Mantel-Haenszel test stratified by the following study-level randomization stratification factors

- screening PTH category (< 600, ≥ 600 to ≤ 1000, and > 1000 pg/mL),
- recent cinacalcet use within 8 weeks prior to randomization (yes and no),
- region (North America and non-North America), and
- study (20120229 and 20120230; integrated analysis only).

Subjects were considered as not achieving the endpoint if they did not have data during the EAP (i.e., nonresponder imputation).

Secondary efficacy endpoint analyses-
The proportion of subjects with predialysis PTH ≤ 300 pg/mL during the EAP was analyzed in the same manner as for primary endpoint.

The following secondary endpoints:

- Percent change from baseline in predialysis PTH during the EAP
- Percent change from baseline in predialysis cCa during the EAP
- Percent change from baseline in predialysis cCa x P during the EAP
- Percent change from baseline in predialysis P during the EAP

were analyzed using a repeated measures mixed effects model. Data from all scheduled visits were included in the model and the model included treatment, stratification factors, study (integrated analysis only), study visit, and study visit by treatment interaction as fixed effects with repeated measures accounting for within-subject correlation.

Exploratory efficacy endpoint analyses-
The following exploratory endpoints:

- Absolute change in FGF-23 and log FGF-23 from baseline to week 12 and week 27
- Descriptive statistics at each scheduled time point
- Absolute change in BSAP levels from baseline to week 12 and week 27
- Absolute change in CTX levels from baseline to week 12 and week 27

were analyzed using descriptive statistics at each scheduled time point.

Subgroup analyses were performed using the following criteria:

- demographics
  - race (black, white / other)
  - age (< 65 years, ≥ 65 years)
  - sex (male, female)
  - region (North America, Europe, Other)

- disease severity
  - screening PTH level (< 600, 600 to ≤ 1000, > 1000 pg/mL)
  - mode of dialysis (hemodialysis, hemodiafiltration)
  - dialysis vintage (> 0 to ≤ 1 year, > 1 to ≤ 5 years, > 5 years)

- concomitant and previous therapy
  - prior cinacalcet use within 8 weeks of randomization (yes, no)
  - baseline dialysate calcium (< 2.5, ≥ 2.5 mEq/L)
  - baseline vitamin D sterol use (yes, no)
  - baseline calcium-containing phosphate binders or calcium supplement use (yes, no)

No interim analysis or formal stopping rules were used for these studies.

Protocol Amendments

Protocol Amendment #1 Issued 12 March 2013 Study 229; Issued 13 March 2013 Study 230

- Allowed initiation of AMG 416 administration Monday-Friday, instead of the previous restriction of Wednesday or Thursday only.
- Clarified that AMG 416 should not be administered SC or via any other route other than

IV, and that it should not be administered concurrently with other IV medications.
- Clarified that if suspended for symptomatic hypocalcemia, dosing should only resume after checking corrected calcium levels, in addition to the currently stated resolution of symptomatic hypocalcemia.
- Allowed adjustment of vitamin D for hypocalcemia during the study.
- Provided a recommended sequence of interventions for treating hypocalcemia with reference to modification of oral calcium supplements, dialysate calcium concentration, and then vitamin D.
- Changed specification that postdialysis blood samples must be collected after the postdialysis ECG, to being collected before the ECG sequence. (Study 229 only)
- Expanded the postdialysis ECG and blood sample collection window from the previous 15-30 minutes postdose, to 10-60 minutes postdose. (Study 229 only)
- Provided a sample "Serious Adverse Event Form" as Appendix D
- Pregnancy testing for women of childbearing potential was increased from the previous 2 times in total (before study start and at end of study), to now be 4 times in total (every 12 weeks).

Protocol Amendment #2 Issued 3 Sept. 2013 Study 229; Issued 4 Sept. 2013 Study 230
- Removed requirement for male contraception in the entry criteria to reflect updated core risks and discomforts safety language
- Included updated standard safety language on instructions for reporting SAEs after the 30-day follow-up visit
- Included updated standard safety language on the shortened notification period for pregnancy and lactation reporting from the original 7 days to now be within 24 hours
- Removed blinding of post-dialysis ECG results (Study 229 only)

Medical Officer's comments-These changes/modifications are expected to have minimal impact on the integrity of the trial and interpretation of the results except possibly for the use of vitamin D analogs to treat hypocalcemia during the study, as vitamin D analogs have also been shown to effectively lower PTH levels in dialysis patients with secondary hyperparathyroidism. For this reason the FDA statistician reanalyzed the efficacy dataset excluding subjects with increases in their vitamin D dose during the study and there was still clear efficacy in the subgroup which did not receive increased vitamin D dosing (See Section 7.1.1).

Data Quality and Integrity: Sponsor's Assurance

The study centers were visited at regular intervals. Monitors were responsible for reviewing adherence to the protocol, compliance with GCP, and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted

to verify entries on the study-specific CRFs. Investigator staff training was provided by the Amgen development team during investigator meetings, study center initiation, "town hall" training sessions, and routine monitoring visits. The sponsor organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under ICH GCP, and training on the detailed study requirements. Central laboratories were used to analyze samples for serum chemistry (including vitamin D, PTH, cCa, cCa x P, phosphorus, BSAP, FGF-23, and CTX) and a centralized ECG provider was used for reading of ECGs. The investigators were responsible for all data entered in the CRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigators were responsible for appropriate retention of essential study documents. Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. An audit of this study was included as part of the independent Global Compliance Auditing program performed by Amgen.

Medical Officer's comments-The applicant's monitoring for data quality and integrity was acceptable.

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with applicable country regulations and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents were retained in accordance with ICH GCP. A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising materials were submitted to the IRBs and IECs for written approval. The investigator was responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval were sent to Amgen. The investigator was responsible for obtaining written informed consent from the subject (or legally acceptable representative) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products were administered.

Financial Disclosure

In order to minimize bias of the clinical study results Amgen employed the following steps:

- Multiple clinical sites
- Clinical site monitoring
- Subject randomization and blinding to treatment assignment
- Blinding of investigators to central lab iPTH data in Phase III studies: 20120229,

20120230, and 20120360
• Treatment assignment was performed by IVRS, not by the investigator, in Phase III studies, (excluding 20120359 and Open Label Extension studies – 20120231 and 20130213)

Study 20120229

There were 5 out of 490 investigators at 125 clinical sites with disclosable financial interests who enrolled 11 total subjects into Study 20120229 and were listed on Form 3455:
These subjects account for 5 out of the 188 study patients (2.6%) in the etelcalcetide treatment group with a positive primary endpoint (> 30% decrease in PTH during the EAP). Excluding these patients from the efficacy data would not have affected the statistical significance of the study results.

Site No STUDYID	Investigator in Study 20120229	Address	Number of enrolled Subjects	Financial Arrangement Subjects Results by treatment assignment
[redacted]	[redacted]	[redacted]	(b) (6)	30,000 scholarship to PhD student (b) (6)
				Research grant (b) (6)
				Research grant
				25,000 honoraria for advisory board and speaking activities (b) (6)
				Honoraria for speaking (b) (6)

PTHI30P = Mean iPTH During EAP Reduced > 30% from Baseline (Observed)

Excluding these five investigators, all of the other investigators in Study 20120229 were listed on Form 3454 as having no arrangements or financial interests requiring disclosure. Amgen certifies that they did not enter into any financial arrangements with these listed clinical investigators, whereby the value of compensation to the investigator could have affected the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f). There were no investigators in this study who did not provide financial disclosure.

Study 20120230

There were 7 out of nearly 400 investigators at 106 clinical sites with disclosable financial interests who enrolled 66 total subjects into Study 20120230 and were listed on Form 3455: The efficacy results for these subjects were similar to the results for the total study population:

- 33/37=89% of the placebo patients at these sites did not achieve a > 30% decrease in PTH from baseline to the EAP compared to 90% of the total study placebo patients.
- 24/29=82% of the etelcalcetide patients at these sites did achieve a > 30% decrease in PTH from baseline to the EAP compared to 75% of the total study etelcalcetide patients, which was only slightly higher.

Therefore excluding these patients from the efficacy data set would not have affected the statistical significance of the study results.

Site No STUDYID	Investigator in Study 2012023 0	Address	Number of enrolled Subjects	Financial Arrangement Subjects Results by treatment assignment
			(b) (6)	Research Grant 75,000 in 2014 100.000 in 2015 (b) (6)
				Registry Support 50.000 (b) (6)
				Research Grant 75,000 (b) (6)
				Advisory Board 12,000 (b) (4) 58,000 (b) (6) (b) (6)
				Honoraria and expenses (b) (6) 77,109 in 2012 42,740 in 2014 (b) (6)
				" (b) (6)
				Owns 8275 shares of Amgen stock (b) (4)

Excluding these 7 investigators all of the other investigators in Study 20120230 were listed on Form 3454 as having no arrangements or financial interests requiring disclosure. Amgen certifies that they did not enter into any financial arrangements with these listed clinical investigators, whereby the value of compensation to the investigator could have affected the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f). There were no investigators in this study who did not provide financial disclosure.

Patient Disposition

Table 3 Subject Disposition & Discontinuation Data from Pooled 6-Month Placebo-Controlled Studies 20120229 & 20120230 (Full Analysis Set)

	20120229		20120230		Total placebo-controlled studies	
	Placebo (N = 254) n (%)	AMG 416 (N = 254) n (%)	Placebo (N = 260) n (%)	AMG 416 (N = 255) n (%)	Placebo (N = 514) n (%)	AMG 416 (N = 509) n (%)
Investigational product accounting						
Subjects who never received investigational product	0 (0.0)	3 (1.2)	1 (0.4)	3 (1.2)	1 (0.2)	6 (1.2)
Subjects who received investigational product	254 (100.0)	251 (98.8)	259 (99.6)	252 (98.8)	513 (99.8)	503 (98.8)
Subjects who completed investigational product	187 (73.6)	211 (83.1)	193 (74.2)	210 (82.4)	380 (73.9)	421 (82.7)
Subjects who discontinued investigational product	67 (26.4)	40 (15.7)	66 (25.4)	42 (16.5)	133 (25.9)	82 (16.1)
Protocol deviation	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
Noncompliance	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.2)	1 (0.2)	4 (0.8)
Adverse event	7 (2.8)	5 (2.0)	6 (2.3)	4 (1.6)	13 (2.5)	9 (1.8)
Lost to follow-up	0 (0.0)	2 (0.8)	2 (0.8)	4 (1.6)	2 (0.4)	6 (1.2)
Death	5 (2.0)	5 (2.0)	5 (1.9)	4 (1.6)	10 (1.9)	9 (1.8)
Decision by sponsor	2 (0.8)	1 (0.4)	4 (1.5)	7 (2.7)	6 (1.2)	8 (1.6)
Subject request	13 (5.1)	17 (6.7)	13 (5.0)	12 (4.7)	26 (5.1)	29 (5.7)
Protocol specified criteria	40 (15.7)	8 (3.1)	34 (13.1)	8 (3.1)	74 (14.4)	16 (3.1)
Investigational product accounting (Cont'd)						
Subject requires significant permanent change in hemodialysis prescription	3 (1.2)	3 (1.2)	1 (0.4)	0 (0.0)	4 (0.8)	3 (0.6)
Subject meets rising IPTH discontinuation criteria after Week 12	29 (11.4)	2 (0.8)	26 (10.0)	1 (0.4)	55 (10.7)	3 (0.6)
Subject is to receive kidney transplant	8 (3.1)	3 (1.2)	6 (2.3)	7 (2.7)	14 (2.7)	10 (2.0)
Subject is to undergo parathyroidectomy	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Study completion accounting						
Subjects who completed study	193 (76.0)	220 (86.6)	204 (78.5)	218 (85.5)	397 (77.2)	438 (86.1)
Subjects who discontinued study	61 (24.0)	34 (13.4)	56 (21.5)	37 (14.5)	117 (22.8)	71 (13.9)
Withdrawal of consent from study	15 (5.9)	12 (4.7)	12 (4.6)	12 (4.7)	27 (5.3)	24 (4.7)
Lost to follow-up	10 (3.9)	11 (4.3)	12 (4.6)	19 (7.5)	22 (4.3)	30 (5.9)
Death	7 (2.8)	9 (3.5)	7 (2.7)	5 (2.0)	14 (2.7)	14 (2.8)
Decision by sponsor	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Protocol specified criteria	29 (11.4)	1 (0.4)	25 (9.6)	1 (0.4)	54 (10.5)	2 (0.4)
Subject meets rising IPTH discontinuation criteria after Week 12	29 (11.4)	1 (0.4)	25 (9.6)	1 (0.4)	54 (10.5)	2 (0.4)

Source Table 1.1 ISE

Medical Officer's comments-Approximately 10% more subjects discontinued in the placebo group from both studies 20120229 and 20120230 which was primarily due to a protocol specified criteria of rising iPTH levels after week 12.

Protocol Violations/Deviations

Table 4 Summary of Protocol Deviations in Study 20120229

	Placebo (N=254) n %	AMG 416 (N=254) n %	Total (N=508) n %
Number of subjects with at least one important protocol deviation	34 (13.4)	46 (18.1)	80 (15.7)
Developed withdrawal criteria but was not withdrawn			
PTH discontinuation criteria met	2 (0.8)	0 (0.0)	2 (0.4)
Entered study even though entry criteria was not satisfied			
ECG of cardiac instability	1 (0.4)	1 (0.4)	2 (0.4)
History of MI, CA, or graft	0 (0.0)	2 (0.8)	2 (0.4)
History of dysrhythmias	1 (0.4)	0 (0.0)	1 (0.2)
History of malignancy	1 (0.4)	1 (0.4)	2 (0.4)
No hemodialysis TIW for at least 3 months	4 (1.6)	1 (0.4)	5 (1.0)
Not available for visits	1 (0.4)	0 (0.0)	1 (0.2)
Screening PTH criteria not met	0 (0.0)	4 (1.6)	4 (0.8)
Screening cCA criteria not met	0 (0.0)	1 (0.4)	1 (0.2)
Seizures within 12 months of screening	0 (0.0)	1 (0.4)	1 (0.2)
Missing data			
Missing baseline antibody sample	6 (2.4)	2 (0.8)	8 (1.6)
Other deviations			
Deviation from the informed consent process	0 (0.0)	1 (0.4)	1 (0.2)
Study Staff unblinded to local PTH	1 (0.4)	5 (2.0)	6 (1.2)
Other treatment compliance			
Missed more than 2 continuous wks of IP	2 (0.8)	4 (1.6)	6 (1.2)
Received an excluded concomitant treatment			
Received cinacalcet during study	2 (0.8)	7 (2.8)	9 (1.8)
Received the wrong treatment or incorrect dose			
IP not withheld for symptomatic hypocalcemia	0 (0.0)	2 (0.8)	2 (0.4)
Low cCa when resuming IP after dose suspension	0 (0.0)	1 (0.4)	1 (0.2)
Received IV IP during dialysis	2 (0.8)	5 (2.0)	7 (1.4)
Received compromised IP	10 (3.9)	11 (4.3)	21 (4.1)
Received incorrect IP assignment that led to AE	1 (0.4)	1 (0.4)	2 (0.4)
Received incorrect IP dose	2 (0.8)	0 (0.0)	2 (0.4)
Received incorrect dose following re-started IP	1 (0.4)	0 (0.0)	1 (0.2)

Source Table 9-2 CSR 20120229

Table 5 Summary of Protocol Deviations in Study 20120230

	Placebo (N = 260) n (%)	AMG 416 (N = 255) n (%)	Total (N = 515) n (%)
Number of subjects with at least 1 important protocol deviation	30 (11.5)	32 (12.5)	62 (12.0)
Developed withdrawal criteria but was not withdrawn			
Hemodialysis prescription changed	0 (0.0)	1 (0.4)	1 (0.2)
Entered study even though entry criteria was not satisfied			
History of angina	2 (0.8)	0 (0.0)	2 (0.4)
History of dysrhythmias	0 (0.0)	1 (0.4)	1 (0.2)
History of malignancy	1 (0.4)	3 (1.2)	4 (0.8)
History of uncontrolled BP	1 (0.4)	2 (0.8)	3 (0.6)
No hemodialysis TIW for at least 3 months	3 (1.2)	3 (1.2)	6 (1.2)
Prior cinacalcet use 4 weeks before screening	1 (0.4)	2 (0.8)	3 (0.6)
Screening PTH criteria not met	2 (0.8)	1 (0.4)	3 (0.6)
Screening cCa criteria not met	1 (0.4)	1 (0.4)	2 (0.4)
Seizures within 12 months of screening	0 (0.0)	1 (0.4)	1 (0.2)
Other deviations			
Deviation from the informed consent process	0 (0.0)	6 (2.4)	6 (1.2)
Study Staff unblinded to local PTH	1 (0.4)	1 (0.4)	2 (0.4)
Other treatment compliance			
Missed more than 2 continuous weeks of IP	5 (1.9)	0 (0.0)	5 (1.0)
Received an excluded concomitant treatment			
Received cinacalcet during study	4 (1.5)	1 (0.4)	5 (1.0)
Received the wrong treatment or incorrect dose			
IP not reduced	0 (0.0)	2 (0.8)	2 (0.4)
IP not withheld for symptomatic hypocalcemia	0 (0.0)	1 (0.4)	1 (0.2)
IP not withheld when calcium less than 7.5 mg/dL	2 (0.8)	1 (0.4)	3 (0.6)
Low cCa when resuming IP after dose suspension	1 (0.4)	0 (0.0)	1 (0.2)
Received compromised IP[a]	6 (2.3)	10 (3.9)	16 (3.1)
Received incorrect IP assignment which leads to an adverse event or hypocalcemia	0 (0.0)	1 (0.4)	1 (0.2)
Received incorrect dose following re-started IP	1 (0.4)	0 (0.0)	1 (0.2)

BP = blood pressure; cCa = corrected calcium; IP = investigational product; PTH = parathyroid hormone; TIW = 3 times weekly.
[a] Most cases of compromised IP were because of temperature excursions (Listing 16-2.2.1).
Full analysis set: all randomized subjects
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.
Source Table 9-2 CSR 20120230

Medical Officer's comments-

While there were slightly more total protocol deviations in the etelcalcetide group compared to placebo (18.1% vs. 13.4% 20120229, and 12.5% vs. 11.5% 20120230), most of the protocol violation subcategories occurred in small numbers of patients and were evenly distributed typically with less than a 2% difference between treatment groups. Treatment with cinacalcet would have resulted in increased efficacy if it was given during the EAP, but also may have put the subjects at greater risk of hypocalcemia. The small % of subjects treated with cinacalcet was unlikely to change the efficacy results.

The most frequently reported subcategory, "Received compromised IPs" seen at a rate of 2 to 4% occurred primarily because of temperature excursions due to shipment delays or delays in time between sample preparation and dosing which could affect efficacy of etelcalcetide but would have no effect on placebo. Subjects received at most between 3 and 9 doses of compromised IPs so the study results are less likely to be affected unless the doses were given during the EAP.

Table of Demographic Characteristics

Table 6 Baseline Demographics in Pivotal Studies

	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)
Sex - n (%)						
Male	140 (55.1)	151 (59.4)	165 (63.5)	162 (63.5)	305 (59.3)	313 (61.5)
Female	114 (44.9)	103 (40.6)	95 (36.5)	93 (36.5)	209 (40.7)	196 (38.5)
Ethnicity - n (%)						
Hispanic/Latino	33 (13.0)	33 (13.0)	33 (12.7)	32 (12.5)	66 (12.8)	65 (12.8)
Not Hispanic/Latino	220 (86.6)	221 (87.0)	227 (87.3)	221 (86.7)	447 (87.0)	442 (86.8)
Missing	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.2)	2 (0.4)
Race - n (%)						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	3 (1.2)	5 (2.0)	6 (2.3)	13 (5.1)	9 (1.8)	18 (3.5)
Black (or African American)	69 (27.2)	72 (28.3)	80 (30.8)	64 (25.1)	149 (29.0)	136 (26.7)
Native Hawaiian or Other Pacific Islander	2 (0.8)	0 (0.0)	3 (1.2)	7 (2.7)	5 (1.0)	7 (1.4)
White	175 (68.9)	173 (68.1)	169 (65.0)	163 (63.9)	344 (66.9)	336 (66.0)
Other	4 (1.6)	4 (1.6)	2 (0.8)	6 (2.4)	6 (1.2)	10 (2.0)
Missing	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.8)	1 (0.2)	2 (0.4)
Age (years)						
Mean	57.1	58.4	59.0	58.4	58.1	58.4
SD	14.5	14.6	13.9	14.6	14.3	14.6
Age group - n (%)						
< 65 years	168 (66.1)	164 (64.6)	169 (65.0)	165 (64.7)	337 (65.6)	329 (64.6)
≥ 65 years	86 (33.9)	90 (35.4)	91 (35.0)	90 (35.3)	177 (34.4)	180 (35.4)
≥ 75 years	27 (10.6)	35 (13.8)	37 (14.2)	39 (15.3)	64 (12.5)	74 (14.5)
BMI (kg/m^2)						
n	252	253	260	255	512	508
Mean	28.35	28.71	28.82	28.95	28.59	28.83
SD	7.07	8.14	6.67	7.33	6.87	7.74

	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)
iPTH (pg/mL)						
Mean	819.7	848.7	851.7	845.0	835.9	846.9
SD	386.0	520.4	552.0	464.3	477.0	492.6
Median	705.8	706.2	725.7	740.3	715.6	723.5
Q1, Q3	562.8, 993.7	551.5, 950.4	553.4, 968.7	551.8, 949.2	556.9, 982.4	551.6, 949.2
Min, Max	298, 2850	337, 4614	378, 6477	359, 4669	298, 6477	337, 4669
Corrected Calcium (mg/dL)						
Mean	9.61	9.65	9.70	9.63	9.65	9.64
SD	0.60	0.66	0.69	0.65	0.65	0.66
Median	9.57	9.60	9.60	9.53	9.60	9.60
Q1, Q3	9.20, 9.97	9.20, 10.03	9.20, 10.07	9.20, 10.03	9.20, 10.00	9.20, 10.03
Min, Max	8.2, 12.1	8.5, 11.7	8.4, 11.8	8.2, 11.9	8.2, 12.1	8.2, 11.9
Phosphorus (mg/dL)						
n	250	250	257	251	507	501
Mean	5.78	5.95	5.83	5.76	5.80	5.86
SD	1.60	1.59	1.45	1.60	1.53	1.59
Median	5.60	5.80	5.60	5.60	5.60	5.70
Q1, Q3	4.60, 6.77	4.75, 6.85	4.80, 6.60	4.60, 6.80	4.70, 6.70	4.70, 6.83
Min, Max	2.3, 10.2	1.1, 12.2	2.7, 11.8	2.5, 11.5	2.3, 11.8	1.1, 12.2

Source Table 2.1 & 2.2 ISE (n is included when less than total pts listed at the top of the table had baseline data for that category.)

These studies enrolled primarily Caucasian subjects (64-69%), followed by blacks (25 to 31%) and very few patients from other races (0 to 5%). While the percentage of blacks in the study population is higher than in the general population this is consistent with the greater incidence of renal disease in this population due to their higher rates of diabetes and hypertension. Most subjects were male 54 to 64%. The mean age was 57 to 59 years, with about 1/3 of the subjects being elderly (34-35% ≥65 years of age and 11-15% ≥75 years of age). Most subjects were overweight with a mean BMI of 28 to 29kg/m^2. Baseline laboratory values included mean serum iPTH values between 820 and 852 pg/mL, mean corrected calcium between 9.6 and 9.7mg/dL and mean serum phosphorous between 5.8 and 6.0 mg/dL (note the ULN for these assays were 72 pg/mL for iPTH, 10.6mg/dL for corrected calcium and 5.1mg/dL for serum phosphorous). In general, the studies were well randomized with baseline demographics similar between the placebo and treatment groups when comparing the total data from both clinical studies 20120229 and 20120230.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 7 Dialysis History and Baseline Causes for CKD in the Pivotal Studies

	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)
Primary cause of ESRD - n (%)						
Diabetes	78 (30.7)	67 (26.4)	84 (32.3)	79 (31.0)	162 (31.5)	146 (28.7)
Hypertension	65 (25.6)	63 (24.8)	58 (22.3)	64 (25.1)	123 (23.9)	127 (25.0)
Other	44 (17.3)	46 (18.1)	32 (12.3)	39 (15.3)	76 (14.8)	85 (16.7)
Glomerulonephritis	30 (11.8)	39 (15.4)	45 (17.3)	30 (11.8)	75 (14.6)	69 (13.6)
Polycystic Kidney Disease	20 (7.9)	19 (7.5)	22 (8.5)	16 (6.3)	42 (8.2)	35 (6.9)
Unknown	9 (3.5)	11 (4.3)	13 (5.0)	17 (6.7)	22 (4.3)	28 (5.5)
Urologic	8 (3.1)	9 (3.5)	6 (2.3)	10 (3.9)	14 (2.7)	19 (3.7)
History of kidney transplant - n (%)						
Yes	34 (13.4)	30 (11.8)	30 (11.5)	28 (11.0)	64 (12.5)	58 (11.4)
No	220 (86.6)	224 (88.2)	230 (88.5)	227 (89.0)	450 (87.5)	451 (88.6)
History of cinacalcet use - n (%)						
Yes	109 (42.9)	103 (40.6)	126 (48.5)	137 (53.7)	235 (45.7)	240 (47.2)
No	145 (57.1)	151 (59.4)	134 (51.5)	118 (46.3)	279 (54.3)	269 (52.8)
Mode of dialysis - n (%)						
Hemodialysis	213 (83.9)	213 (83.9)	225 (86.5)	224 (87.8)	438 (85.2)	437 (85.9)
Hemodiafiltration	41 (16.1)	41 (16.1)	35 (13.5)	31 (12.2)	76 (14.8)	72 (14.1)
Hemodialysis vintage (years)						
n	254	254	260	255	514	509
Mean	5.14	5.86	5.34	5.37	5.24	5.62
SD	4.74	5.50	4.89	5.13	4.81	5.32
Median	3.77	3.95	3.81	4.00	3.79	3.98
Q1, Q3	1.65, 6.85	1.95, 8.36	2.00, 6.77	2.17, 7.10	1.79, 6.85	1.98, 7.75
Min, Max	0.3, 32.2	0.1, 31.5	0.3, 27.5	0.3, 32.1	0.3, 32.2	0.1, 32.1

Source Table 2.4 ISE

The primary cause of CKD was diabetes mellitus, followed by hypertension and most patients had been on hemodialysis for a mean of about 5 years. About half of the subjects between 43% and 53% had been previously exposed to cinacalcet, the only currently approved calcimimetic.

In general medical histories for hypertension, diabetes and coronary heart disease, were similar between treatment groups. There was a slightly higher rate of atrial fibrillation in the placebo groups in both studies (totals 9.5% vs. 4.3%). While that could contribute to more arrhythmia AEs in the placebo group it is unlikely to impact the primary endpoint analysis.

Table 8 Medical History of Subjects in Pivotal Studies

	20120229		20120230		Total placebo-controlled studies	
Preferred Term	Placebo (N = 254)	AMG 416 (N = 254)	Placebo (N = 260)	AMG 416 (N = 255)	Placebo (N = 514)	AMG 416 (N = 509)
Hypertension	245 (96.5)	238 (93.7)	245 (94.2)	240 (94.1)	490 (95.3)	478 (93.9)
Dyslipidaemia	139 (54.7)	138 (54.3)	149 (57.3)	131 (51.4)	288 (56.0)	269 (52.8)
Type 2 diabetes mellitus	98 (38.6)	101 (39.8)	118 (45.4)	110 (43.1)	216 (42.0)	211 (41.5)
Coronary artery disease	76 (29.9)	90 (35.4)	86 (33.1)	65 (25.5)	162 (31.5)	155 (30.5)
Retinopathy	59 (23.2)	60 (23.6)	68 (26.2)	61 (23.9)	127 (24.7)	121 (23.8)
Peripheral vascular disorder	56 (22.0)	48 (18.9)	55 (21.2)	49 (19.2)	111 (21.6)	97 (19.1)
Myocardial infarction	30 (11.8)	40 (15.7)	36 (13.8)	35 (13.7)	66 (12.8)	75 (14.7)
Cardiac valve disease	36 (14.2)	32 (12.6)	43 (16.5)	33 (12.9)	79 (15.4)	65 (12.8)
Angina pectoris	27 (10.6)	33 (13.0)	26 (10.0)	24 (9.4)	53 (10.3)	57 (11.2)
Cerebrovascular accident	20 (7.9)	28 (11.0)	24 (9.2)	21 (8.2)	44 (8.6)	49 (9.6)
Coronary artery bypass	14 (5.5)	30 (11.8)	19 (7.3)	18 (7.1)	33 (6.4)	48 (9.4)
Percutaneous coronary intervention	24 (9.4)	22 (8.7)	23 (8.8)	24 (9.4)	47 (9.1)	46 (9.0)
Arrhythmia supraventricular	18 (7.1)	22 (8.7)	23 (8.8)	19 (7.5)	41 (8.0)	41 (8.1)
Skin ulcer	19 (7.5)	21 (8.3)	20 (7.7)	18 (7.1)	39 (7.6)	39 (7.7)
Atrial fibrillation	27 (10.6)	11 (4.3)	22 (8.5)	11 (4.3)	49 (9.5)	22 (4.3)
Cardiac pacemaker insertion	7 (2.8)	11 (4.3)	11 (4.2)	11 (4.3)	18 (3.5)	22 (4.3)
Peripheral revascularisation	11 (4.3)	10 (3.9)	10 (3.8)	11 (4.3)	21 (4.1)	21 (4.1)
Transient ischaemic attack	12 (4.7)	10 (3.9)	15 (5.8)	11 (4.3)	27 (5.3)	21 (4.1)
Type 1 diabetes mellitus	12 (4.7)	6 (2.4)	11 (4.2)	14 (5.5)	23 (4.5)	20 (3.9)
Ventricular fibrillation	5 (2.0)	7 (2.8)	12 (4.6)	7 (2.7)	17 (3.3)	14 (2.8)
Convulsion	11 (4.3)	5 (2.0)	6 (2.3)	8 (3.1)	17 (3.3)	13 (2.6)
Carotid revascularisation	3 (1.2)	4 (1.6)	2 (0.8)	3 (1.2)	5 (1.0)	7 (1.4)
Implantable defibrillator insertion	0 (0.0)	4 (1.6)	5 (1.9)	3 (1.2)	5 (1.0)	7 (1.4)
Aortic aneurysm repair	3 (1.2)	3 (1.2)	2 (0.8)	1 (0.4)	5 (1.0)	4 (0.8)
Renal revascularisation surgery	2 (0.8)	1 (0.4)	0 (0.0)	2 (0.8)	2 (0.4)	3 (0.6)

Source Table 2.6 ISE

Table 9 Baseline Use of Concomitant Medications of Interest

	20120229		20120230		Total placebo-controlled studies	
	Placebo (N = 254) n (%)	AMG 416 (N = 254) n (%)	Placebo (N = 260) n (%)	AMG 416 (N = 255) n (%)	Placebo (N = 514) n (%)	AMG 416 (N = 509) n (%)
Number of subjects reporting use of concomitant medications of interest	245 (96.5)	244 (96.1)	246 (94.6)	236 (92.5)	491 (95.5)	480 (94.3)
Nutritional vitamin D	63 (24.8)	55 (21.7)	86 (33.1)	81 (31.8)	149 (29.0)	136 (26.7)
Vitamin D sterol	185 (72.8)	191 (75.2)	160 (61.5)	160 (62.7)	345 (67.1)	351 (69.0)
Calcium supplements	9 (3.5)	18 (7.1)	6 (2.3)	22 (8.6)	15 (2.9)	40 (7.9)
Phosphate binder	213 (83.9)	216 (85.0)	220 (84.6)	202 (79.2)	433 (84.2)	418 (82.1)
Calcium-containing phosphate binder or calcium supplement	93 (36.6)	99 (39.0)	107 (41.2)	88 (34.5)	200 (38.9)	187 (36.7)

Source Table 2.3 ISE.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance-
Investigational drug was administered after completion of the each hemodialysis session; therefore treatment noncompliance only occurred if subjects missed regular dialysis sessions. Treatment compliance measured as the number of subjects who missed more than two weeks of investigational drug product was less than 2% per treatment group (see Table 9-2 CSRs

20120229 & 20110230, Table 4 & Table 5) and so would be unlikely to affect efficacy results. Whether more frequent shorter periods of missed (dialysis sessions/drug dosing), such as one week or less, would have impacted on the efficacy results is unknown, but this is less likely given that in these CKD patients with greatly decreased renal function the drug has an estimated half-life of 3 to 5 days and cannot be renally excreted but is primarily removed during each dialysis session prior to repeat dosing. So if a dialysis session is skipped it also delays the removal of the investigational product given after the prior dialysis session which maintains a certain level of activity.

Concomitant Medications-

Table 10 Incidence of Vitamin D Sterol Dose Increase from Baseline during the Pivotal Studies

	20120229		20120230		Total placebo-controlled studies		20120360	
	Placebo (N = 254) n (%)	AMG 416 (N = 254) n (%)	Placebo (N = 260) n (%)	AMG 416 (N = 255) n (%)	Placebo (N = 514) n (%)	AMG 416 (N = 509) n (%)	Cinacalcet (N = 343) n (%)	AMG 416 (N = 340) n (%)
Vitamin D sterol dose change from baseline								
Increase	31 (12.2)	85 (33.5)	22 (8.5)	72 (28.2)	53 (10.3)	157 (30.8)	105 (30.6)	125 (36.8)
No increase	223 (87.8)	169 (66.5)	238 (91.5)	183 (71.8)	461 (89.7)	352 (69.2)	238 (69.4)	215 (63.2)

Total placebo-controlled studies: Studies 20120229 and 20120230
Full analysis set: all randomized subjects in the pool
Increase: subjects with any postbaseline vitamin D sterol dose increase from baseline, or subjects with no baseline vitamin D sterol use along with any postbaseline vitamin D sterol use.
No increase: subjects with no post-baseline vitamin D sterol dose increase from baseline, subjects with any baseline vitamin D sterol use along with no postbaseline vitamin D sterol use, or subjects with no baseline vitamin D sterol use along with no postbaseline vitamin D sterol use.
Source Table 2 Section 1.11.3 applicant's response to information request received 2/17/2016.

Medical Officer's comments-

There was a 20% relative increase in the use of active vitamin D analogs in the etelcalcetide treatment groups compared to the placebo treatment groups in the pooled data from the pivotal studies. Since active vitamin D analogs are known to be effective in the treatment of secondary hyperparathyroidism in the dialysis population it was not unexpected that the % of responders with > 30% reduction in iPTH from baseline was higher in the subgroup of patients with an increase in their vitamin D dose during the study compared to those who did not increase their vitamin D dose (78% vs. 73%, see Fig. 1 sponsor's 03 Feb 2016 submission). That said excluding data from the subjects with an increase in vitamin D dose during the pivotal studies from the primary analysis did not affect the statistical significance of the study results for the primary endpoint as the % of responders with > 30% reduction in iPTH was still much higher in the etelcalcetide treated group compared to placebo even if subjects with vitamin D increases during the studies were excluded (e.g. study 20120229- 73.4% vs. 8.5%, for study 20120230- 72.7% vs. 8.4%, data calculated by FDA Statistician).

Table 11 Incidence of Calcium Supplement Dose Increase from Baseline during the Pivotal Studies

Change from baseline	20120229		20120230		Total placebo-controlled studies		20120360	
	Placebo (N = 254) n (%)	AMG 416 (N = 254) n (%)	Placebo (N = 260) n (%)	AMG 416 (N = 255) n (%)	Placebo (N = 514) n (%)	AMG 416 (N = 509) n (%)	Cinacalcet (N = 343) n (%)	AMG 416 (N = 340) n (%)
Increase	27 (10.6)	121 (47.6)	19 (7.3)	133 (52.2)	46 (8.9)	254 (49.9)	136 (39.7)	136 (40.0)
No increase	227 (89.4)	133 (52.4)	241 (92.7)	122 (47.8)	468 (91.1)	255 (50.1)	207 (60.3)	204 (60.0)

AMG 416 = etelcalcetide
Total placebo-controlled studies: Studies 20120229 and 20120230.
Full analysis set: all randomized subjects in the pool
Increase: subjects with any postbaseline calcium supplement dose increase from baseline, or subjects with no baseline calcium supplement use along with any postbaseline calcium supplement use
No increase: subjects with no postbaseline calcium supplement dose increase from baseline, subjects with any baseline calcium supplement use along with no postbaseline calcium supplement use, or subjects with no baseline calcium supplement use along with no postbaseline calcium supplement use
Calcium supplements include calcium-containing phosphate binder or calcium supplement reported on the concomitant medication electronic case report form.
Source Table 1 Section 1.11.3 applicant's response to information request received 2/29/2016

Medical Officer's comments-

There was a 40% relative increase in the use of active calcium supplements in the etelcalcetide treatment groups compared to the placebo treatment groups in the pooled data from the pivotal studies. Given that calcium supplements will increase serum calcium and as such can lower serum PTH it is expected that subjects treated with calcium supplements would have a greater number of responders with >30% reduction in iPTH at the EAP compared to baseline. An analysis by the FDA statistician confirmed the greater rate of responders in the etelcalcetide group in subjects receiving calcium supplements (84%) compared to those with no increase in calcium supplements (65%). That said excluding data from the subjects with an increase in calcium supplements during the pivotal studies from the primary analysis did not affect the statistical significance of the study results for the primary endpoint as the % of responders with > 30% reduction in iPTH was still much higher in the etelcalcetide treated group compared to placebo even if subjects with calcium supplement increases during the studies were excluded (e.g. study 20120229- 68.4% vs. 7.9%, for study 20120230- 62.3% vs. 10.0%, data calculated by FDA Statistician).

Rescue Medications-
High doses of etelcalcetide can result in hypocalcemia which can be treated with vitamin D sterols and calcium supplements which are common concomitant medications in the dialysis

study population. See Concomitant Medications above for information about the increased use of vitamin D sterols and calcium supplements in the clinical studies.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was a responder analysis looking at the proportion of subjects in the ITT population attaining a mean decrease of >30% in serum iPTH from pre-treatment baseline during the EAP, weeks 20 to 27. Subjects who discontinued from the study prior to the EAP or had no serum iPTH determinations in the EAP were considered non-responders. Results were statistically significant, 74% vs. 8.3%, p<0.001 as seen in Table 12.

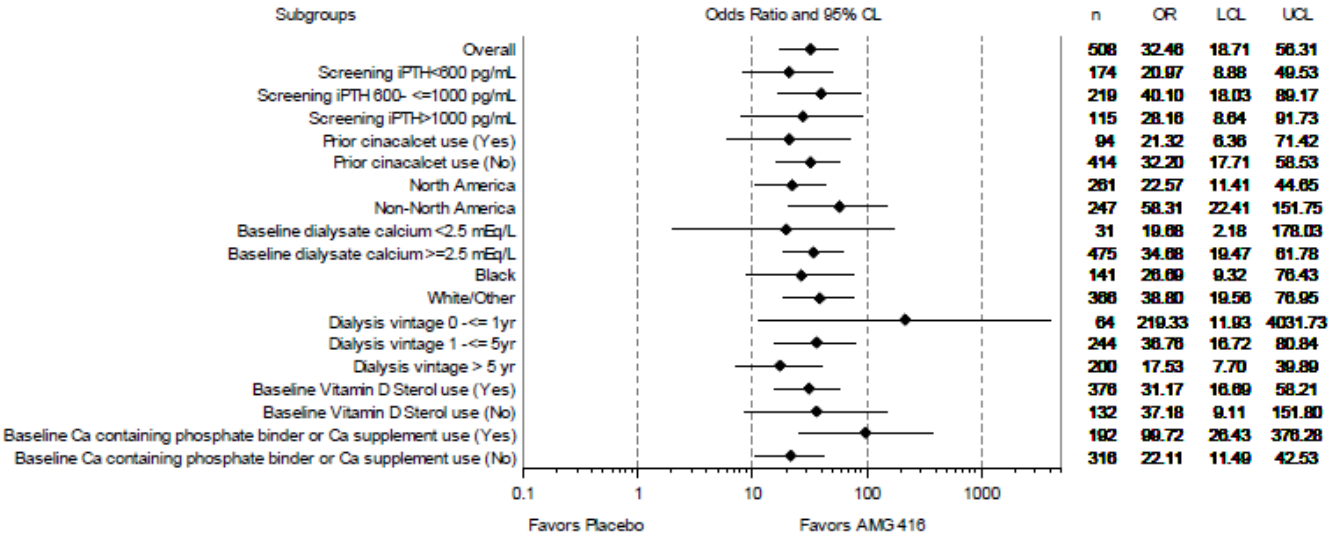
Table 12 Primary Endpoint for Study 20120229- Responders with > 30% Reduction in iPTH during the EAP (ITT population)

	Placebo (N = 254)	AMG 416 (N = 254)	Treatment Difference
Subject Status			
Number of subjects	254	254	
Yes - n (%) [a]	21 (8.3)	188 (74.0)	
Screening iPTH < 600 pg/mL	8 (3.1)	63 (24.8)	
Screening iPTH 600 - ≤ 1000 pg/mL	11 (4.3)	92 (36.2)	
Screening iPTH > 1000 pg/mL	2 (0.8)	33 (13.0)	
Prior cinacalcet use	2 (0.8)	26 (10.2)	
No prior cinacalcet use	19 (7.5)	162 (63.8)	
North America	14 (5.5)	98 (38.6)	
Non-North America	7 (2.8)	90 (35.4)	
No - n(%) [a]	233 (91.7)	66 (26.0)	
Screening iPTH < 600 pg/mL	76 (29.9)	24 (9.4)	
Screening iPTH 600 - ≤ 1000 pg/mL	103 (40.6)	23 (9.1)	
Screening iPTH > 1000 pg/mL	54 (21.3)	19 (7.5)	
Prior cinacalcet use	32 (12.6)	7 (2.8)	
No prior cinacalcet use	201 (79.1)	59 (23.2)	
North America	115 (45.3)	34 (13.4)	
Non-North America	118 (46.5)	32 (12.6)	
CMH-stratified [b] odds ratio (AMG 416: Placebo)			32.46
(95% CI)			(18.71, 56.31)
p-value [c]			< 0.001

Full analysis set: all randomized subjects
n = Number of subjects with observed data in the analysis set. CI = Confidence Interval.
[a] Subject has iPTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).
[b] Stratification factors based on screening iPTH level, prior cinacalcet use within 8 weeks prior to randomization, and region were from IXRS
[c] Cochran-Mantel-Haenszel (CMH) test
Source Table 14-4.1. CSR 20120229

Efficacy was consistent across all subgroups tested including, baseline iPTH categories, prior use of cinacalcet, geographic region, baseline dialysate calcium, race, dialysis vintage, baseline use of vitamin D analogs, baseline use of phosphate binder or calcium supplement (Figure 4).

Figure 4 Treatment Difference in Primary Endpoint Study 20120229 (Full Analysis Set)



Source Fig 10-1 CSR 20120229

Medical Officer's comments

There was no consistent difference in efficacy with respect to baseline screening iPTH.

Efficacy in subjects with no prior cinacalcet use shows that the study was not driven by the results from a subset of patients who had previously shown a clinical response to treatment with another calcimimetic.

While the point estimate for efficacy in subjects from North America is lower than from Non-North American subjects for unknown reasons, there is clear evidence of efficacy in the North American population as the lower limit of the 95% CI for the odds ratio is well above 1. The applicant was asked if they could speculate about the reason for the differences in the different geographic subgroups and in their SDN 9 submission from 2/29/2016 they mentioned that differences in baseline characteristics across the region subgroups may have contributed to these results. However, which of these baseline characteristics might be important is not clear as for example the data in this figure show no consistent differences in efficacy with respect to baseline iPTH. That said, efficacy does appear to

trend better for subjects with the shortest duration of dialysis vintage (e.g. less than 1 yr > 1-5yrs > over 5 yrs) who are likely to have less severe bone disease which may be why they are more responsive to PTH reduction.

Data Quality and Integrity – Reviewers' Assessment

Medical Officer's comments- This medical reviewer agrees with OSI's assessment of the clinical inspection sites, See Section 4.1.

The applicant's monitoring for data quality and integrity was acceptable.

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy endpoints were prespecified using a hierarchical testing approach in the following sequence:

1. proportion of subjects with mean predialysis PTH ≤ 300 pg/mL during the EAP
2. % change from baseline to EAP in iPTH
3. % change from baseline to EAP in cCa
4. % change from baseline to EAP in cCa x P
5. % change from baseline to EAP in phosphorus

The first secondary endpoint measures PTH lowering to a goal of ≤ 300pg/mL, which is consistent with the treatment goal in the earlier KDOQI guidelines for patients with CKD Stage 5 on renal dialysis e.g. 150 to 300pg/mL, but which has since been replaced by the more liberal KDIGO guidelines to 130 to 600pg/mL.

Medical Officer's comments-

Given the mean iPTH at baseline was approximately 830pg/mL, treatment to a goal of ≤300pg/mL represents a mean decrease of at least 64%. A substantial proportion of subjects in the etelcalcetide treatment group i.e. 50% were able to reach this treatment goal compared to only 5% in the placebo group (p<0.001).

Table 13 Proportion of Subjects Treated to Goal of ≤300pg/mL during the EAP Study 20120229 (Full Analysis Set)

	Placebo (N = 254)	AMG 416 (N = 254)	Treatment Difference
Subjects achieving PTH ≤ 300 pg/mL during EAP[a], n (%)	13 (5.1)	126 (49.6)	
CMH stratified[b] odds ratio (AMG 416: placebo)			22.08
(95% CI)			(11.47, 42.48)
p-value[c]			< 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EAP = efficacy assessment phase; n = number of subjects with observed data in the analysis set; PTH = parathyroid hormone.
[a] Subjects who had PTH ≤ 300 pg/mL during the EAP (study visits during week 20 to week 27, inclusive). Subjects who had no scheduled assessments during the EAP were considered to be non-responders.
[b] Stratification factors based on screening PTH level, prior cinacalcet use within 8 weeks prior to randomization, and region were from the interactive voice/web reponse system.
[c] CMH test

Source Table 10-2 CSR 20120229

All four of the other secondary endpoints i.e. % change from baseline to EAP in iPTH, cCa, cCaxP and phosphorus were also statistically significant. The mean difference between treatment groups were -71%, -8.4%, -15%, and -7.5% for iPTH, cCa, cCa x P and phosphorus, respectively.

Table 14 Percent Change from Baseline in Mean iPTH, cCA, cCaXP, and Phosphorous Study 20120229 (Full Analysis Set)

Percent change from baseline to EAP in predialysis:	PTH	cCa	cCa × P	Phosphorus
Placebo (N = 254)				
n	219	219	213	214
Mean (SE), %	13.00 (2.81)	1.18 (0.29)	-0.19 (1.44)	-1.31 (1.42)
AMG 416 (N = 254)				
n	229	229	227	227
Mean (SE), %	-55.11 (1.94)	-7.29 (0.53)	-14.34 (2.06)	-7.71 (2.16)
Treatment difference (AMG 416 – placebo)				
Adjusted analysis[a]				
Estimate[b] (SE), %	-71.11 (3.39)	-8.38 (0.58)	-14.99 (2.41)	-7.45 (2.47)
(95% CI), %	(-77.77, -64.46)	(-9.52, -7.23)	(-19.73, -10.25)	(-12.31, -2.59)
p-value	< 0.001	< 0.001	< 0.001	0.003

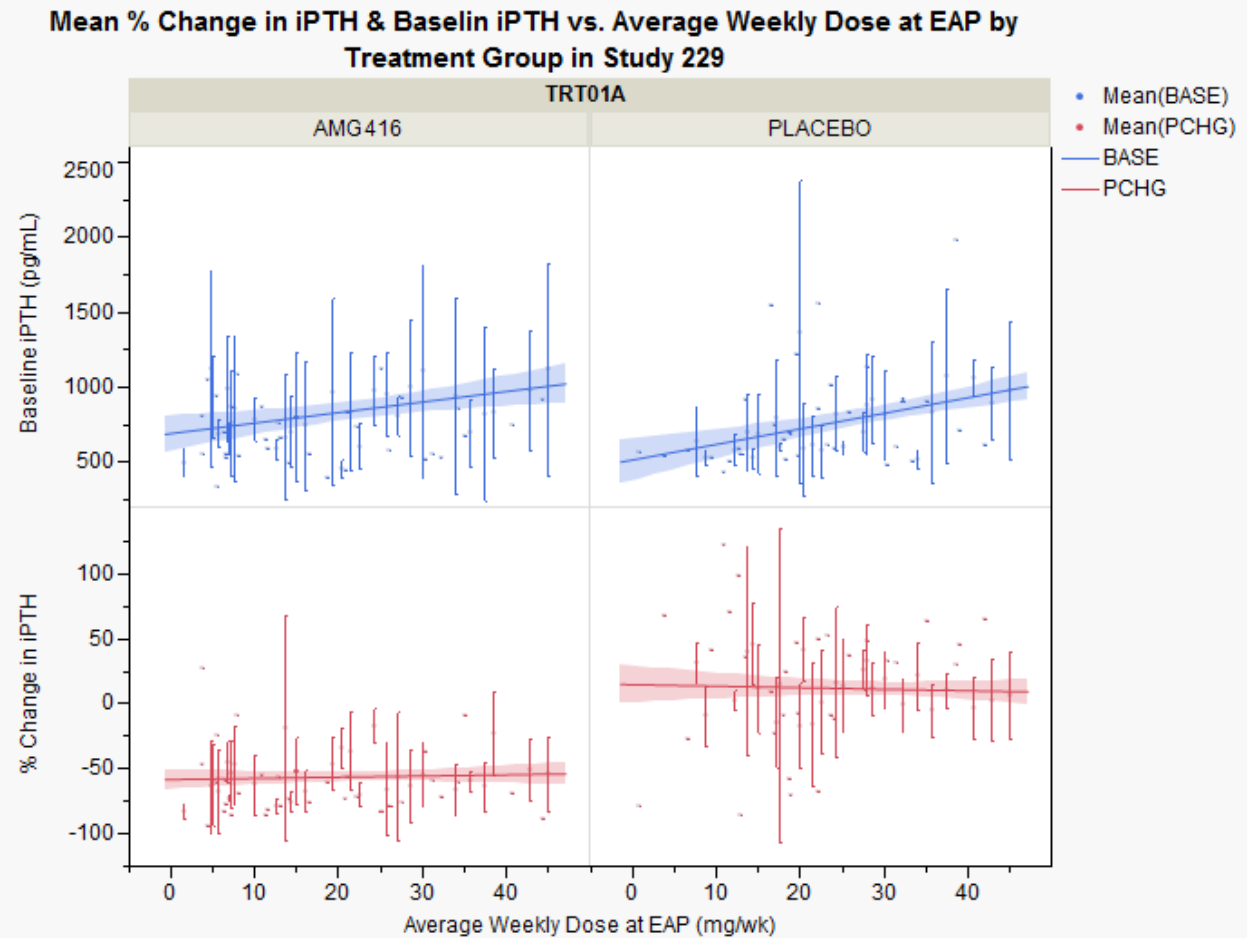
cCa = corrected calcium; cCa × P = corrected calcium phosphorus product; CI = confidence interval; EAP = efficacy assessment phase; n = number of subjects with observed data in the analysis set; PTH = parathyroid hormone; SE = standard error.
[a] Mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates.
[b] Estimated difference in mean percent change during the EAP for corresponding lab parameter between the treatment groups (AMG 416-placebo).

Source Table 10-3 CSR 20120229

Dose/Dose Response

Patients with higher baseline serum IPTH values in both the etelcalcetide and placebo treatment groups were titrated to higher doses during the EAP (see the positive slope in the blues lines in the top of Figure 5), but there was no correlation with the % reduction in mean iPTH from baseline to EAP and the final weekly dose during the EAP (see the flat red lines at the bottom of Figure 5).

Figure 5 Dose Response in Study 20120229

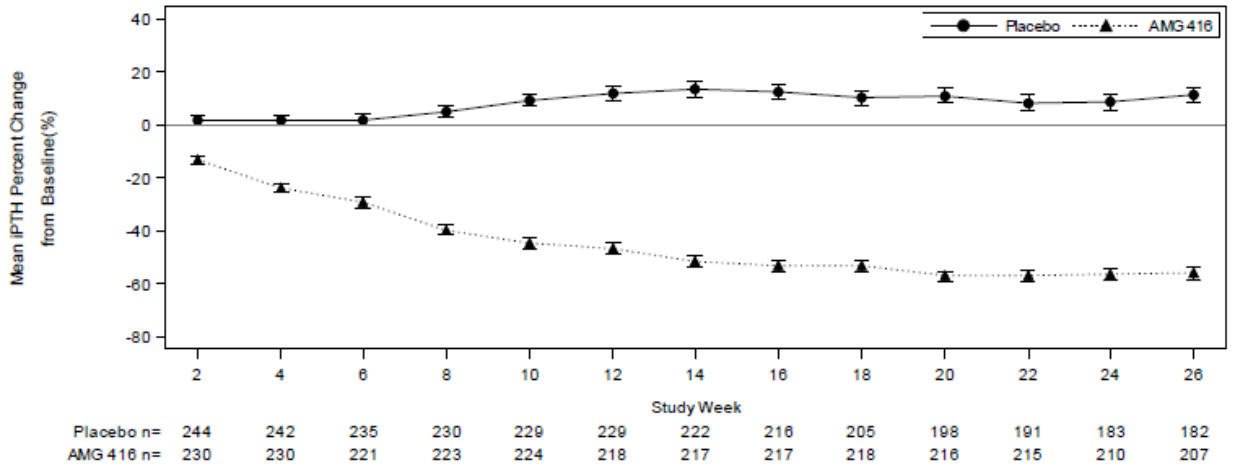


JMP analysis of PCHG and BASE for PARAM=Mean iPTH (pg/mL) During EAP (Observed) from ADLB2 ISE dataset and PARAM= AVG WEEKLY DOSE at EAP (MG/WK) from ADEX ISE dataset

Durability of Response

Efficacy with respect to mean % decrease in iPTH is clearly evident by week 2, levels off by week 16 but is sustained for the entire 26 weeks of the study.

Figure 6 Mean (SE) PTH over Time by Treatment group Study 20120229 (Safety Analysis Set)



Safety analysis set: subjects who received at least one dose of IP
On-treatment approach: Data collected on or prior to the last non-missing dose of IP are included.
Vertical lines represent the Standard Error

Source Fig. 10-2 CSR 20120229

Medical Officer's comments-

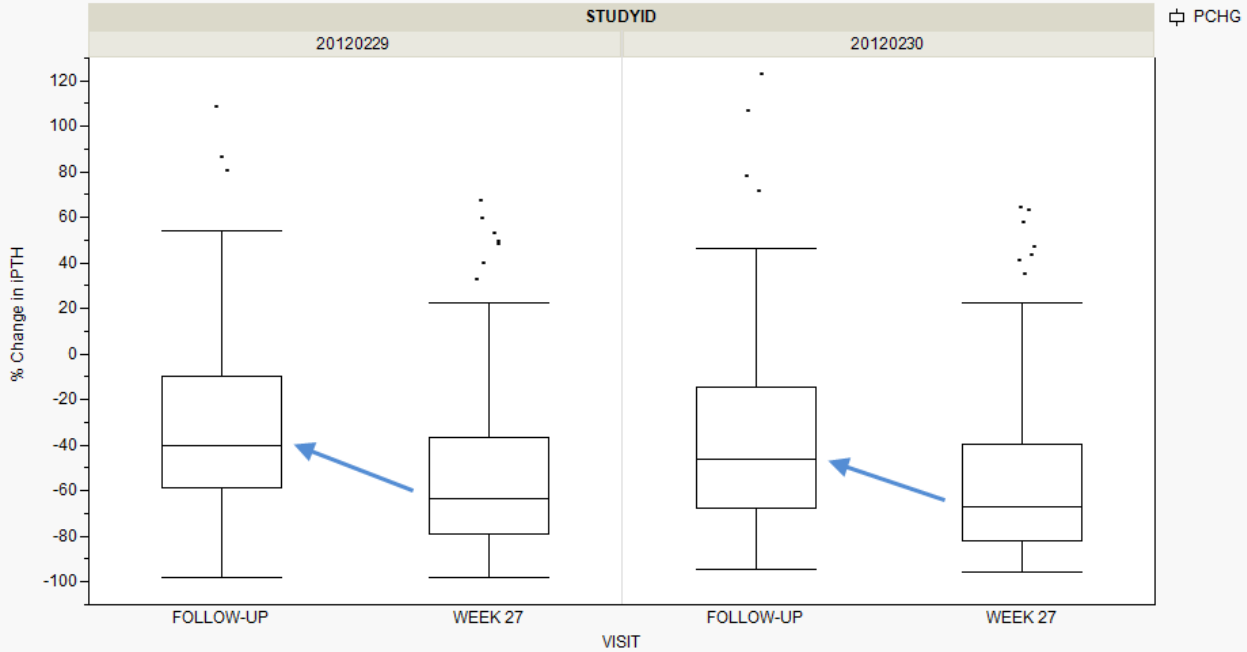
The low dropout rate of 10% at week 26 and the small standard error in the values support the durability of the response. The somewhat higher dropout rate of 25% in the placebo group is to be expected given the protocol specified criteria of rising iPTH levels after week 12 as a reason for discontinuation from the study.

Persistence of Effect

Patients were scheduled for a follow up visit off drug medication 30 days after the week 27 visit, but the sponsor did not include the data in Figure 7. This medical officer analyzed the mean % change in iPTH at the week 27 visit and the follow up visits after study day 180 to determine if there was persistence of activity after the study drug was discontinued. Efficacy in the etelcalcetide treatment group at the week 27 visit went from a median value of -63% to -40% at the follow up visit one month later in Study 20120229 for a relative decrease in efficacy of 36%. Similarly in Study 20120230 efficacy went from a median value of -67% at week 27 to -46% at the follow up visit one month later for a relative decrease in efficacy of 31%. Taken together these data demonstrate persistence of substantial efficacy for several weeks after

discontinuation of the investigational product.

Figure 7 % Change in iPTH after Dose Discontinuation from Week 27 to the Follow Up Visit



JMP analysis of ISE dataset ADLB2, PARAM=PTHIC, ADY >180 for Follow-Up visits only, STUDYID=20120229 or STUDYID=20120230, Plot of PCHG vs. VISIT

Additional Analyses Conducted on the Individual Trial

Exploratory Endpoints-

Bone Biomarkers-

Mean changes in FGF-23, BSAP, and CTX concentrations from baseline to week 12 and week 27 were characterized as exploratory endpoints in this study. No formal testing was performed on these endpoints. Treatment with etelcalcetide was associated with a decrease in log FGF-23, CTX, and BSAP from baseline to week 27 compared with placebo.

Table 15 Bone Biomarkers FGF-23, BSAP and CTX at Weeks 12 and 27 in Study 20120229 (Full Analysis Set)

	Placebo (N = 254)	AMG 416 (N = 254)
Percent change from baseline to Week 12 in log FGF-23		
n	227	220
Mean (SE) (%)	0.58 (0.57)	-14.56 (0.72)
Percent change from baseline to Week 27 in log FGF-23		
n	187	212
Mean (SE) (%)	1.47 (0.75)	-12.58 (1.00)
Percent change from baseline to Week 12 in BSAP		
n	227	216
Mean (SE) (%)	5.49 (1.92)	11.62 (3.43)
Percent change from baseline to Week 27 in BSAP		
n	186	210
Mean (SE) (%)	17.72 (3.85)	-14.63 (3.71)
Percent change from baseline to Week 12 in CTX		
n	220	216
Mean (SE) (%)	5.92 (1.88)	-23.35 (2.24)
Percent change from baseline to Week 27 in CTX		
n	182	206
Mean (SE) (%)	4.47 (2.92)	-33.89 (2.95)

BSAP = bone-specific alkaline phosphatase; CTX = collagen type 1 cross-linked C-telopeptide; FGF-23 = fibroblast growth factor-23; SE = standard error.

Source Table 11-1 CSR 20120229

Medical Officer's comments-

FGF-23 functions to increase phosphate excretion by the kidney. The decrease in FGF-23 seen with etelcalcetide treatment probably reflects the decrease in mean serum phosphorous. The clinical significance of these changes is unknown.

BSAP, bone specific alkaline phosphatase, is a glycoprotein synthesized by osteoblasts which reflects bone biosynthetic activity. BSAP initially increases at week 12 followed by a decrease in activity at week 27.

CTX, the carboxy-terminal telopeptide, is a marker of bone resorption and turnover. CTX decreases both at week 12 and even further at week 27.

Abnormally high elevated levels of PTH in dialysis patients trigger increased bone turnover resulting in abnormal bone structure and an increased rate of fracture seen with renal osteodystrophy. The initial increase in BSAP and decrease in CTX seen at week 12 may represent a relative net increase in bone formation. The subsequent decrease in both BSAP and CTX at week 27 may represent a net decrease in the abnormally high bone turnover seen with renal osteodystrophy. Whether these changes in bone biomarkers seen with etelcalcetide treatment actually represent improvement in bone architecture and bone strength is unknown. Bone biopsy data, although still a surrogate endpoint could potentially be helpful in elucidating the potential clinical benefit of treatment with etelcalcetide, but it was not performed in this study.

6.2. Study 20120230-A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects with Chronic Kidney Disease on Hemodialysis

6.2.1. Study Design

The study design for CTAP101-CL-3002 was identical to CTAP101-CL-3001, see section 6.1.1.

6.2.2. Study Results

Financial Disclosure

See Section 6.1.2; data for both studies 20120229 & 20120230 was presented together for easier comparison.

Patient Disposition

See Section 6.1.2; data for both studies 20120229 & 20120230 was presented together for easier comparison.

Protocol Violations/Deviations

See Section 6.1.2; data for both studies 20120229 & 20120230 was presented together for easier comparison.

Table of Demographic Characteristics

See Section 6.1.2, **Table 6**.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

See Section 6.1.2, Tables 7, 8 and 9; data for both studies 20120229 & 20120230 was presented together for easier comparison.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

See Section 6.1.2; data for both studies 20120229 & 20120230 was presented together for easier comparison.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was a responder analysis looking at the proportion of subjects in the ITT population attaining a mean decrease of >30% in serum iPTH from pre-treatment baseline during the EAP, weeks 20 to 27. Subjects who discontinued from the study prior to the EAP or had no serum iPTH determinations in the EAP were considered non-responders. Results were statistically significant, 75% vs. 9.6%, p<0.001 as seen in Table 16. These results are similar to what was seen previously in Study 20120229 (74% vs. 8.2%, p<001).

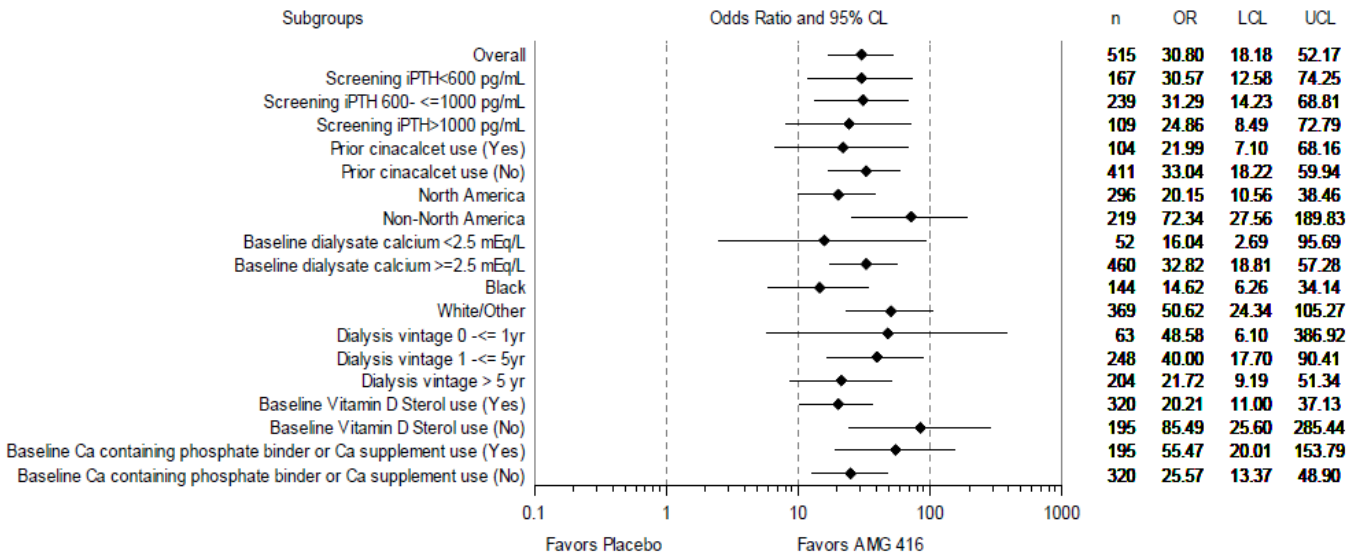
Table 16 Primary Endpoint for Study 20120230- Responders with > 30% Reduction in iPTH during the EAP (ITT population)

	Placebo (N = 260)	AMG 416 (N = 255)	Treatment Difference
Subject Status			
Number of subjects	260	255	
Yes - n (%) [a]	25 (9.6)	192 (75.3)	
Screening iPTH < 600 pg/mL	10 (3.8)	67 (26.3)	
Screening iPTH 600 - ≤ 1000 pg/mL	8 (3.1)	85 (33.3)	
Screening iPTH > 1000 pg/mL	7 (2.7)	40 (15.7)	
Prior cinacalcet use	3 (1.2)	18 (7.1)	
No prior cinacalcet use	22 (8.5)	174 (68.2)	
North America	17 (6.5)	102 (40.0)	
Non-North America	8 (3.1)	90 (35.3)	
No - n(%) [a]	235 (90.4)	63 (24.7)	
Screening iPTH < 600 pg/mL	74 (28.5)	17 (6.7)	
Screening iPTH 600 - ≤ 1000 pg/mL	113 (43.5)	33 (12.9)	
Screening iPTH > 1000 pg/mL	48 (18.5)	13 (5.1)	
Prior cinacalcet use	30 (11.5)	11 (4.3)	
No prior cinacalcet use	205 (78.8)	52 (20.4)	
North America	133 (51.2)	44 (17.3)	
Non-North America	102 (39.2)	19 (7.5)	
CMH-stratified [b] odds ratio (AMG 416: Placebo)			30.80
(95% CI)			(18.18, 52.17)
p-value [c]			< 0.001

Full analysis set: all randomized subjects
n = Number of subjects with observed data in the analysis set. CI = Confidence Interval.
[a] Subject has iPTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).
[b] Stratification factors based on screening iPTH level, prior cinacalcet use within 8 weeks prior to randomization, and region were from IXRS
[c] Cochran-Mantel-Haenszel (CMH) test
Source Table 14-4.1 CSR 20120230

Efficacy was consistent across all subgroups tested including, baseline iPTH categories, prior use of cinacalcet, geographic region, baseline dialysate calcium, race, dialysis vintage, baseline use of vitamin D analogs, baseline use of phosphate binder or calcium supplement (Figure 4).

Figure 8 Treatment Difference in Primary Endpoint Study 20120230 (Full Analysis Set)



Full analysis set: all randomized subjects. Stratification factors w ere from IXRS.
NE = Not Estimable
Source Fig 10-1 CSR 20120229

Medical Officer's comments

As seen previously in Study 20120229 there is no consistent difference in efficacy with respect to baseline screening iPTH; there is clear efficacy in subjects without previous exposure to cinacalcet; efficacy in subjects from North America is lower than from Non-North American subjects possibly due to a difference in baseline characteristics across regions as discussed previously in more detail, and efficacy does appear to trend better for subjects with the shortest duration of dialysis vintage who are likely to have less severe bone disease which may be why they are more responsive to PTH reduction.

Data Quality and Integrity – Reviewers' Assessment

Medical Officer's comments- This medical reviewer agrees with OSI's assessment of the clinical inspection sites, See Section 4.1.

The applicant's monitoring for data quality and integrity was acceptable.

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy endpoints were prespecified using a hierarchical testing approach in the following sequence:

1. proportion of subjects with predialysis PTH ≤ 300 pg/mL
2. % change from baseline to EAP in iPTH
3. % change from baseline to EAP in cCa
4. % change from baseline to EAP in cCa x P
5. % change from baseline to EAP in phosphorus

The first secondary endpoint measures PTH lowering to a goal of ≤ 300pg/mL, which is consistent with the treatment goal in the earlier KDOQI guidelines for patients with CKD Stage 5 on renal dialysis e.g. 150 to 300pg/mL, but which has since been replaced by the more liberal KDIGO guidelines to 130 to 600pg/mL.

Medical Officer's comments-

Given the mean iPTH at baseline was approximately 850pg/mL, treatment to a goal of ≤300pg/mL represents a mean decrease of at least 65%. A substantial proportion of subjects in the etelcalcetide treatment group i.e. 53% were able to reach this treatment goal compared to only 5% in the placebo group (p<0.001). The results are similar to what was seen previously in Study 2012029 (i.e. 50% and 5%, respectively).

Table 17 Proportion of Subjects Treated to Goal of ≤300pg/mL during the EAP Study 20120230 (Full Analysis Set)

	Placebo (N = 260)	AMG 416 (N = 255)	Treatment Difference
Subjects achieving PTH ≤ 300 pg/mL during EAP[a], n (%)	12 (4.6)	136 (53.3)	
CMH stratified[b] odds ratio (AMG 416: placebo)			33.92
(95% CI)			(16.35, 70.37)
p-value[c]			< 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EAP = efficacy assessment phase; PTH = parathyroid hormone.
[a] Subject had PTH ≤ 300 pg/mL during the EAP (study visits during week 20 to week 27, inclusive). Subjects who had no scheduled assessments during the EAP were considered to be nonresponders.
[b] Stratification factors based on screening PTH level, prior cinacalcet use within 8 weeks prior to randomization, and region were from the interactive voice/web reponse system.
[c] CMH test

Source Table 10-2 CSR 20120230

All four of the other secondary endpoints i.e. % change from baseline to EAP in iPTH, cCa, cCaxP and phosphorus were also statistically significant. The mean difference between treatment groups were -71%, -7.2%, -15%, and -8.0% for iPTH, cCa, cCa x P and phosphorus, respectively. These results are similar to what was seen previously in Study 20120229 (-71%, -8.4%, -15%, and -7.5%, respectively).

Table 18 Percent Change from Baseline in Mean iPTH, cCA, cCaXP, and Phosphorous Study 20120230 (Full Analysis Set)

Percent change from baseline to EAP in predialysis:	PTH	cCa	cCa x P	Phosphorus
Placebo (N = 260)				
n	237	237	234	234
Mean (SE), %	13.72 (2.50)	0.58 (0.29)	-1.06 (1.42)	-1.60 (1.42)
AMG 416 (N = 255)				
n	227	227	223	223
Mean (SE), %	-57.39 (1.91)	-6.69 (0.55)	-15.84 (1.57)	-9.63 (1.61)
Treatment difference				
Adjusted analysis[a]				
Estimate[b] (SE), %	-71.34 (3.15)	-7.20 (0.60)	-14.58 (2.07)	-8.04 (2.09)
(95% CI), %	(-77.53, -65.14)	(-8.38, -6.03)	(-18.65, -10.51)	(-12.15, -3.92)
p-value	< 0.001	< 0.001	< 0.001	< 0.001

cCa = corrected calcium; cCa x P = corrected calcium phosphorus product; CI = confidence interval; EAP = efficacy assessment phase; n = number of subjects with observed data in the analysis set; PTH = parathyroid hormone; SE = standard error.

[a] Mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates.

[b] Estimated difference in mean percent change during the EAP for corresponding lab parameter between the treatment groups (AMG 416-placebo).

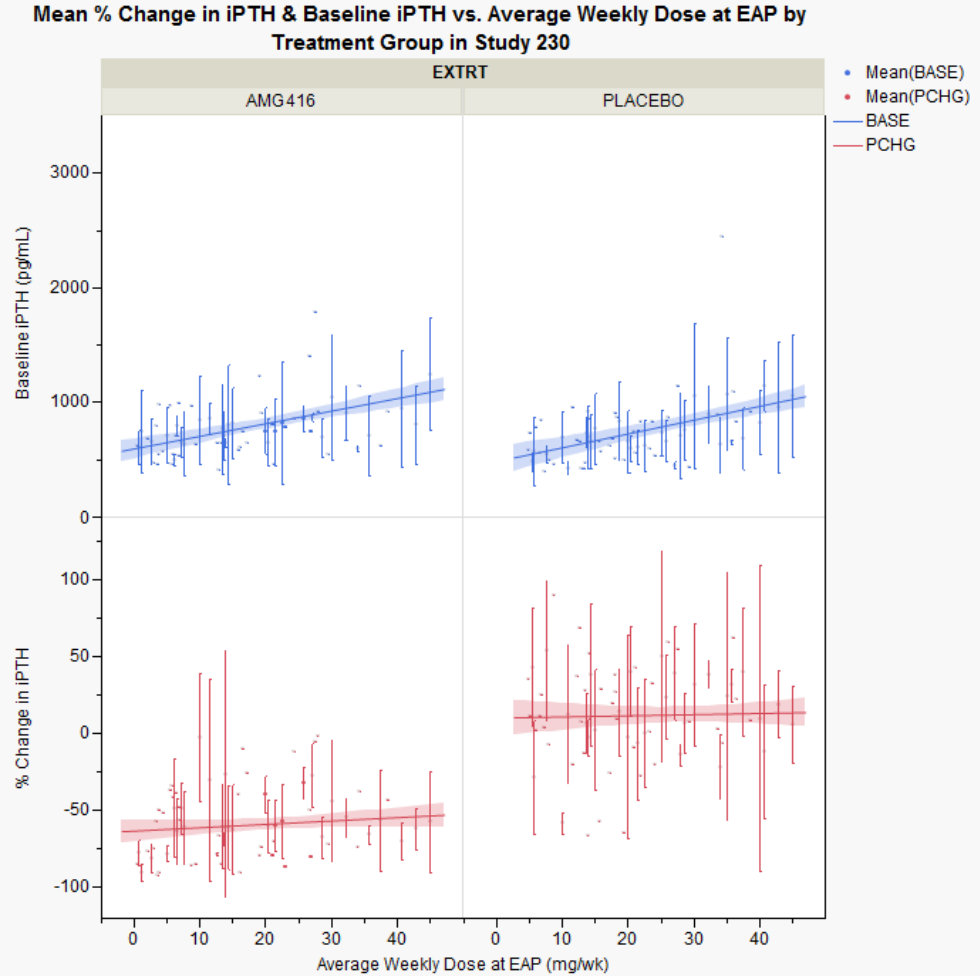
Source Table 10-3 CSR 20120230

Dose/Dose Response

Similar to what was observed in Study 20120229 patients with higher baseline serum IPTH values in both the etelcalcetide and placebo treatment groups were titrated to higher doses during the EAP (see the positive slope in the blues lines in the top of Figure 9), but in contrast to

Study 20120229 where there was no clear correlation with the % reduction in mean iPTH from baseline to EAP and the final weekly dose during the EAP there is a slight positive slope in the line for subjects treated with etelcalcetide (see the red lines at the bottom left of Figure 9) representing a slight decrease in efficacy at the higher doses despite treatment of subjects with higher baseline iPTH levels with the higher doses.

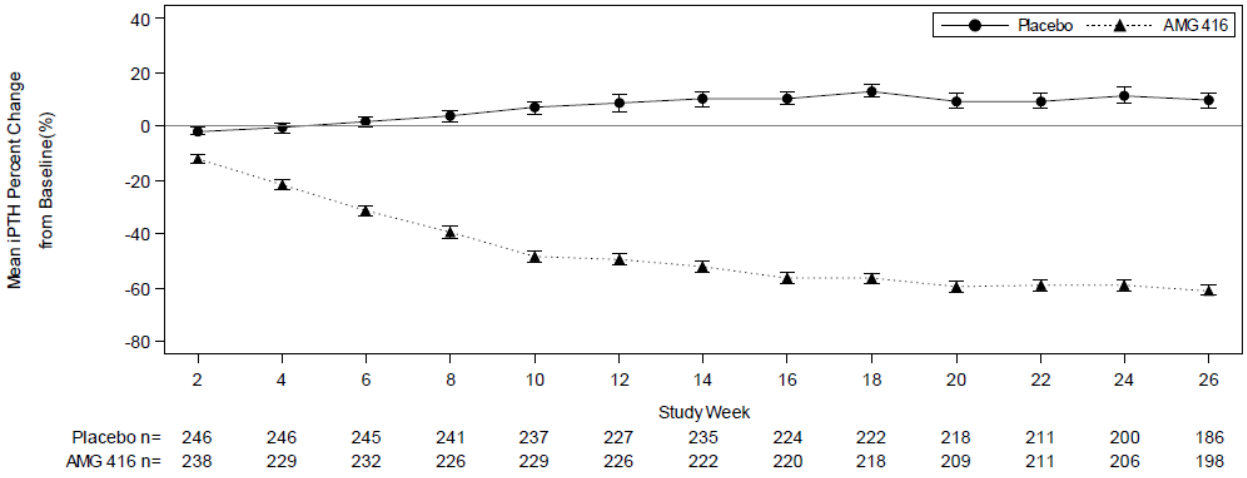
Figure 9 Dose Response in Study 2012030



Durability of Response

Similar to what was observed in Study 20120229 efficacy with respect to mean % decrease in iPTH is clearly evident by week 2, levels off by week 16 but is sustained for the entire 26 weeks of the study.

Figure 10 Mean (SE) PTH over Time by Treatment group Study 2012030 (Safety Analysis Set)



Safety analysis set: subjects who received at least one dose of IP
On-treatment approach: Data collected on or prior to the last non-missing dose of IP are included.
Vertical lines represent the Standard Error
Source Fig. 10-2 CSR 20120230

Persistence of Effect

There is persistence of limited efficacy for several weeks after discontinuation of the investigational product. Data for both pivotal studies was presented under "Persistence of Effect" in section 6.1.1 (see Figure 7).

Additional Analyses Conducted on the Individual Trial

Exploratory Endpoints-

Bone Biomarkers-

Mean changes in FGF-23, BSAP, and CTX concentrations from baseline to week 12 and week 27 were characterized as exploratory endpoints in this study. No formal testing was performed on these endpoints. Treatment with etelcalcetide was associated with a decrease in log FGF-23, CTX, and BSAP from baseline to week 27 compared with placebo similar to what was seen in study 20120229.

Table 19 Bone Biomarkers FGF-23, BSAP and CTX at Weeks 12 and 27 in Study 20120230 (Full Analysis Set)

	Placebo (N = 260)	AMG 416 (N = 255)
Percent change from baseline to Week 12 in log FGF-23		
n	235	227
Mean (SE) (%)	0.97 (0.56)	-14.79 (0.87)
Percent change from baseline to Week 27 in log FGF-23		
n	200	209
Mean (SE) (%)	-0.20 (0.89)	-11.19 (1.21)
Percent change from baseline to Week 12 in BSAP		
n	224	214
Mean (SE) (%)	12.02 (2.83)	8.21 (3.04)
Percent change from baseline to Week 27 in BSAP		
n	194	201
Mean (SE) (%)	24.72 (4.34)	-22.56 (2.51)
Percent change from baseline to Week 12 in CTX		
n	229	219
Mean (SE) (%)	5.81 (2.08)	-29.82 (1.95)
Percent change from baseline to Week 27 in CTX		
n	184	195
Mean (SE) (%)	4.79 (3.37)	-43.42 (2.43)

BSAP = bone-specific alkaline phosphatase; CTX = collagen type 1 cross-linked C-telopeptide; FGF-23 = fibroblast growth factor-23; SE = standard error.

6.3. A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism

6.3.1. Study Design

Overview and Objective

The primary objective of this study was to demonstrate that treatment with etelcalcetide is not inferior to treatment with cinacalcet for lowering serum intact PTH levels by > 30% from baseline among hemodialysis patients with CKD and secondary hyperparathyroidism. The secondary objectives were to assess whether treatment with etelcalcetide is superior to treatment with cinacalcet as measured by:

- proportion of subjects with > 50% decrease in serum PTH from baseline,
- proportion of subjects with > 30% decrease in serum PTH from baseline,
- mean number of days of vomiting or nausea per week,
- % change from baseline in predialysis cCa during the EAP,
- proportion of subjects with mean serum phosphorus $\leq$4.5mg/dL during the EAP,
- mean severity of nausea in the first 8 weeks, and
- mean number of episodes of vomiting per week in the first 8 weeks.

Information about nausea and vomiting was collected using a patient reported outcome (PRO) instrument.

Trial Design

Study 20120360 was designed as a 26-week, randomized, double-blind, double-dummy, active-controlled, dose-titration, Phase 3 study to compare etelcalcetide and cinacalcet in hemodialysis patients with CKD and secondary hyperparathyroidism. Subjects were randomized 1:1 to IV etelcalcetide and oral placebo or oral cinacalcet and IV placebo. Randomization was stratified by region: North America vs. non-North America and baseline serum iPTH (< 900 pg/mL, or $\geq$900 pg/mL) obtained during the 8-week screening phase. IV study drugs were administered 3 times a week (TIW) while oral study drugs were administered daily for the 26 week treatment period. Doses could be titrated up at weeks 5, 9, 13, and 17 to achieve predialysis serum PTH in the range: (100 pg/mL < PTH $\leq$300 pg/mL) while maintaining serum cCa $\geq$8.3 mg/dL. The dose titration conditions were similar between treatment groups except that the etelcalcetide group was titrated by half the regular dose if the iPTH was near the treatment goal i.e. between 300 to 450pg/mL:

PTH (pg/mL)	IV Investigational Product Dose	Oral Investigational Product Dose*
PTH > 450	Increase dose by 5 mg	Increase dose by 30 mg
300 < PTH ≤ 450	Increase dose by 2.5 mg	Increase dose by 30 mg
PTH ≤ 300	Maintain dose	Maintain dose

*Note that the oral investigational product dose increases from 120 mg to 180 mg

Titration to the maximal dose in the cinacalcet group could go from 30→60→90→120→180mg and would take 4 titrations taking up the entire 17 week titration period, while titration to the maximal dose in the etelcalcetide group could go from 5→10→15mg and reach the maximal dose after the second titration assuming iPTH levels stayed above 450pg/mL. Therefore subjects could be titrated to the maximum dose faster in the etelcalcetide group, assuming they could tolerate the more rapid titration (i.e. continued to have an elevated iPTH, normal corrected serum calcium level and no related AEs). Since subjects were not analyzed for efficacy until weeks 20 to 27, during the efficacy assessment phase (EAP), there was still adequate time for both treatment groups to be titrated up to the maximal possible dose prior to the efficacy assessment.

Dose increases were to occur at weeks 5, 9, 13 and 17 unless:

- iPTH < 300pg/mL
- corrected serum calcium < 8.3mg/dL or pt had symptomatic hypocalcemia
- ongoing Adverse Event that in the opinion of the clinical investigator precluded a dose increase
- the subject missed 3 or more IV doses/hemodialysis sessions in the past 3 wks or the drug dose was reduced in the prior 3 wks

Dose suspension was to occur if:

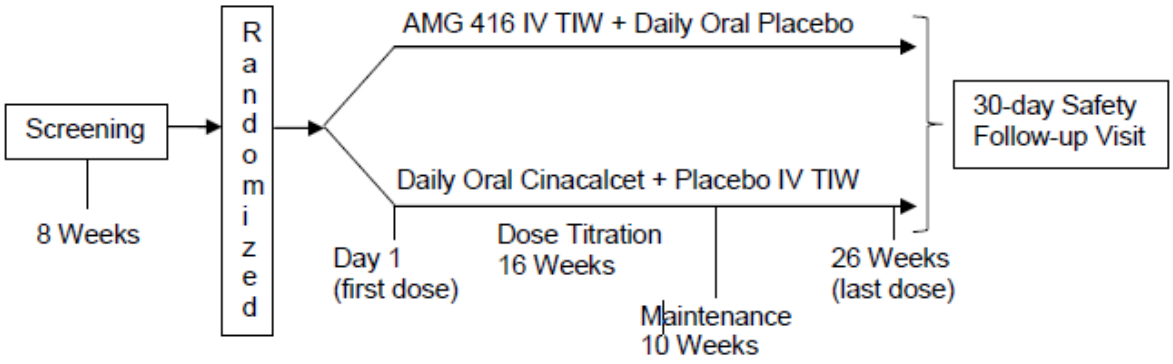
- iPTH < 100pg/mL on two consecutive measurements
- corrected serum calcium < 7.5mg/dL or pt had symptomatic hypocalcemia
- ongoing Adverse Event that in the opinion of the clinical investigator necessitated dose suspension

Dosing could be resumed at the same dose if the investigator deemed the AE was not related to the study drug or at a reduced dose once the AE had resolved and the pt had stabilized.

Dose titration was handled by an interactive voice/web response system (IXRS) which took the predialysis serum iPTH and corrected Ca results from the prior week into account in making dosing decisions. Investigator input was not to affect dosing decisions unless they submitted specific adverse events that they considered significant enough to affect dosing.

Subjects were followed up for safety for 30 days after the last dose of investigational product. All subjects, regardless of treatment assignment, received standard of care as prescribed by their individual clinical investigator, with calcium supplements, phosphate binders, and nutritional vitamin D supplements. If treatment with calcitriol or vitamin D analogs was ongoing when subjects were enrolled in the study, the doses were to remain constant for the duration of study. However, treatment with vitamin D analogs could be initiated, interrupted, or adjusted for safety reasons. The study was conducted at 164 centers in Austria, Belgium, Canada, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, New Zealand, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Turkey, and the United States.

Figure 11 Study Design for Study 20120360



IV = intravenous; TIW = 3 times a week

Inclusion criteria for (including but not limited to):

- 18 years of age or older
- Receiving hemodialysis TIW for at least 3 months
- Dialysate calcium concentration must be on a stable dose of ≥2.25 mEq/L prior to randomization and expected to stay on that stable dose for the duration of the study.
- Subjects receiving vitamin D sterols, phosphate binders or calcium supplements must be on a stable dose of the medication and expected to maintain those stable doses for the duration of the study.
- Serum iPTH >500 pg/mL within two weeks of enrollment
- Serum cCa ≥8.3 mg/dL within two weeks of enrollment

- Stable medical condition based on medical history, PE, and routine labs in the judgment of the investigator
- Female subjects of childbearing potential must agree to remain abstinent or use effective contraception for the duration of the study and for 3 months after the last dose, and must have a negative serum pregnancy test within 2 weeks of the first study dose.

Exclusion criteria for (including but not limited to):

- History of kidney transplant or parathyroidectomy or anticipated to have the procedure during the study period.
- Previously received etelcalcetide in a prior clinical trial
- Exposure to cinacalcet within 3 months prior to screening labs
- Pregnant or nursing female
- Abnormal screening labs including but not limited to:
    - serum albumin ≤3.0g/dL
    - serum magnesium <1.5mg/dL
    - SGOT or SGPT >2.5xULN
- History of symptomatic ventricular dysrhythmias or Torsade de Pointes
- History of MI, coronary angioplasty, or CABG within past 6 months
- History of any illness that in the opinion of the investigator might confound the study results or pose an additional risk to the subject

Medical Officer's comments-

These inclusion/exclusion criteria are in general similar to those used in the earlier pivotal trials except that a single higher baseline iPTH value of > 500pg/mL was required during the screening period for enrollment instead of the mean value of >400pg/mL from at least two measurements which was the inclusion criteria from the earlier pivotal trials. The change to the single value > 500pg/mL was part of Amendment 2 to the original protocol which had required 2 consecutive iPTH values > 600pg/mL for enrollment.

Table 20 Schedule of Assessments for 20120360

Study Week (Day)	Screen	E	D1	1	2	3	4	T 5	6	7	8	T 9	10	11	12	T 13	14	15	16	T 17	M 18	M 19
Informed consent	X																					
Inclusion/exclusion	X																					
Demographics	X																					
Medical history	X																					
Physical examination	X																					
Randomization		X																				
Daily tablet IP (by subject)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TIW admin of IV IP (by site)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose titration								X				X				X				X		
Prior and concomitant meds	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pill count					X		X		X		X		X		X		X		X		X	
Daily NVSA	At least 7X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KDQOL-36™	X						X				X											
FLIE	X						X				X											
Before Dialysis																						
ECG			X																			
Pregnancy	X		X												X							
Hematology	X																					
Chemistry	X																					
Phosphorus			X				X				X				X				X			
Albumin and calcium			X		X		X		X		X		X		X		X		X		X	
PTH	X		X		X		X		X		X		X		X		X		X		X	
25(OH)D			X																			
BSAP			X												X							
FGF-23			X												X							
CTX			X												X							
ADA			X												X							
Postdialysis																						
Vital signs (heart rate, BP)			X																			
Height/weight			X																			

Study Week (Day)	EAP 20	EAP 21	EAP 22	EAP 23	EAP 24	EAP 25	EAP 26	EAP 27	SFU 30	ET	SD
Informed consent											
Inclusion/exclusion											
Demographics											
Medical history											
Physical examination									X	X	
Randomization											
Daily tablet IP (by subject)	X	X	X	X	X	X	X				
TIW admin of IV IP (by site)	X	X	X	X	X	X	X				
Dose titration											
Prior and concomitant meds	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X
Pill count	X		X		X		X	X		X	
Daily NVSA	X	X	X	X	X	X	X			X	
KDQOL-36™							X			X	
FLIE							X			X	
Before Dialysis											
ECG								X		X	
Pregnancy					X				X	X	
Hematology									X	X	
Chemistry									X	X	
Phosphorus	X				X		X	X		X	
Albumin and calcium	X		X		X		X	X		X	X
PTH	X		X		X		X	X	X	X	
25(OH)D								X		X	
BSAP								X		X	
FGF-23								X		X	
CTX								X		X	
ADA									X	X	
Postdialysis											
Vital Signs (heart rate, BP)								X		X	
Weight								X		X	

25(OH)D = 25-hydroxyvitamin D; ADA = antidrug antibody; admin = administration; BP = blood pressure; BSAP = bone-specific alkaline phosphatase; CTX = serum collagen type 1 cross-linked C-telopeptide; EAP = efficacy assessment phase; ECG = electrocardiogram; ET = early termination; FGF-23 = fibroblast growth factor-23; FLIE = Functional Living Index - Emesis; IP = investigational product; IV = intravenous; KDQOL-36™ = Kidney Disease and Quality of Life Short Form 36; NVSA = Nausea/Vomiting Symptom Assessment; PTH = parathyroid hormone; SD = suspended dose; SFU 30 = 30-day safety follow-up visit; TIW = 3 times a week

Study Endpoints

The primary endpoint is based on the upper bound of the two sided 95% confidence interval (95% CI) for the stratified difference in the proportion of subjects who achieve a > 30% reduction in mean iPTH from baseline to EAP, which was the primary endpoint in the pivotal trials, described previously and discussed in more detail under section 6.1.1. The primary noninferiority analysis between etelcalcetide and the active control, cinacalcet, determined etelcalcetide to be non-inferior if the upper bound of the two-sided 95% CI of the treatment difference (cinacalcet – etelcalcetide) was not greater than 12%.

Statistical Analysis Plan

The Full Analysis Set (FAS), which includes all randomized subjects, was used for the primary analysis, and the first two key secondary endpoints.

The Primary Endpoint was the estimate of the upper bound of the 95% CI for the stratified difference in the proportion of subjects with >30% reduction in PTH level from baseline to EAP (noninferiority) analyzed using a Mantel-Haenazel method with adjustment for the randomization stratification factors based on the FAS. Etelcalcetide was considered non-inferior if the upper bound of the two-sided 95% CI of the treatment difference (cinacalcet – AMG 416) was smaller than 12%. Imputation under the noninferiority null method was applied to subjects who did not have data during the EAP. The imputation was performed 5 times to account for variability introduced by imputation.

In addition two sensitivity analyses were conducted:

- Efficacy Evaluable Analysis Set (EEAS): Only subjects with PTH data during the EAP are included.
- modified Last Observation Carried Forward (LOCF):For subjects without PTH data during the EAP, the mean of the last 2 pre-dialysis PTH values obtained after Day 1 will be carried forward. If only one value is available, this single value will be carried forward to the EAP. A similar imputation approach as the primary analysis will be applied to subjects without a post-baseline PTH value.

The three key secondary endpoints were to be tested sequentially:

1. Achievement of > 50% reduction from baseline in PTH during the EAP (superiority)
2. Achievement of > 30% reduction from baseline in PTH during the EAP (superiority)
3. Mean number of days of vomiting or nausea per week in the first 8 weeks of treatment

The first two key secondary endpoints were analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors of mean screening PTH and region based on the FAS. Subjects were considered as not achieving the endpoint if they did not have data during the EAP. The third key secondary endpoint was analyzed using a generalized linear

mixed model with Poisson regression, including the randomization stratification factors and other prespecified covariates.

If all 3 key secondary endpoints are statistically significant, the rest of the secondary endpoints were to be tested at the 5% significance level. The Hochberg procedure was to be used to adjust for multiple comparisons among the other secondary endpoints.

4. Percent change from baseline in mean predialysis serum cCa during the EAP was to be analyzed using a repeated measures missed effects model, including treatment group, randomization stratification factors, study week, and study week by treatment as fixed effects.
5. Achievement of mean predialysis serum phosphorus $\leq$4.5 mg/dL during the EAP was to be analyzed using a CMH test stratified by the randomization stratification factors, mean screening iPTH and region, using the nonresponder method of imputation for subjects without laboratory values during the EAP.
6. Mean severity of nausea in the first 8 weeks was to be analyzed using an ANCOVA stratified by the randomization stratification factors, mean screening PTH and region.
7. Mean number of episodes of vomiting per week in the first 8 weeks was to be analyzed using a generalized linear mixed model using Poisson regression, including the randomization stratification factors, mean screening PTH and region and other prespecified covariates, number of episodes of vomiting, treatment, stratification factors, study weeks and treatment by study weeks.

Medical Officer's comments-

Given that the 3rd key secondary endpoint "nausea and vomiting during the first 8 weeks of treatment" was not statistically significant, secondary endpoints 4 through 7 were not formally tested for statistical significance.

Protocol Amendments

No subjects were enrolled prior to the first amendment.
Amendment 1- 04 March 2013 (including but not limited to:)
Two subjects enrolled between this date and the date of the next amendment.

- Allowed adjustment of vitamin D for hypocalcemia during the study. Provided a recommended sequence of interventions for treating hypocalcemia with reference to the modification of oral calcium supplements, dialysate calcium concentration, and then vitamin D.
- Clarified that etelcalcetide was not to be administered subcutaneously or by any route other than IV, and that it was not to be administered concurrently with other IV medications.

- Changed the assay for iPTH testing from plasma to serum to be consistent with previous etelcalcetide studies.

Amendment 2- 30 August 2013 (including but not limited to:)
There were 681 subjects enrolled between this date and the date of the next amendment.

- Changed the eligibility criteria from two consecutive iPTH concentrations > 600 pg/mL to one iPTH concentration > 500 pg/mL.
- Changed the inclusion criteria to allow changes up to 50% in the maximum dose for protocol-specified concomitant therapies (vitamin D, calcium supplements, and phosphate binders).

Amendment 3- 17 October 2014
Study enrollment was completed at the time of this amendment.
Added a key secondary endpoint based on efficacy (i.e. >30% reduction in iPTH) and reprioritized the order of sequential statistical testing of the key secondary endpoints based on the results of recently-concluded, phase 3 data from placebo-controlled Studies 20120229 and 20120230. The previous version of the protocol had 2 key secondary endpoints that were to be tested sequentially for superiority in the following order if the primary endpoint met the noninferiority criterion based on the prespecified noninferiority margin:

1. Mean number of days of vomiting or nausea per week in the first 8 weeks
2. Achievement of a > 50% reduction in mean predialysis serum PTH from baseline during the EAP

To properly control for type I error for superiority testing, achievement of a > 30% reduction from baseline in mean predialysis serum PTH during the EAP was added as a key secondary endpoint, and the three key secondary endpoints were specified in the following revised sequence for superiority testing:

1. Achievement of a > 50% reduction in PTH from baseline during the EAP
2. Achievement of a > 30% reduction in PTH from baseline during the EAP
3. Mean number of days of vomiting or nausea per week in the first 8 weeks

The changes were implemented before study completion, while the study (20120360) data was still blinded.

Medical Officer's comments-

Revision of the protocol analysis plan is acceptable as long as it was performed prior to unblinding of the study data as the applicant states. The purpose of the revision was primarily to change the endpoint of nausea and vomiting during the initial 8 wks of therapy from the first secondary endpoint tested to the third endpoint tested, probably because the applicant observed higher than expected event rates of nausea and vomiting in the initial

pivotal trials. As will be described in more detail in section 6.3.2 Study Results, the revision of the sequence of testing was prudent as only the first two endpoints gave p-values < 0.05 while the third endpoint, the mean number of days of vomiting or nausea during the initial 8 wks of treatment, gave a point estimate in favor of treatment with etelcalcetide but the p-value was 0.27, and so not statistically significant.

Data Quality and Integrity: Sponsor's Assurance

See Section 6.1.1. Data quality assurance was similar to what had been previously described for studies 20120229 and 20120230.

6.3.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with applicable country regulations and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Financial Disclosure

Study 20120360
There were 2 out of 588 investigators at almost 200 clinical sites with disclosable financial interests who enrolled 5 total subjects into Study 20120229 and were listed on Form 3455: Excluding the results from these 5 subjects from the 683 study patients (0.7%) would not affect the study results.

Site No	Investigator	Address	Subjects Enrolled	Financial Disclosure
[redacted]			(b) (6)	Amgen Support 40,000 Euro
				600 shares of Amgen stock worth 67,050 as of 2014

Patient Disposition

Table 21 Subject Disposition & Discontinuation from Study 20120360

	Cinacalcet (N = 343) n (%)	AMG 416 (N = 340) n (%)	Total (N = 683) n (%)
Full Analysis Set Inclusion	343 (100.0)	340 (100.0)	683 (100.0)
Completer Analysis Set Inclusion	310 (90.4)	298 (87.6)	608 (89.0)
Safety Analysis Set Inclusion	341 (99.4)	338 (99.4)	679 (99.4)
Per Protocol Analysis Set Inclusion	287 (83.7)	272 (80.0)	559 (81.8)
Investigational product accounting (Full Analysis Set)			
Subjects who never received investigational product	2 (0.6)	2 (0.6)	4 (0.6)
Subjects who received investigational product	341 (99.4)	338 (99.4)	679 (99.4)
Subjects who completed investigational product	282 (82.2)	271 (79.7)	553 (81.0)
Subjects who discontinued investigational product	61 (17.8)	69 (20.3)	130 (19.0)
Adverse event	16 (4.7)	19 (5.6)	35 (5.1)
Lost to follow-up	0 (0.0)	2 (0.6)	2 (0.3)
Death	4 (1.2)	5 (1.5)	9 (1.3)
Decision by sponsor	2 (0.6)	0 (0.0)	2 (0.3)
Subject request	34 (9.9)	28 (8.2)	62 (9.1)
Protocol-specified criteria	5 (1.5)	15 (4.4)	20 (2.9)
Subject was to receive kidney transplant	5 (1.5)	15 (4.4)	20 (2.9)
Study completion accounting (Full Analysis Set)			
Subjects who completed study	294 (85.7)	287 (84.4)	581 (85.1)
Subjects who discontinued study	49 (14.3)	53 (15.6)	102 (14.9)
Withdrawal of consent from study[a]	32 (9.3)	31 (9.1)	63 (9.2)
Lost to follow-up	9 (2.6)	12 (3.5)	21 (3.1)
Death	6 (1.7)	10 (2.9)	16 (2.3)
Decision by sponsor	2 (0.6)	0 (0.0)	2 (0.3)

Analysis sets are defined in Table 8-4.
[a] Eight subjects from Site 66059 withdrew consent from the study. Of the 8 subjects, 6 subjects withdrew consent on 21 November 2014 (dataset adsl.sas7bdat 19 February 2015). Subjects withdrew consent subsequent to the investigator's decision to withdraw from the study.

Source Table 9-1 CSR 20120360

Medical Officer's comments-

Slightly more subjects discontinued the study drug due to the protocol-specified criteria to receive a kidney transplant in the etelcalcetide treatment group (4.4% vs. 1.5%) but the total % of subjects that discontinued the study was actually similar between treatment groups (15.6% for etelcalcetide and 14.3 % for cinacalcet). In general the subject disposition

was similar between treatment groups and this medical reviewer believes that the small differences were unlikely to significantly impact the study results.

Protocol Violations/Deviations

Table 22 Summary of Protocol Deviations in Study 20120360

	Cinacalcet (N = 343) n (%)	AMG 416 (N = 340) n (%)	Total (N = 683) n (%)
Number of subjects with at least 1 important protocol deviation	46 (13.4)	46 (13.5)	92 (13.5)
Entered study even though entry criteria were not satisfied			
History of MI, CA, or CABG	0 (0.0)	1 (0.3)	1 (0.1)
History of malignancy	1 (0.3)	1 (0.3)	2 (0.3)
No hemodialysis TIW for at least 3 months	0 (0.0)	3 (0.9)	3 (0.4)
Pregnant or breastfeeding	1 (0.3)	0 (0.0)	1 (0.1)
Prior cinacalcet use	0 (0.0)	1 (0.3)	1 (0.1)
Screening cCa criteria not met	0 (0.0)	1 (0.3)	1 (0.1)
Unstable medical condition	0 (0.0)	1 (0.3)	1 (0.1)
Missing data (other than TA or TC)			
Missing antibody sample	0 (0.0)	2 (0.6)	2 (0.3)
Other deviations			
Deviation from informed consent process	1 (0.3)	3 (0.9)	4 (0.6)
Other treatment adherence			
Missed more than 14 consecutive days of IP	15 (4.4)	14 (4.1)	29 (4.2)
Received an excluded concomitant treatment			
Received cinacalcet during study	3 (0.9)	5 (1.5)	8 (1.2)
Received the wrong treatment or incorrect dose			
IP not reduced	1 (0.3)	2 (0.6)	3 (0.4)
IP not withheld due to low calcium	2 (0.6)	2 (0.6)	4 (0.6)
Low cCa when resuming IP after suspension	2 (0.6)	3 (0.9)	5 (0.7)
Received compromised IP	7 (2.0)	5 (1.5)	12 (1.8)
Received incorrect IP assignment	11 (3.2)	10 (2.9)	21 (3.1)
Received incorrect IP dose	1 (0.3)	1 (0.3)	2 (0.3)
Received incorrect dose after restarting IP	5 (1.5)	0 (0.0)	5 (0.7)

CA = coronary angioplasty; CABG = coronary arterial bypass grafting; cCa = corrected calcium; IP = investigational product; MI = myocardial infarction; TA (important protocol deviation category) = received the wrong treatment or incorrect dose; TC (important protocol deviation category) = other treatment adherence; TIW = 3 times a week
Deviation categories are not mutually exclusive. Multiple deviations within the same category were counted once per subject.

Source Table 9-2 CSR 20120360

Medical Officer's comments-

In general the protocol violation subcategories were similar between treatment groups and were unlikely to affect the study results. Violations which might have affected efficacy and safety were:

1) the use of non study related cinacalcet during the study, but that occurred in only 0.9% of subjects in the cinacalcet group and 1.5% of subjects in the etelcalcetide group

2) missing 14 consecutive days of treatment with the investigational drug product which occurred in 4.4% of subjects in the cinacalcet group and 4.1% of subjects in the etelcalcetide group

3) received compromised investigational drug which occurred in 2.0% of subjects in the cinacalcet group and 1.5% of subjects in the etelcalcetide group

4) received incorrect drug assignment which occurred in 3.2% of subjects in the cinacalcet group and 2.9% of subjects in the etelcalcetide group but these occurred in small and similar proportions of subjects in both treatment arms.

Table 23 Table of Demographic Characteristics for Study 20120360 (Full Analyses Set)

	Cinacalcet (N = 343)	AMG 416 (N = 340)	Total (N = 683)
Sex - n (%)			
Male	192 (56.0)	192 (56.5)	384 (56.2)
Female	151 (44.0)	148 (43.5)	299 (43.8)
Ethnicity - n (%)			
Hispanic/Latino	41 (12.0)	38 (11.2)	79 (11.6)
Not Hispanic/Latino	302 (88.0)	302 (88.8)	604 (88.4)
Race - n (%)			
Asian	7 (2.0)	9 (2.6)	16 (2.3)
Black	52 (15.2)	54 (15.9)	106 (15.5)
Native Hawaiian or Other Pacific Islander	3 (0.9)	6 (1.8)	9 (1.3)
White	277 (80.8)	261 (76.8)	538 (78.8)
Other	4 (1.2)	10 (2.9)	14 (2.0)
Age (years)			
n	343	340	683
Mean	55.3	54.0	54.7
SD	14.4	13.8	14.1
Median	56.0	55.0	55.0
Q1, Q3	45.0, 66.0	44.0, 64.0	45.0, 65.0
Min, Max	21, 86	18, 87	18, 87
Age group - n (%)			
< 65 years	243 (70.8)	262 (77.1)	505 (73.9)
≥ 65 years	100 (29.2)	78 (22.9)	178 (26.1)
≥ 75 years	33 (9.6)	23 (6.8)	56 (8.2)

Q1 = first quartile; Q3 = third quartile; SD = standard deviation

Source Table 9-3 CSR 20120360

Study 20120360 enrolled primarily Caucasian subjects (77 to 81%), followed by blacks (15 to 16%) and very few patients from other races (0 to 3%) (Table 23). Most subjects were male 56%. The mean age was 54 to 55 years, with slightly less than 1/3 of the subjects being elderly (23-29% ≥65 years of age and 7-10% ≥75 years of age). Baseline laboratory values included mean serum iPTH values between 1092-1138 pg/mL somewhat higher than the mean values of 820 and 852 pg/mL used in the pivotal studies (Table 24). Mean corrected calcium between 9.6 and 9.7mg/dL and mean serum phosphorous of 5.8 mg/dL were similar to the mean values used in the pivotal trials (note the ULN for these assays were 72 pg/mL for iPTH, 10.6mg/dL for corrected calcium and 5.1mg/dL for serum phosphorous).

Medical Officer's comments-

In general, the studies were well randomized with baseline demographics similar between treatment groups.

Table 24 Summary of Baseline Disease Characteristics Study 20120360 (Full Analysis Set)

	Cinacalcet (N = 343)	AMG 416 (N = 340)	Total (N = 683)
Dialysis vintage – n (%)			
0 to ≤ 1 year	48 (14.0)	46 (13.5)	94 (13.8)
> 1 to ≤ 5 years	146 (42.6)	149 (43.8)	295 (43.2)
> 5 years	149 (43.4)	145 (42.6)	294 (43.0)
Baseline dialysate calcium (mEq/L) – n (%)			
< 3.0 mEq/L	189 (55.1)	191 (56.2)	380 (55.6)
≥ 3.0 mEq/L	154 (44.9)	149 (43.8)	303 (44.4)
PTH (pg/mL)			
n	343	340	683
Mean (SD)	1138.71 (706.77)	1092.12 (622.81)	1115.52 (666.22)
Median	929.80	899.73	915.70
Q1, Q3	694.05, 1327.30	684.88, 1265.63	693.15, 1308.55
Min, Max	323.1, 4840.3	298.0, 4380.3	298.0, 4840.3
Corrected calcium (mg/dL)			
n	343	340	683
Mean (SD)	9.58 (0.67)	9.67 (0.71)	9.62 (0.69)
Median	9.55	9.60	9.60
Q1, Q3	9.10, 10.00	9.20, 10.10	9.15, 10.05
Min, Max	8.1, 12.8	7.7, 12.3	7.7, 12.8
Phosphorus (mg/dL)			
n	341	337	678
Mean (SD)	5.82 (1.58)	5.81 (1.69)	5.81 (1.63)
Median	5.65	5.75	5.70
Q1, Q3	4.75, 6.70	4.75, 6.90	4.75, 6.80
Min, Max	2.2, 11.5	1.8, 12.7	1.8, 12.7
Corrected calcium phosphorus product (mg^2/dL^2)			
n	341	337	678
Mean (SD)	55.65 (15.37)	56.36 (17.15)	56.00 (16.27)
Median	54.18	54.42	54.36
Q1, Q3	44.44, 64.86	46.01, 66.66	44.92, 65.69
Min, Max	22.1, 110.4	15.9, 113.5	15.9, 113.5

PTH = parathyroid hormone; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

Source Table 9-4 CSR 20120360

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Median adherence to use of investigational drug product was excellent at 97% for cinacalcet and 100% for etelcalcetide between weeks 1 and 26 (see Table 14-3.2 in CSR 20120360).

Table 25 Use of Concomitant Medications of Interest at Baseline and during Study 20120360

	Cinacalcet (N = 341) n (%)	AMG 416 (N = 338) n (%)
Number of subjects reporting use of concomitant medications of interest at baseline	316 (92.7)	310 (91.7)
Nutritional vitamin D	69 (20.2)	73 (21.6)
Vitamin D sterol	205 (60.1)	199 (58.9)
Calcium supplements	160 (46.9)	160 (47.3)
Phosphate binder	164 (48.1)	170 (50.3)
Calcium-containing phosphate binder or calcium supplement	167 (49.0)	172 (50.9)
Number of subjects reporting use of concomitant medications of interest during the study	335 (98.2)	331 (97.9)
Nutritional vitamin D	82 (24.0)	88 (26.0)
Vitamin D sterol	260 (76.2)	262 (77.5)
Calcium supplements	230 (67.4)	231 (68.3)
Phosphate binder	171 (50.1)	179 (53.0)
Calcium-containing phosphate binder or calcium supplement	235 (68.9)	239 (70.7)

Source Table 12-13 CSR 20120360

Medical Officer's comments-

Baseline use of concomitant medications of interest was similar between treatment groups but somewhat different from the pivotal trials, which is one reason why in general it is not possible to make direct efficacy and safety comparisons across different trials. For example the pivotal trials typically had only 3 to 8% baseline use of calcium supplements compared to the 47% baseline use in this trial, while the baseline phosphate binder use was 82 to 84% in the pivotal trials and only 48 to 50% in this trial.

There was an increase in the use of vitamin D analogs during the study of about 16 to 19%, which was similar to the 20% increase seen in the pivotal trials. There was an increase in the use of calcium supplements during the study of about 20 to 21%, which was half of the 40% increase seen in the pivotal trials, but there was also an about 20% higher use of calcium-containing phosphate binders in this study which would make up for the difference. While increased use of vitamin D analogs and calcium supplements in this study might contribute to the lower iPTH levels observed with treatment and thereby affect the efficacy

results, the study was well randomized with similar changes in concomitant medications of interest in both treatment arms which should cancel each other out.

Dose Titration

Dose increases could occur at 4 week intervals during weeks 5, 9, 13 and 17. After week 17 doses were supposed to stay constant until week 27 unless there was a reason for dose suspension or dose reduction due to low serum calcium < 7.5mg/dL, symptomatic hypocalcemia, or two consecutive low iPTH < 100pg/mL, which were still being measured every two weeks. The proportion of Responders and Non-responders at each dose level for each study treatment at the end of the study was calculated by the applicant and is listed in the tables below.

Table 160630-5.2.1. Proportion of Subjects Receiving Each Dose Level of AMG 416 at the End of Study by Responders and Non-responders (Study 20120360) (Safety Analysis Set)

Visit Dose Level	AMG 416 (N = 338) n (%)
Responders	232
Week 26 - N1	210
0.0 mg	37 (17.6)
2.5 mg	26 (12.4)
5.0 mg	45 (21.4)
7.5 mg	13 (6.2)
10.0 mg	41 (19.5)
12.5 mg	10 (4.8)
15.0 mg	30 (14.3)
Missed dose	8 (3.8)
Non-responders	106
Week 26 - N1	62
0.0 mg	3 (4.8)
2.5 mg	11 (17.7)
5.0 mg	14 (22.6)
7.5 mg	2 (3.2)
10.0 mg	16 (25.8)
12.5 mg	0 (0.0)
15.0 mg	14 (22.6)
Missed dose	2 (3.2)

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Safety analysis set: subjects who received at least one dose of IP. Percentages are based on N1.
Responders are those who were in the safety analysis set and had IPTH >30% reduction from baseline during the EAP. Non-responders are those who were in the safety analysis set and didn't have IPTH >30% reduction from baseline during the EAP.

Table 160630-5.2.2. Proportion of Subjects Dispensed with Each Dose Level of Cinacalcet at the End of Study by Responders and Non-responders (Study 20120360) (Safety Analysis Set)

Duration Dose Level	Cinacalcet (N = 341) n (%)
Responders	198
Week 25 to Week 26 - N1	184
30 mg	67 (36.4)
60 mg	43 (23.4)
90 mg	28 (15.2)
120 mg	14 (7.6)
180 mg	10 (5.4)
0 or Missing	22 (12.0)
Non-responders	143
Week 25 to Week 26 - N1	96
30 mg	28 (29.2)
60 mg	18 (18.8)
90 mg	16 (16.7)
120 mg	9 (9.4)
180 mg	16 (16.7)
0 or Missing	9 (9.4)

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Safety analysis set: subjects who received at least one dose of IP. Percentages are based on N1.
On treatment approach: data collected on or prior to the last non-missing dose of IP and at follow up are summarized by visit.
Responders are those who were in the safety analysis set and had IPTH >30% reduction from baseline during the EAP. Non-responders are those who were in the safety analysis set and didn't have IPTH >30% reduction from baseline during the EAP.

Source Response to 30 Jun 2016 Info Request

These data show that most responders were adequately treated with lower doses ≤5mg (51%) in the etelcalcetide treatment group and 30 to 60mg (60%) in the cinacalcet treatment group. In fact the applicant calculated that most responders were titrated to stable doses by 9 to 10 weeks, around the time of the second possible titration. However, it appears that more responders in the etelcalcetide group were titrated to the highest dose of 15mg (14%) compared to the highest dose of cinacalcet of 180mg (5%). As expected the nonresponders in both groups were titrated to higher doses than the responders. But here again it seems that more subjects in the etelcalcetide group were titrated to the highest dose of 15mg (23%) compared to the highest dose of cinacalcet of 180mg (17%). These findings raise the concern that titration in the cinacalcet group may not have been optimized to the maximal effective dose during the limited 17 week titration period, which would not permit a fair superiority comparison between treatments. To address this concern the applicant was asked to recalculate how many subjects would have been recommended to have a dose increase at the next hypothetical dose increase visit at week 21 in case a longer titration period had been included in the study protocol. The applicant performed an analysis based on the IXRS dose titration algorithm which determined that there were 29 cinacalcet nonresponders who would have been eligible for a dose increase compared to only 7 etelcalcetide nonresponders if dose titration had been permitted during week 21 (see Response to 13 July 2016 Information Request). This difference of 29-7=22 subjects is substantial as the efficacy data for the difference in 50% and 30% responder rates between the two treatment groups (see Table 27) corresponded to a difference in only 40 and 34 subjects, respectively, so a difference of 22 subjects or over half of the number of responders would likely have affected the statistical significance of the superiority analysis. According to the applicants own analysis conversion of 10 or more cinacalcet nonresponders to responders would have negated the statistical significance of the endpoint. That said it is not known how many of the 29 cinacalcet and 7 etelcalcetide nonresponders would have become responders with an additional dose increase. For example the applicant states that 15 of the 29 cinacalcet nonresponders had iPTH levels above baseline at week 21; so it seems unlikely that an additional single dose increase would have resulted in an iPTH reduction of >50% or >30% with respect to baseline. The applicant estimated that mean incremental cinacalcet dose increases of 30 to 60mg, 60 to 90mg, 90 to 120mg or 120 to 180mg had resulted in only modest < 10% additional reduction in iPTH in other nonresponders. However, such considerations are at most a best guess for what could have happened following an additional dose titration and it is the medical reviewer's assessment that they do not sway the concern that efficacy may have been at least partially overestimated in the etelcalcetide group in this study because of suboptimal dose titration in the cinacalcet group. To better understand the reason for the suboptimal cinacalcet dose titration, the applicant was asked to capture the reasons for dose changes during the titration phase by the IXRS dose titration algorithm. The analysis did not identify a clear reason for the delayed titration in the cinacalcet group although it determined that difference was not due to hypocalcemia or other AEs which in general were slightly more common in the etelcalcetide group. Had the reason for the failure to adequately titrate the cinacalcet group been due to a

significantly higher rate in AEs for nausea and vomiting for example the better tolerability with etelcalcetide would be a reasonable reason to support a superiority claim. The analysis did confirm that dose increases were much more common in the later weeks of the trial in the cinacalcet group suggesting that a longer titration period may have been necessary to ensure optimal dose titration in this group:

Titration Visit	Number of Patients Requiring a Dose Increase		
	Cinacalcet	AMG 416	Difference
Week 5	140	94	46
Week 9	96	30	66
Week 13	68	17	51
Week 17	63	20	43
Source SDN 018 (8/15/16) Response to 25 July 2016 IR			

and consistent with the applicant's findings that more subjects in the cinacalcet group (29 vs. 7) would have been recommended to have a dose increase at the next hypothetical dose increase visit at week 21 if a longer titration period had been included in the study protocol.

In conclusion, while the efficacy results in Tables 26 and 27 below will show greater efficacy in the etelcalcetide group compared to the cinacalcet group, given the concern raised in this discussion about the potential for inadequate dose titration primarily in the cinacalcet group during the 17 week titration phase it is recommended that another study be performed to confirm the superiority of treatment with etelcalcetide compared to cinacalcet (b) (4) This second study should include a longer titration phase and attempt to better capture prospectively treatment decisions for maintaining dose and dose suspension during the dose titration phase.

Efficacy Results – Primary Endpoint

The estimated stratified treatment difference in responders with a > 30% reduction from baseline in serum PTH during the EAP (cinacalcet - etelcalcetide) was -10.48% (95% CI: -17.45%, -3.51%). Therefore the primary endpoint, the upper bound of the 95%CI of the treatment difference which was -3.51% was well below the noninferiority margin of +12%. Similar results were also seen from the following sensitivity analyses:

- the Completer Analysis Set (mean -14%, 95% CI: -21, -7; sponsor's CSR Table 14-4.2)
- the Per Protocol Analysis Set (mean -12%, 95% CI: -20, -5; sponsor's CSR Table 14-4.4)
- the Last Value Carried Forward (LVCF) Set using the mean of the last 2 post study day 1 PTH values for imputation (mean -13%, 95% CI: -20, -6; sponsor's CSR Table 14-4.3).

Table 26 Primary Endpoint for the Active Controlled Study 20120360

	Cinacalcet (N = 343)	AMG 416 (N = 340)	Treatment Difference
Subject Status			
Number of subjects	310	298	
Yes - n (%) [a]	198 (63.9)	232 (77.9)	
Screening iPTH < 900 pg/mL	112 (36.1)	120 (40.3)	
Screening iPTH >= 900 pg/mL	86 (27.7)	112 (37.6)	
North America	54 (17.4)	67 (22.5)	
Non-North America	144 (46.5)	165 (55.4)	
No - n (%) [a]	112 (36.1)	66 (22.1)	
Screening iPTH < 900 pg/mL	46 (14.8)	23 (7.7)	
Screening iPTH >= 900 pg/mL	66 (21.3)	43 (14.4)	
North America	43 (13.9)	20 (6.7)	
Non-North America	69 (22.3)	46 (15.4)	
Stratified[b] treatment difference of proportion[c] for subjects who achieve iPTH reduction > 30% during EAP (%)			-10.48
95% CI(%)[d]			(-17.45, -3.51)

Full analysis set: all randomized subjects
n=Number of subjects with observed data before imputation. CI=Confidence Interval.
[a]Subject has iPTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).
[b]Stratification factors based on mean screening iPTH level (<900 pg/mL, ≥ 900 pg/mL), and region (North America and Non-North America) from IXRS
[c]Mantel-Haenszel (M-H) estimator of the proportion difference of cinacalcet minus AMG 416
[d]If the upper bound of 95% CI is smaller than 12% (the non-inferiority margin), then AMG 416 is considered non-inferior to cinacalcet.
Source Table 14-4.1. CSR 20120360

Data Quality and Integrity – Reviewers' Assessment

Medical Officer's comments- This medical reviewer agrees with OSI's assessment of the clinical inspection sites, see Section 4.1.

The applicant's monitoring for data quality and integrity was acceptable.

Efficacy Results – Secondary and other relevant endpoints

The first two key secondary endpoints of > 50% and > 30% reduction from baseline iPTH to EAP between treatment groups support the greater efficacy of etelcalcetide compared to cinacalcet with statistically significant p-values of 0.001 and 0.004, respectively using non responder imputation to control for missing data (**Table 27**).

Table 27 Proportion of Subjects with > 50% or > 30% Reduction in iPTH from Baseline to EAP (Non responder Imputation, Full Analysis Set, Study 20120360)

	> 50% Reduction			> 30% Reduction		
	Cinacalcet (N = 343)	AMG 416 (N = 340)	Treatment Difference	Cinacalcet (N = 343)	AMG 416 (N = 340)	Treatment Difference
Number of subjects[a]	343	340		343	340	
Subjects with respective reduction from baseline in PTH during EAP – n (%)[b]	138 (40.2)	178 (52.4)		198 (57.7)	232 (68.2)	
CMH-stratified[c] odds ratio (AMG 416:Cinacalcet)			1.65			1.59
95% CI			1.21, 2.23			1.16, 2.17
p-valued[c]			0.001			0.004

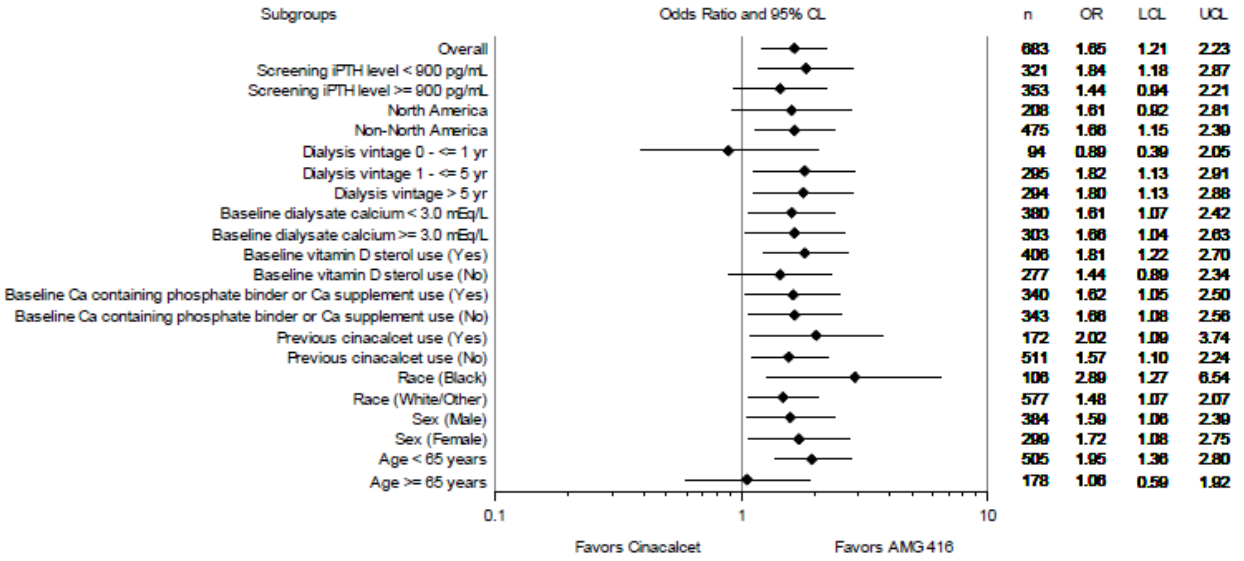
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EAP = efficacy assessment phase;
PTH = parathyroid hormone
n = number of subjects with observed data after nonresponder imputation
[a] Number of subjects after nonresponder imputation
[b] Subject had PTH reduction > 50% or > 30% (as applicable) during the EAP (weeks 20 to 27, inclusive).
[c] Stratification factors were based on mean screening PTH concentration and region.
[d] CMH test

Source CSR 20120360 Table 10-2

Excluding data from subjects with an increase in active vitamin D analog dose or serum calcium supplements did lower the effect size slightly but did not affect the difference between etelcalcetide vs. cinacalcet groups (e.g. 40% vs. 27% for >50% reduction and 55% vs. 46% for >30% reduction, See Response to 13 July 2016 Information Request).

No significant interactions were seen in subgroups based on screening iPTH < 900 vs. ≥ 900pg/mL, region, dialysis vintage, baseline dialysate calcium, baseline vitamin analog use, baseline calcium phosphate binder or calcium supplement use, previous cinacalcet use, race, gender or age < 65 vs. ≥65. The point estimate for each of these subgoups favored treatment with etelcalcetide except for subjects with dialysis vintage of < 1yr (**Figure 12**). Similar results were seen in the proportion of subjects with > 30% reduction in iPTH from baseline to EAP (data not shown).

Figure 12 Treatment Difference of Subjects with >50% Reduction in iPTH from Baseline to EAP by Subgroup (Nonresponder Imputation, Full Analysis Set, Study 20120360).

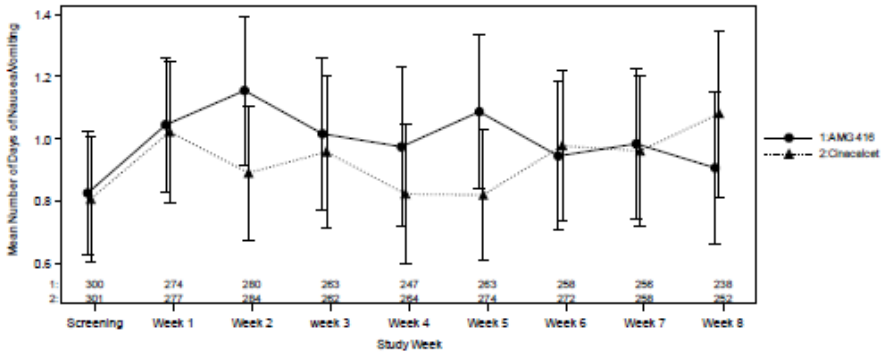


Full analysis set: all randomized subjects
CMH-stratified odds ratios and 95% confidence intervals are presented.

Source CSR 20120360 Fig. 14-4.1.

The third key secondary endpoint tested using a hierarchical approach was the mean number of days of vomiting or nausea during the first 8 weeks of treatment. Similar results were seen with a mean slightly in favor of etelcalcetide (mean=1.2, 95%CI: 0.89, 1.49, p-value=0.27, see CSR Table 10-3).

Figure 13 Mean (95% CI) Number of days of Nausea or Vomiting per Week for the First 8 Weeks of Treatment by Treatment Group (Full Analysis Set)



For responses < 7 days in a week, data from that week did not contribute to the analysis.
Vertical lines represent the 95% confidence interval around the mean.

Source CSR 20120360 Fig. 10-2

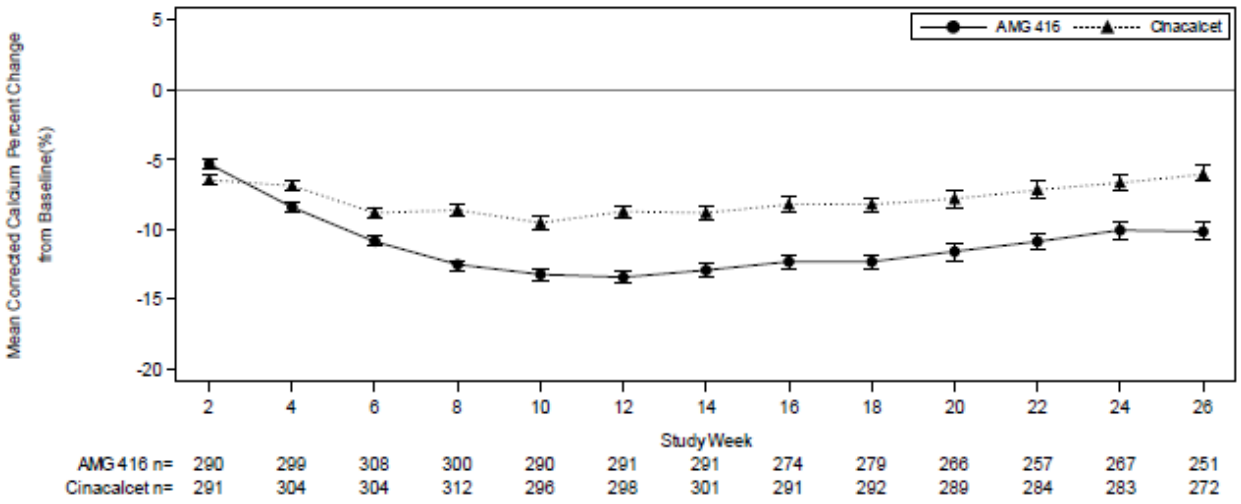
Given that the 3rd key secondary endpoint was not statistically significant the other secondary endpoints were not formally tested for statistical significance. Nevertheless, the 6th and 7th secondary endpoints that looked at "severity of nausea during the first 8 wks" and "episodes of vomiting during the first 8 weeks" also showed only minimal improvements in the point estimates in favor of etelcalcetide compared to cinacalcet with p-values of 0.71 and 0.26, respectively.

Medical Officer's comments-

The applicant had hypothesized that part of the nausea and vomiting associated with the use of cinacalcet may be due to direct gastrointestinal (GI) irritation from the oral medication and that etelcalcetide which was given intravenously (IV) might thereby result in fewer GI symptoms. However, the data shows that there was minimal benefit with regards to symptoms of nausea and vomiting with the IV formulation of etelcalcetide. Whether this occurred because most of the symptoms of nausea and vomiting seen with the use of these calcimimetics are related to other physiologic actions such as hypocalcemia associated with these medications rather than local toxicity associated with the route of administration is unknown. It is possible that the greater efficacy seen with etelcalcetide (Table 27) and the greater risk of hypocalcemia (Figure 14) may have counterbalanced and canceled out any benefit from not giving a potentially irritating oral formulation.

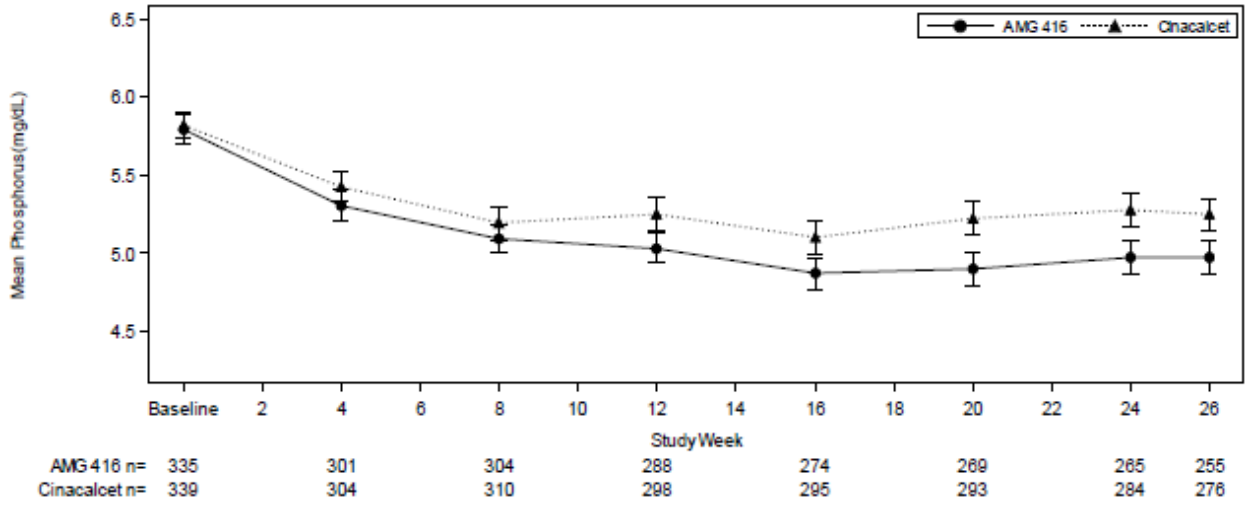
The other two key secondary endpoints looked at serum calcium (4th) and serum phosphorous (5th) over time. Given that the 3rd key secondary endpoint was not statistically significant, based on the hierarchical testing procedure these two endpoints were not formally tested for statistical significance. Treatment with etelcalcetide resulted in lower mean serum calcium (**Figure 14**) and mean serum phosphorous (**Figure 15**) levels over time compared to treatment with cinacalcet consistent with the greater iPTH lowering seen with etelcalcetide treatment.

Figure 14 Mean (SE) % Change in Corrected Serum Calcium over Time by Study Treatment (Safety Analyses Set, Study 20120360)



Source CSR 20120360 Fig. 10-3, data collected on or before last non missing dose summarized by study visit

Figure 15 Mean (SE) Phosphorous Concentration over Time by Study Treatment (Safety Analyses Set, Study 20120360)



Source CSR 20120360 Fig. 10-4, data collected on or before last non missing dose summarized by study visit

Medical Officer's comments-

While the lower serum calcium and phosphorous levels seen with treatment with etelcalcetide with increasing duration of treatment suggest greater efficacy, there is a significant drop out of subjects during the 26 week treatment period which is greater in the etelcalcetide treatment group in both of these figures which could affect the interpretability of these results.

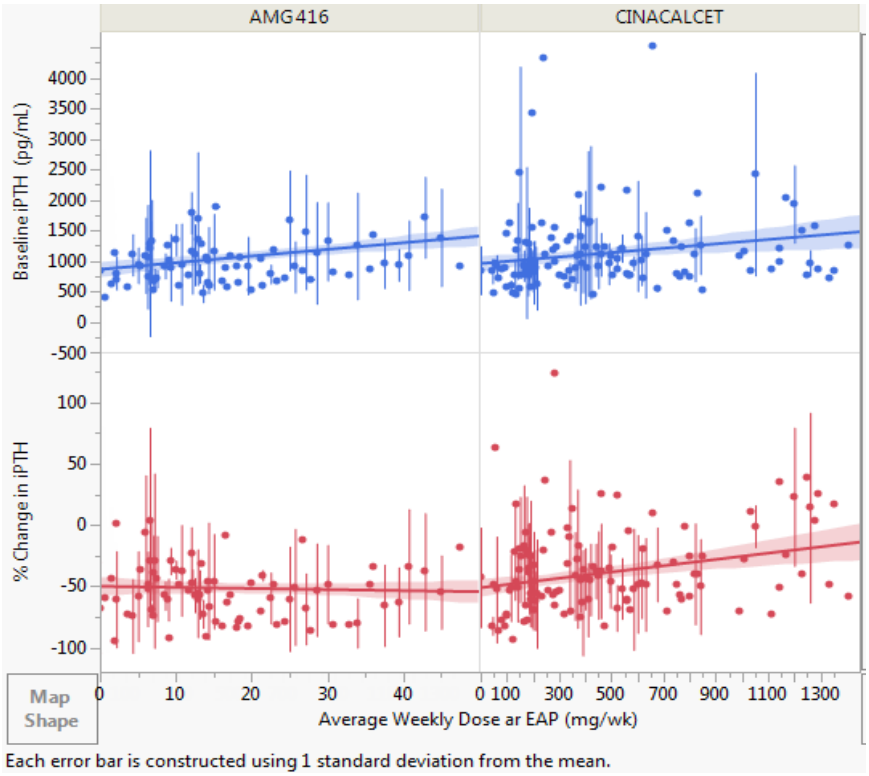
Dose/Dose Response

Similar to the results in the pivotal studies, 20120229 & 20120230, the patients with higher baseline serum iPTH values in study 20120360 were also titrated to slightly higher doses during the EAP (see the positive slope in the blue lines in the top of **Figure 16**). There was also no correlation with the % reduction in mean iPTH from baseline to EAP and the final weekly dose during the EAP for etelcalcetide (see the flat red line at the bottom of **Figure 16**, left panel). That said there appeared to be a slight positive slope in the red line at bottom right panel suggesting less efficacy in the limited number of subjects treated to higher doses with cinacalcet.

Medical Officer's comments-

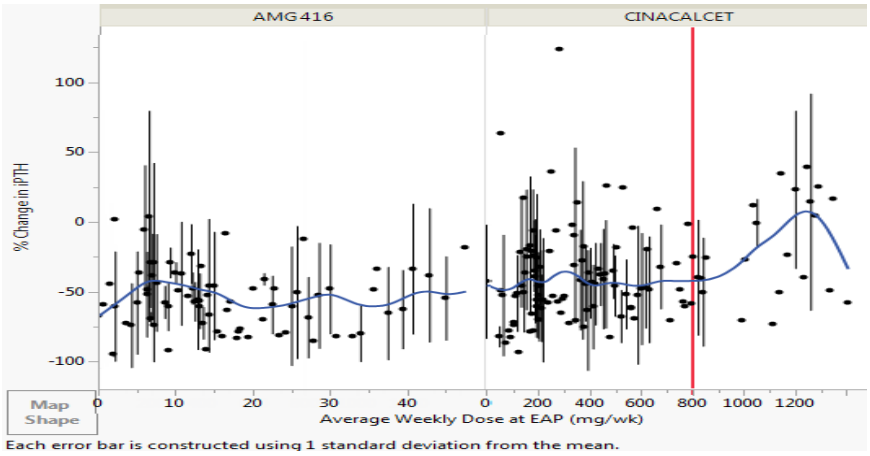
Even though this study enrolled patients with higher baseline iPTH levels and likely more severe bone disease the efficacy seen with etelcalcetide was similar to what was seen in the pivotal trials with a straight line in the bottom left panel of Figure 16, corresponding to about a -50% change in iPTH across all dose ranges. In contrast, it appears that there may be less efficacy (i.e. less decrease in iPTH) with cinacalcet in patients titrated to higher doses. A nonlinear plot of these data (Figure 17) shows that the loss in efficacy for cinacalcet occurs at doses of 800mg/wk (see red vertical line in plot) and greater.

Figure 16 Linear Plot of Dose Response at EAP in Study 20120360



JMP analysis of PCHG and BASE from PARAM=Mean iPTH (pg/mL) During EAP (Observed), and PARAMCD=AVGDSEAP, PARAM=AVG WEEKLY DOSE at EAP (MG/WK) from ADEX dataset

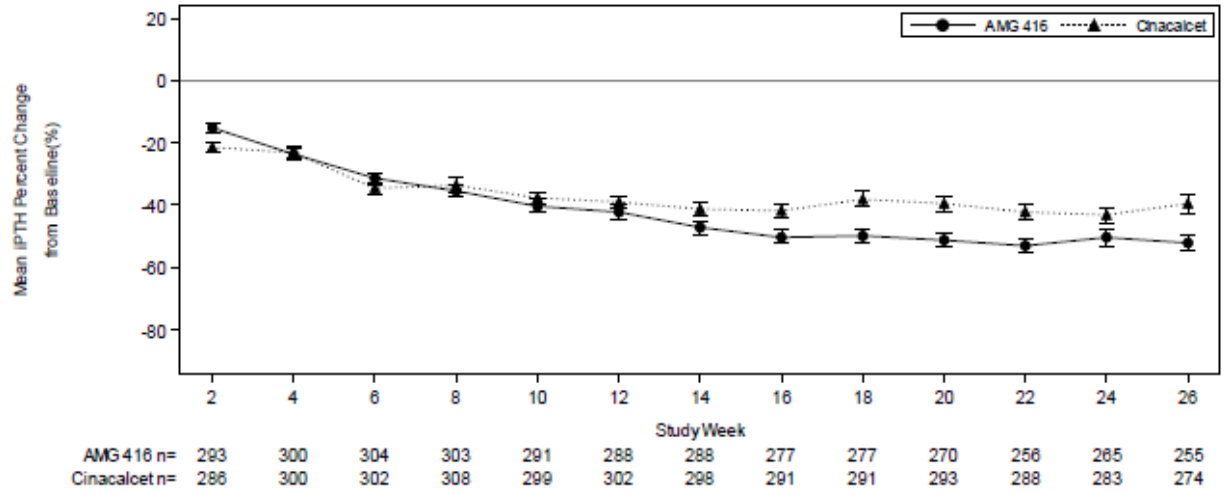
Figure 17 Nonlinear Plot of Dose Response at EAP in Study 20120360



Durability of Response

Efficacy with respect to mean % decrease in iPTH is seen by week 2. Greater efficacy in the etelcalcetide treatment group compared to the cinacalcet group first becomes apparent around week 14 and continues through the end of the study at week 26.

Figure 18 Mean (SE) % Change from Baseline in iPTH over Time by Treatment Group Study 20120360 (Safety Analyses Set)



iPTH = parathyroid hormone

On-treatment approach: data collected on or before the last nonmissing dose of investigational product were summarized by visit.

Source Fig. 10-1 CSR 20120360

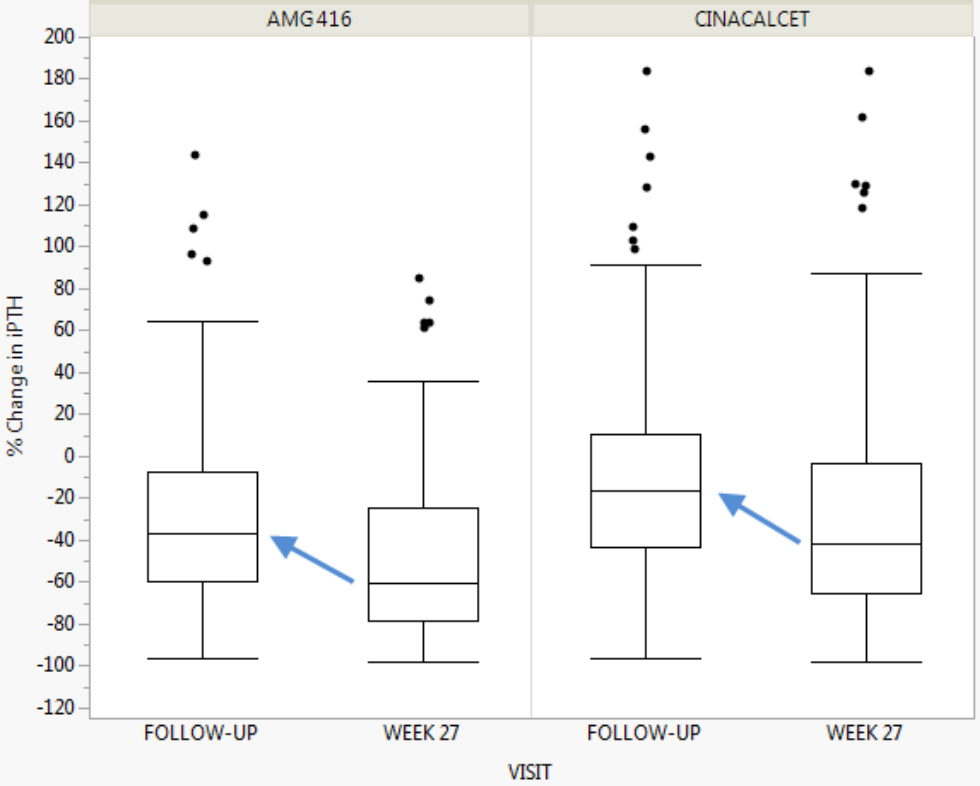
Medical Officer's comments-

The dropout rate is slightly higher for the etelcalcetide group starting with the visit on week 8 and continuing through the rest of the study. It is possible that if subjects with less efficacy dropped out preferentially in the etelcalcetide treatment group that this might have contributed to the apparent difference in efficacy seen with longer duration of treatment. Therefore, selective loss of subjects with lower efficacy from the etelcalcetide group could potentially negate the interpretation of greater efficacy in the etelcalcetide treatment represented by the separation between the two curves at week 14 and later.

Persistence of Effect

Patients were scheduled for a follow up visit off drug medication 30 days after the week 27 visit, but the sponsor did not include the data in Figure 18. This medical officer analyzed the mean % change in iPTH at the "week 27" visit and the "follow up" visits after study day 180 to determine if there was persistence of activity after the study drug was discontinued. Efficacy in the etelcalcetide treatment group at the week 27 visit went from a median value of -60% to -37%, for a relative decrease of 38% similar to what had been seen in the pivotal trials. Efficacy in the cinacalcet treatment group at the week 27 visit went from a median value of -42% to -16%, for a relative decrease in efficacy of 62%. These data demonstrate persistence of limited efficacy for several weeks after discontinuation of the both calcimimetic products, although the efficacy of cinacalcet appears to drop off more rapidly with time.

Figure 19 % Change in iPTH after Dose Discontinuation from Week 27 to the Follow-Up Visit



JMP analysis Study 20120360 ADLB dataset, PARAMCD=PTHIC, VISIT=FOLLOW-UP or VISIT=WEEK 27, for FOLLOW-UP visits ADY> 180, Plot of PCHG vs. VISIT

Additional Analyses Conducted on the Individual Trial

Exploratory Endpoints-

Bone Biomarkers-
Mean changes in BSAP and CTX concentrations from baseline to week 27 were characterized as exploratory endpoints in this study. No formal testing was performed on these endpoints. Treatment with etelcalcetide was associated with a greater decrease in BSAP, and CTX, from baseline to week 27 compared to treatment with cinacalcet consistent with the greater efficacy seen with respect to iPTH lowering (Table 27).

Table 28 % Change in Bone Biomarkers FGF-23, BSAP and CTX at Weeks 12 & 27 (Full Analysis Set, Study 20120360)

	Cinacalcet (N = 343)	AMG 416 (N = 340)
Percent change from baseline to week 12 (%) in BSAP		
n	298	284
Mean	8.54	10.32
Percent change from baseline to week 27 (%) in BSAP		
n	280	270
Mean	-2.55	-18.17
Percent change from baseline to week 12 (%) in CTX		
n	285	274
Mean	-13.57	-22.13
Percent change from baseline to week 27 (%) in CTX		
n	268	259
Mean	-10.97	-31.55

Source CSR 20120360 Table 14-4.29, Table 14-4.30, and Table 14-4.31

Medical Officer's comments-

BSAP, bone specific alkaline phosphatase, is a glycoprotein synthesized by osteoblasts which reflects bone biosynthetic activity. BSAP initially increases at week 12 followed by a decrease in activity at week 27.

CTX, the carboxy-terminal telopeptide, is a marker of bone resorption and turnover. CTX decreases both at week 12 and even further at week 27.

Abnormally high elevated levels of PTH in dialysis patients trigger increased bone turnover resulting in abnormal bone structure and an increased rate of fracture seen with renal osteodystrophy. The initial increase in BSAP and decrease in CTX seen at week 12 may represent a relative net increase in bone formation. The subsequent decrease in both BSAP

and CTX at week 27 may represent a net decrease in the abnormally high bone turnover seen with renal osteodystrophy. The changes in the etelcalcetide group in Study 201202360 are similar to what was seen in the earlier pivotal trials, 20120229 & 20120230, and appear to be substantially greater than seen with cinacalcet. Whether these changes in bone biomarkers seen with etelcalcetide treatment actually represent improvement in bone architecture and bone strength is unknown. Bone biopsy data, although still a surrogate endpoint could potentially be helpful in elucidating the potential clinical benefit of treatment with etelcalcetide, but it was not performed in this study. The much greater changes in bone biomarkers seen with etelcalcetide compared to cinacalcet go along with the greater changes in iPTH and bring into question the possibility that some of the subjects with very low iPTH levels seen in the etelcalcetide treatment groups may be at greater risk of adynamic bone disease than expected with the use of cinacalcet.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. **Primary Endpoints**

Serum iPTH is a measure of secondary hyperparathyroidism which is a contributing factor in the development of renal osteodystrophy seen in subjects with CKD. That said iPTH is still a surrogate for the rate of bone turnover and change in bone structure seen in these patients. The current clinical program was designed to use iPTH as a clinical surrogate given the difficulty in enrolling enough hemodialysis patients for a study powered to look at repeat bone biopsy data or long term cardiovascular mortality. Serum iPTH has already been used in the approval of two other vitamin D analogs for the treatment of secondary hyperparathyroidism in dialysis patients and for the approval of the only other currently marketed calcimimetic, cinacalcet, for a similar indication. For a more detailed discussion of the use of iPTH as a surrogate see the longer discussion under Study Endpoints in section 6.1.1.

Baseline demographics, severity of secondary hyperparathyroidism, dialysis history and medical history were similar between treatment groups in the two pivotal trials as described in greater detail in section 6.1.2 (Table 6 through Table 9).

The primary efficacy endpoint in the two pivotal studies, 20120229 & 20129230, was a responder analysis looking at the proportion of subjects in the ITT population attaining a mean decrease of >30% in serum iPTH from pre-treatment baseline to the EAP, weeks 20 to 27. Subjects who discontinued from the study prior to the EAP or had no serum iPTH determinations in the EAP were considered non-responders. Results were statistically

significant, in both studies 74% vs. 8.3%, p<0.001 and 75% vs. 9.6%, p<0.001 as seen in Table 29.

Table 29 Responders with >30% Reduction in iPTH during the EAP in the ITT Population (Primary Endpoint) for Pivotal Studies 20120229 & 20120230

	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)
Achieved >30% reduction in iPTH during the EAP[a] - n (%)						
Yes	21 (8.3)	188 (74.0)	25 (9.6)	192 (75.3)	46 (8.9)	380 (74.7)
No	233 (91.7)	66 (26.0)	235 (90.4)	63 (24.7)	468 (91.1)	129 (25.3)
CMH-stratified[b] odds ratio (AMG 416: Placebo)		32.46		30.80		31.60
(95% CI)		(18.71, 56.31)		(18.18, 52.17)		(21.59, 46.25)
p-value[c]		< 0.001		< 0.001		< 0.001

This pool includes data from the two placebo-controlled studies 20120229 and 20120230.
Full analysis set: all randomized subjects in the pool. n=Number of subjects with observed data. CI=Confidence Interval.
[a]Subjects have iPTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).
[b]For individual studies, stratification factors are screening iPTH level, prior cinacalcet use, and region; for integrated studies, stratification factors are screening iPTH level, prior cinacalcet use, region, and study.
[c]Cochran-Mantel-Haenszel (CMH) test
Source Table 4.1 ISE

The treatment protocol permitted the use of active vitamin D analogs and calcium supplements both of which could have been increased during the study and which could have affected the study results by causing a decrease in serum iPTH levels as described in more detail under Concomitant Medications in section 6.1.2. An analysis by the FDA statistician excluding subjects who had increases in either the use of the active vitamin D analogs or calcium supplements was performed to account for this. It showed that while excluding data from subjects with an increase in vitamin D dose or serum calcium supplements during the pivotal studies did lower the effect size it did not affect the statistical significance of the study results for the primary endpoint as the % of responders with > 30% reduction in iPTH was still much higher in the etelcalcetide treated group compared to placebo (64.3% vs. 8.1%-study 20120229, and 61.4% vs. 8.6%-study 20120230, data calculated by FDA Statistician).

7.1.2. Secondary and Other Endpoints

Secondary efficacy endpoints were prespecified using a hierarchical testing approach in the following sequence:

1. proportion of subjects with mean predialysis PTH ≤ 300 pg/mL during the EAP
2. % change from baseline to EAP in iPTH
3. % change from baseline to EAP in cCa
4. % change from baseline to EAP in cCa x P
5. % change from baseline to EAP in phosphorus

All five secondary endpoints were statistically significant.

Table 30 Proportion of Subjects Achieving Mean iPTH ≤300pg/mL (1st Secondary Endpoint) during the EAP (Studies 20120229 & 20120230, and 6-month Pooled Data, FAS)

	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)
Subjects with ≤ 300 pg/mL in PTH during the EAP[a] – n (%)	13 (5.1)	126 (49.6)	12 (4.6)	136 (53.3)	25 (4.9)	262 (51.5)
CMH-stratified[b] odds ratio (AMG 416: Placebo)		22.08		33.92		27.02
(95% CI)		(11.47, 42.48)		(16.35, 70.37)		(16.62, 43.93)
p-value[c]		< 0.001		< 0.001		< 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel test; EAP = efficacy assessment phase; n = number of subjects with observed data; PTH = parathyroid hormone.
[a] Subjects have PTH reduction > 30% (yes) or ≤ 30 % (no) during the EAP (study visits during week 20 to week 27, inclusive).
[b] For individual studies, stratification factors are screening PTH level, prior cinacalcet use, and region; for integrated studies, stratification factors are screening PTH level, prior cinacalcet use, region, and study.
[c] Cochran-Mantel-Haenszel (CMH) test
[d] Subjects have PTH ≤ 300 pg/mL (yes) or >300 pg/mL (no) during the EAP (study visits during week 20 to week 27, inclusive).
Source: ISE Table 4.1.

Table 31 % Change from Baseline in Mean iPTH, Corrected Calcium, Phosphorous, and Corrected Calcium Phosphorous Cross Product (2nd – 5th Secondary Endpoints, Studies 20120229 & 20120230, and 6-month Pooled Data, FAS)

		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)
PTH							
Baseline (pg/mL)	n	254	254	260	255	514	509
	Mean (SE)	819.74 (24.22)	848.70 (32.65)	851.67 (34.23)	845.03 (29.08)	835.89 (21.04)	846.86 (21.83)
EAP (pg/mL)	n	219	229	237	227	456	456
	Mean (SE)	897.39 (32.21)	383.57 (25.40)	960.28 (48.09)	363.35 (26.26)	930.07 (29.40)	373.51 (18.25)
% change from baseline	Mean (SE)	13.00 (2.81)	-55.11 (1.94)	13.72 (2.50)	-57.39 (1.91)	13.37 (1.87)	-56.25 (1.36)
Treatment difference – adjusted analysis[a]							
Estimate (SE), %			-71.11 (3.39)		-71.34 (3.15)		-71.30 (2.31)
(95% CI), %			(-77.77, -64.46)		(-77.53, -65.14)		(-75.84, -66.76)
p-value			< 0.001		< 0.001		< 0.001
cCa							
Baseline (mg/dL)	n	254	254	260	255	514	509
	Mean (SE)	9.61 (0.04)	9.65 (0.04)	9.70 (0.04)	9.63 (0.04)	9.65 (0.03)	9.64 (0.03)
EAP (mg/dL)	n	219	229	237	227	456	456
	Mean (SE)	9.72 (0.04)	8.92 (0.05)	9.71 (0.04)	8.93 (0.04)	9.71 (0.03)	8.93 (0.03)
% change from baseline	Mean (SE)	1.18 (0.29)	-7.29 (0.53)	0.58 (0.29)	-6.69 (0.55)	0.87 (0.20)	-7.00 (0.39)
Treatment difference – adjusted analysis[a]							
Estimate (SE), %			-8.38 (0.58)		-7.20 (0.60)		-7.77 (0.42)
(95% CI), %			(-9.52, -7.23)		(-8.38, -6.03)		(-8.60, -6.94)
p-value			< 0.001		< 0.001		< 0.001
Phosphorus							
Baseline (mg/dL)	n	250	250	257	251	507	501
	Mean (SE)	5.78 (0.10)	5.95 (0.10)	5.83 (0.09)	5.76 (0.10)	5.80 (0.07)	5.86 (0.07)
EAP (mg/dL)	n	218	229	237	227	455	456
	Mean (SE)	5.61 (0.10)	5.30 (0.11)	5.58 (0.08)	5.09 (0.11)	5.59 (0.06)	5.19 (0.08)
% change from baseline	Mean (SE)	-1.31 (1.42)	-7.71 (2.16)	-1.60 (1.42)	-9.63 (1.61)	-1.46 (1.00)	-8.66 (1.35)
Treatment difference – adjusted analysis[a]							
Estimate (SE), %			-7.45 (2.47)		-8.04 (2.09)		-7.59 (1.62)
(95% CI), %			(-12.31, -2.59)		(-12.15, -3.92)		(-10.77, -4.40)
p-value			0.003		< 0.001		< 0.001
cCa x P							
Baseline (mg^2/dL^2)	n	249	250	257	251	506	501
	Mean (SE)	55.54 (1.00)	57.37 (0.98)	56.37 (0.90)	55.30 (0.96)	55.96 (0.67)	56.34 (0.69)
EAP (mg^2/dL^2)	n	218	229	237	227	455	456
	Mean (SE)	54.54 (1.01)	47.39 (1.03)	54.11 (0.82)	45.40 (1.04)	54.32 (0.65)	46.40 (0.73)
% change from baseline	Mean (SE)	-0.19 (1.44)	-14.34 (2.06)	-1.06 (1.42)	-15.84 (1.57)	-0.64 (1.01)	-15.09 (1.30)
Treatment difference – adjusted analysis[a]							
Estimate (SE), %			-14.99 (2.41)		-14.58 (2.07)		-14.68 (1.59)
(95% CI), %			(-19.73, -10.25)		(-18.65, -10.51)		(-17.81, -11.56)
p-value			< 0.001		< 0.001		< 0.001

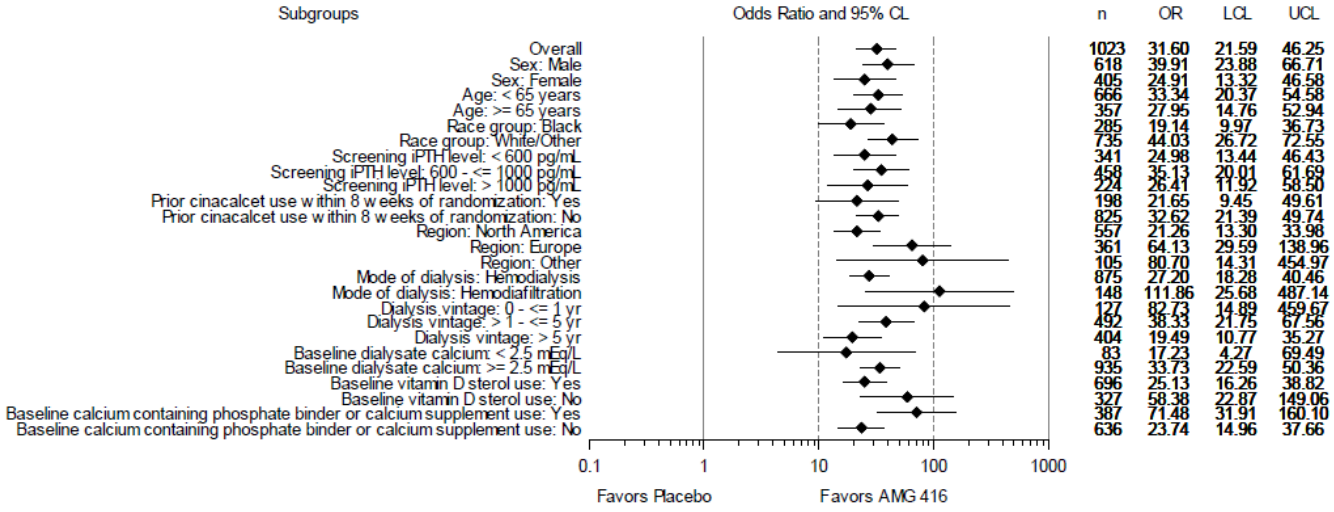
cCa = corrected calcium; cCa x P = calcium phosphorus product; EAP = efficacy assessment phase; PTH = intact parathyroid hormone.
[a] Mixed-effects model includes treatment and stratification factors as covariates. For individual study, stratification factors are screening PTH level, prior cinacalcet use, and region; for integrated studies, stratification factors are screening PTH level, prior cinacalcet use, region, and study.
Source: ISE Tables 4.5 to 4.8.

7.1.3. Subpopulations

There was no difference in efficacy, measured using the primary endpoint, irrespective of gender, age, race, prior use of cinacalcet or baseline screening iPTH. Efficacy in subjects from North America was lower than from Non-North American subjects

possibly due to a difference in baseline characteristics across regions as discussed in more detail in section 6.1.2, and efficacy does appear to trend better for subjects with the shortest duration of dialysis vintage who are likely to have less severe bone disease which may be why they are more responsive to PTH reduction. Point estimates also appear somewhat better for subjects with hemodiafiltration vs. hemodialysis, baseline vitamin D analog use=No, and baseline calcium supplement use=Yes, but for unclear reasons.

Figure 20 Treatment Difference in Primary Endpoint by Study Subgroup (Full Analysis Set)

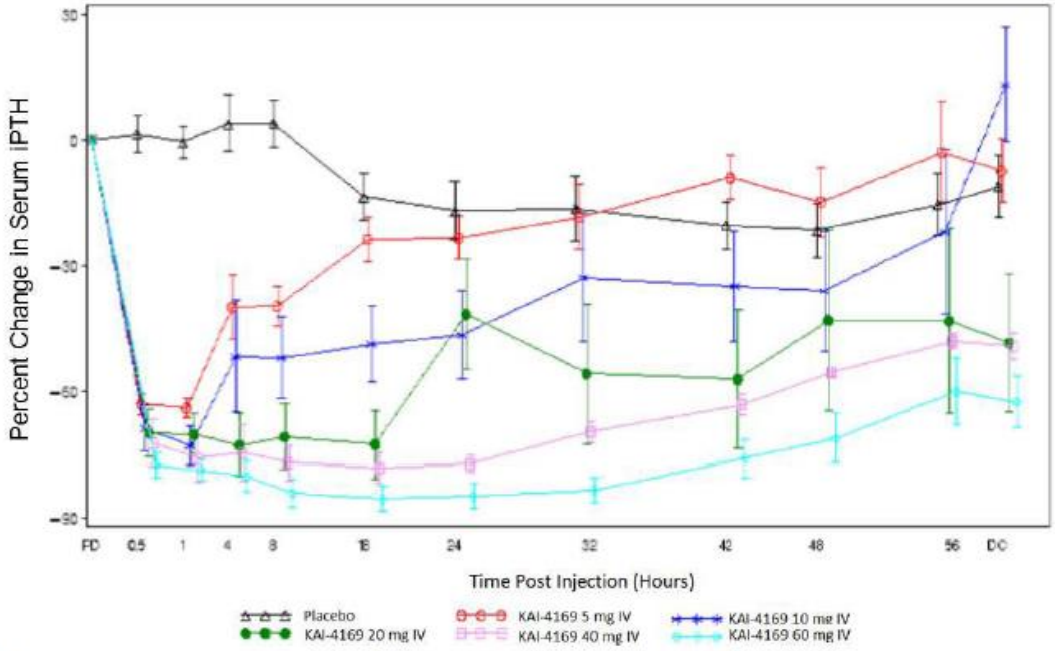


Source Fig. 2 Summary of Clinical Efficacy

7.1.4. Dose and Dose-Response

The phase 2 study 20130139 confirmed near maximal reduction in iPTH with the 5 and 10mg doses. Therefore the phase 3 studies were designed with a starting dose of 5 mg TIW and titration in 2.5- or 5-mg increments every 4 weeks to a maximum dose of 15 mg TIW.

Figure 21 Dose Response in iPTH in Hemodialysis Patients with Secondary Hyperparathyroidism (MITT Population) in Study 20130139



CKD = chronic kidney disease; DC = discharge; iPTH = intact parathyroid hormone; IV = intravenous; PD = predose; PTH = parathyroid hormone; SEM=standard error of the mean
Note: Treatments are offset for ease of interpretation

Source: Figure 14 of Study 20130139 CSR

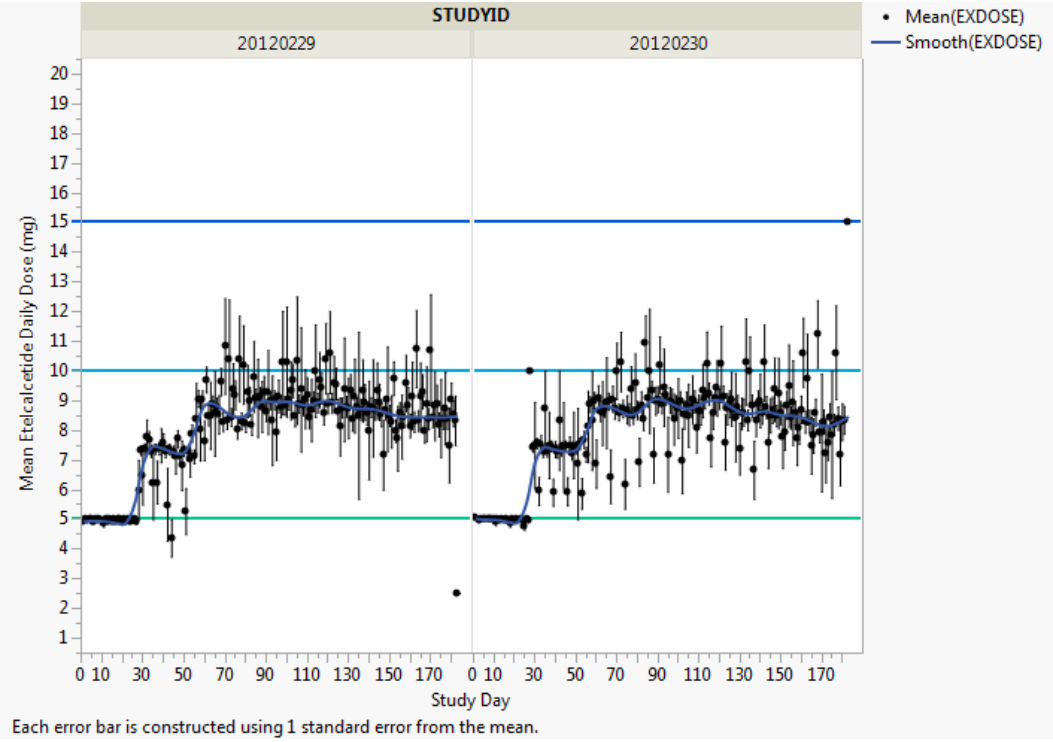
Table 32 Dose Response-Maximum Decrease in iPTH (MITT Population) in Study 20130139

	Placebo (pooled) N = 20	KAI-4169 IV				
		5 mg N = 4	10 mg N = 3	20 mg N = 4	40 mg N = 4	60 mg N = 4
N	20	4	3	4	4	4
Mean (SD) (pg/mL)	-36.087 (20.235)	-64.094 (4.547)	-73.060 (7.959)	-75.242 (13.867)	-83.498 (3.003)	-86.191 (6.154)
Median (Range) (pg/mL)	-35.769 (-91.76- 0.00)	-65.846 (-67.31- -57.3)	-71.033 (-81.84- -66.3)	-71.659 (-95.03- -62.6)	-82.351 (-87.89- -81.4)	-87.118 (-91.84- -78.6)

MITT = modified intent-to-treat, SD = standard deviation
Source Table 16 CSR Study 20130139

Mean iPTH levels ranged primarily between 5 and 10mg over the entire 6 month double-blind study period as shown in Figure 22. That said this medical reviewer estimated that a significant proportion of subjects treated with etelcalcetide were titrated to doses below 5mg for at least one visit during the course of the study, i.e. 60/254=24% and 68/255=27% in studies 20120229 and 20120230, respectively. Similarly, a significant proportion of subjects were titrated up to the highest proposed dose of 15mg: 54/254=21% and 58/255=23% for at least one visit in studies 20120229 and 20120230, respectively.

Figure 22 Mean Daily (SEM) Etelcalcetide Dose in Studies 20120229 & 20120230 by Study Day During Weeks 1 through 26



Source Data taken from a graphbuilder analysis with JMP software using the ISE ADEX dataset, with AVIST=WEEK1 through WEEK26, PARAMCD=DAILYDOS, EXTRT=AMG416

Medical Officer's comments-

The starting dose of 5mg is acceptable even though about a ¼ of patients ended up titrating to lower doses (see Table 34, for most frequent doses). The maximal dose of 15mg is acceptable as it was the most frequent dose in between 8-16% of patients.

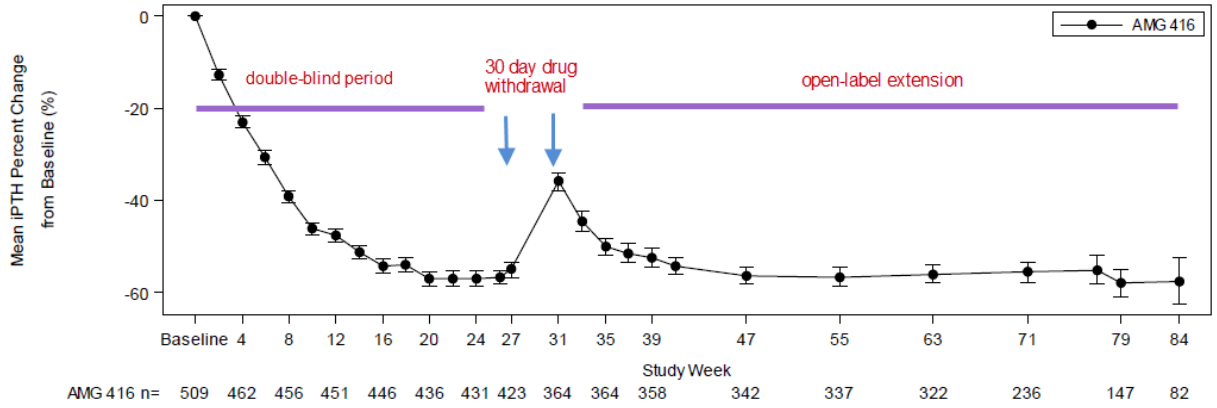
TIW dosing is supported by the long elimination half-life of 3.5 to 7.6 days in dialysis patients (see Section 4.5.2).

Simulation modeling performed by the sponsor from data from Study 119343 demonstrated minimal change in serum levels of etelcalcetide between weeks 3 and 4 supporting the 4 week dose titration schedule. There was however, continued slow gradual accumulation of drug levels out to 6 months so while the plasma accumulation ratio of etelcalcetide was 2- to 3-fold by week 4 it was slightly higher at 3- to 5-fold by month 6. Plasma accumulation with long term dosing may explain why there appears to be a slight downward trend in the mean etelcalcetide dose between 3 and 6 months (i.e. study days 90 to 180) in Figure 22.

Demographic characteristics (body weight, age, gender, race), liver function biomarkers (aspartate aminotransferase, alanine aminotransferase, serum albumin, total bilirubin, and alkaline phosphatase), disease characteristics (PTH, calcium, phosphorus, serum creatinine), and concomitant medications (vitamin D, phosphate binders and calcium supplements) had no discernible impact on etelcalcetide PK parameters (see sponsor's submission section 2.7.2). Therefore, no dose adjustments are necessary for these parameters in hemodialysis patients with secondary hyperparathyroidism.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Figure 23 Mean (SE) Decrease in iPTH from Three Phase 3 Parent Studies, 20120229, 20120230, 20120360 and the Open Label Extension 20120231 in Subjects on Etelcalcetide



This pool includes data from the phase 3 placebo-controlled parent studies and the subsequent OLE study 20120231 starting from the baseline of the parent study until the end or the pre-specified cutoff date of the OLE study, whichever is earlier, in subjects randomized to AMG 416 in the parent studies.

Full analysis set: all randomized subjects in the pool

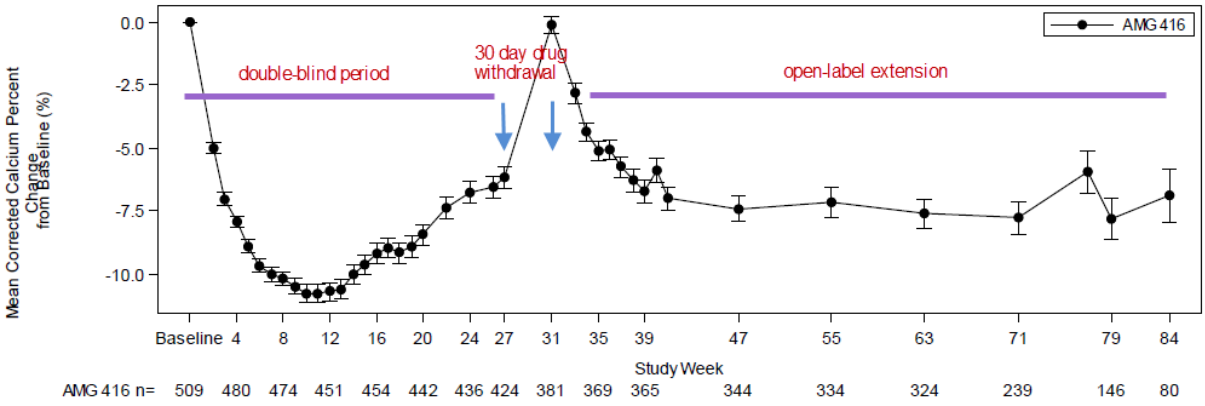
Weeks 27 to 31 were the 30-day drug-free period (the 30-day follow-up period of the phase 3 study before entry into the extension study).

Efficacy with respect to % decrease in iPTH is clearly evident by week 2 with decreases in mean levels of > 30% by week 6. The decrease in iPTH levels appears to level off by week 20 at about -57% and is fairly stable until the end of the double-blind period at week 27. At the end of the double-blind period drug was discontinued from week 27 to 30 to look at persistence in effect. During the 4 week drug withdrawal mean serum iPTH levels increased from about -57% to -35% for a relative difference of about 38%, showing that there is considerable persistence in efficacy for several weeks after etelcalcetide is discontinued. Etelcalcetide was restarted during the open-label extension from weeks 31 through 84. By 16 weeks after restarting etelcalcetide (i.e. week 47) mean iPTH had leveled off again at around -57% and stayed fairly consistently at that level for the duration of the study. While there was no evidence of tolerance to the study drug over the time period studied the number of subjects on treatment at week 71 is only about 50% of the original so it is possible that subjects with less efficacy may have selectively withdrawn from the study and that may have affected the observed results. Consistent with this the

applicant states “subjects who had clinically relevant reductions in PTH during the 6-month, placebo-controlled studies were more likely to enroll in the open-label extension study”, which would likely result in an overestimation of long term efficacy during the extension study.

In contrast to the effect on iPTH there does seem to be some tolerance with respect to the mean corrected calcium and phosphorous levels during continued treatment. Mean corrected serum calcium levels reach a nadir of -10% from baseline to about 12 weeks and then start to recover to a level of about -7% by week 27, the end of the double-blind period. During the 4 week withdrawal mean corrected serum calcium levels return to baseline. During the open-label extension mean corrected serum calcium levels decline again but only to about the -7% level seen at the end of the initial double-blind period.

Figure 24 Mean (SE) decrease in Corrected Serum Calcium from Three Phase 3 Parent Studies, 20120229, 20120230, 20120360 and the Open Label Extension 20120231 in Subjects on Etelcalcetide



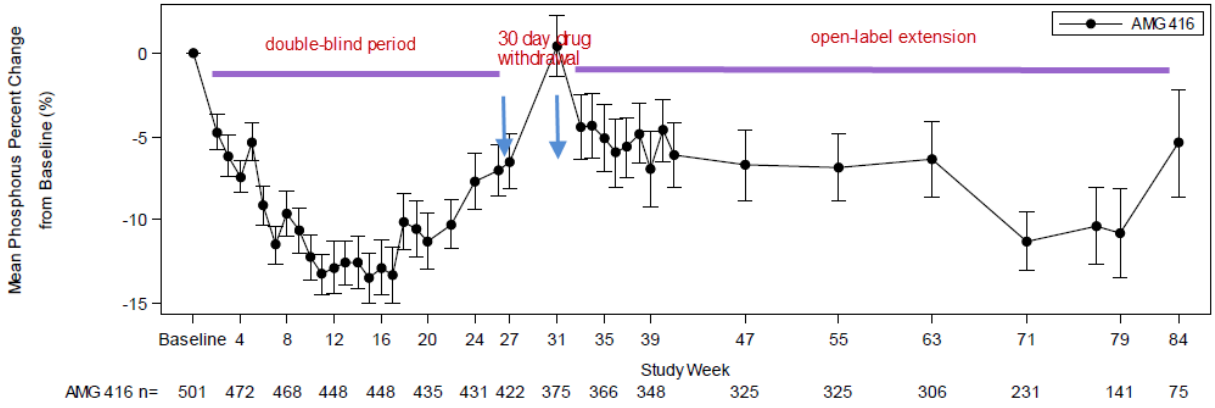
This pool includes data from the phase 3 placebo-controlled parent studies and the subsequent OLE study 20120231 starting from the baseline of the parent study until the end or the pre-specified cutoff date of the OLE study, whichever is earlier, in subjects randomized to AMG 416 in the parent studies.

Full analysis set: all randomized subjects in the pool

Weeks 27 to 31 were the 30-day drug-free period (the 30-day follow-up period of the phase 3 study before entry into the extension study).

Similar results are also seen for mean serum phosphorus which reach a nadir of about -13% at week 12 and then recover to a level of about -7% by week 27, the end of the double-blind period. Serum phosphorous levels also return to baseline at the end of the 4 week withdrawal period and then decline again to about the same level seen at the end of the initial double-blind period or about -7% during the open-label extension.

Figure 25 Mean (SE) decrease in Serum Phosphorus from Three Phase 3 Parent Studies, 20120229, 20120230, 20120360 and the Open Label Extension 20120231 in Subjects on Etelcalcetide



This pool includes data from the phase 3 placebo-controlled parent studies and the subsequent OLE study 20120231 starting from the baseline of the parent study until the end or the pre-specified cutoff date of the OLE study, whichever is earlier, in subjects randomized to AMG 416 in the parent studies.

Full analysis set: all randomized subjects in the pool

Weeks 27 to 31 were the 30-day drug-free period (the 30-day follow-up period of the phase 3 study before entry into the extension study).

Medical Officer's comments-

It is not known why there is tolerance to some of the decline in serum calcium and phosphorous levels while there does not appear to be similar tolerance to the effect on mean iPTH. It is possible that the difference may be due to increased use of serum calcium supplements, and vitamin D analogs initiated by the clinical investigators during the study in response to the initial etelcalcetide related decreases in serum calcium.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Decreased efficacy could be a potential problem if the drug were given prior to the end of the hemodialysis session as it is dialyzable; however dialysis sessions usually follow strict protocols which should make this less likely.

7.2.2. Other Relevant Benefits

Given that the drug is to be given intravenously following dialysis, compliance at the dialysis unit is likely to be less of a problem than with an oral medication like, the other currently approved calcimimetic, cinacalcet, which has to be taking daily by the dialysis patient. In addition etelcalcetide has no known risk for pharmacokinetic drug-drug interactions due to the lack of interaction with CYP450 enzymes, unlike cinacalcet which is a strong inhibitor of CYP2D6

and is partially metabolized by CYP3A4. These are potential benefits as dialysis patients are typically taking a large number of concomitant medications.

Etelcalcetide showed greater efficacy compared to the currently approved calcimimetic, cinacalcet, with respect to iPTH lowering in the head to head, double-blind, double-dummy study 20120360 (see Section 6.3.2). So it could be beneficial to subjects who don't get an adequate response to treatment with cinacalcet.

The initial PD study suggested there might be less nausea and vomiting with the IV formulation of etelcalcetide compared to the oral drug cinacalcet. However, the clinical data from the longer and larger phase 3 trials was not able to confirm that, possibly because the increased efficacy seen with etelcalcetide compared to cinacalcet contributed to lower serum calcium levels which may have increased the nausea and vomiting symptoms, cancelling out any benefit from not having to take a locally irritating oral medication. That said it is possible that certain patients that have nausea and vomiting with one calcimimetic might have a differential response to other members of the class. So it is still beneficial to have an additional calcimimetic available for patients who might have selective intolerability to cinacalcet.

7.3. Integrated Assessment of Effectiveness

The applicant has completed two randomized, placebo-controlled studies 20120229 and 20120230 in hemodialysis patients with secondary hyperparathyroidism which showed statistically significant differences in the primary endpoint, the proportion of subjects in the ITT population attaining a mean decrease of >30% in serum iPTH from the pretreatment baseline to the efficacy assessment period (weeks 20 to 27) relative to placebo (i.e. 74% vs. 8.2 %, and 75% vs. 9.6%, for studies 20120229 and 20120230, respectively). Excluding data from subjects with an increase in active vitamin D analog dose or serum calcium supplements during the pivotal studies did lower the effect size slightly but did not affect the statistical significance of the study results (e.g. 64.3% vs. 8.1%, and 61.4% vs. 8.6%, for studies 20120229 and 20120230, respectively).

Results were also statistically significant for the first secondary endpoint of treatment to iPTH goal of $\leq$ 300pg/mL, which was similar to the primary endpoint treatment to iPTH goal of $\leq$ 250pg/mL used for the approval of the first calcimimetic Sensipar (cinacalcet) (see Study Endpoints under Section 6.1.1 for a further discussion of the use of iPTH as a surrogate for clinical benefit). At the time of the Sensipar approval National Kidney Foundation guidelines had recommended an iPTH target of 150 to 300pg/mL for subjects with Stage 5 CKD on hemodialysis. The more recent KDIGO guidelines from 2009 recommend a larger reference range of 2 to 9-times the upper limit of the iPTH assay typically corresponding to 130 to 600pg/mL in this study population.

The mean decrease in iPTH from baseline to the efficacy assessment period was -55% vs. +13% and -57% vs. +14%, for studies 20120229 and 20120230, respectively, well above the > 30% decrease in iPTH used for the primary endpoint. The changes in bone biomarker data, which were exploratory endpoints, were consistent with a net decrease in high bone turnover associated with renal osteodystrophy, adding further support for clinical benefit. That said, what improvement in PTH levels is necessary for clinical benefit is still not well defined. Bone biopsy data, which is also a surrogate endpoint, would have been better than bone biomarker data at showing the decrease in serum PTH levels was resulting in a reduction in renal osteodystrophy. However, it is difficult to recruit a sufficient number of patients into the type of trial that could generate useful bone biopsy data. Similarly, cardiovascular outcome data, which would be a better estimate for clinical benefit, is also difficult to generate in this study population as demonstrated by the EVOVLE study which compared Sensipar to placebo. This long term cardiovascular outcome trial enrolled 3883 subjects with secondary hyperparathyroidism due to CKD on hemodialysis for up to 5 years and looked for a benefit in all-cause mortality or non-fatal cardiovascular events due to treatment. In the end the study was considered a failure. While there was a trend in favor of non-fatal cardiovascular events over the first few years the benefit seemed to dissipate by year 5. The study was confounded by a large number of dropouts, nearly 70%, and by inappropriate treatment of subjects with commercially available cinacalcet which was twice as common in the placebo group (23 vs. 11%). This failed trial highlights the difficulty in performing a long term placebo-controlled cardiovascular outcome trial in this study population, and why the iPTH surrogate was used instead in these clinical trials.

The randomized, double-blind, double-dummy, study 20120360 showed greater efficacy in the etelcalcetide group compared to cinacalcet with respect to the proportion of subjects having a > 50% or > 30% reduction in iPTH from baseline, (52% vs. 40% and 68% vs. 58%, respectively). Excluding data from subjects with an increase in active vitamin D analog dose or serum calcium supplements did lower the effect size slightly but did not affect the difference between etelcalcetide vs. cinacalcet groups (e.g. 40% vs. 27% for >50% reduction and 55% vs. 46% for >30% reduction, See Response to 13 July 2016 Information Request). Therefore, etelcalcetide provides a potential benefit to subjects who may need a greater level of PTH lowering assuming the results can be verified in a second study. In addition, given that the product is to be given TIW intravenously following routine hemodialysis at the dialysis unit, compliance is likely to be less of a problem than with cinacalcet; the only other approved calcimimetic, which has to be given as a daily oral medication to hemodialysis patients who may already be receiving a large number of other oral medications. Another potential benefit is the use as an alternative therapy in subjects who are not able to tolerate cinacalcet. For example, while nausea and vomiting, which are among the most common adverse reactions associated with calcimimetics, were not statistically significantly less common with etelcalcetide compared to cinacalcet, the point estimate was slightly in favor of etelcalcetide, so it is possible that for certain patients who may not tolerate cinacalcet because of these symptoms etelcalcetide may provide a

reasonable alternative.

With respect to presentation of the PTH data in the labeling it is recommended that mean % change from baseline in iPTH for the 6- month, double-blind, placebo-controlled pivotal studies 20120229 and 20120230 (Figure 6 and Figure 10) be pooled into a single figure, similar to the presentation in the Sensipar PI. Tabular data showing mean baseline iPTH, % change in iPTH from baseline, and % of subjects with > 30% reduction in iPTH from baseline (i.e. the primary endpoint) should be provided. Tabular data with the following statistically significant secondary endpoints: patients with $\leq$300pg/mL in iPTH at EAP, corrected mean and % change from baseline in serum calcium and serum phosphorous, as proposed in Table 3 of the applicants draft Package Insert are also acceptable. (b) (4)

(b) (4)

8 Review of Safety

8.1. Safety Review Approach

Safety data included all subjects who were enrolled and treated with at least 1 dose of study drug or active comparator. The safety profile was primarily based on data from the two pivotal 6-month placebo-controlled phase 3 studies (20120229 and 20120230) which had identical study protocols so the data could be pooled and the active-controlled phase 3 study with cinacalcet (20120360). Additional evidence of long term safety came from studies (20120231 and 20130213). The clinical studies supporting this submission were conducted in the United States, and 25 other countries, including Canada, Australia, and countries in Europe.

This safety review focused on AEs seen with the other currently approved calcimimetic, cinacalcet, namely hypocalcemia, hypophosphatemia and low serum PTH/adynamic bone disease. Special attention was given to symptoms associated with hypocalcemia, including paresthesias, muscle symptoms, convulsions, QT prolongation, ventricular arrhythmias, hypotension and worsening of heart failure. Additional AEs that came up during the course of the review included liver test elevations, and GI hemorrhage.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety profile of etelcalcetide consists primarily from data from 2 pivotal placebo-controlled phase 3 studies (20120229 and 20120230) and 1 active-controlled phase 3 study with cinacalcet (20120360). Additional evidence of safety comes from 3 supportive phase 3 (20120231, 20130213, and 20120359) and 3 supportive phase 2 studies (20120330, 20120331, and 20120334). Two of the supportive phase 3 studies are ongoing open-label phase 3 studies designed to assess the long-term safety of etelcalcetide (20120231 and 20130213).

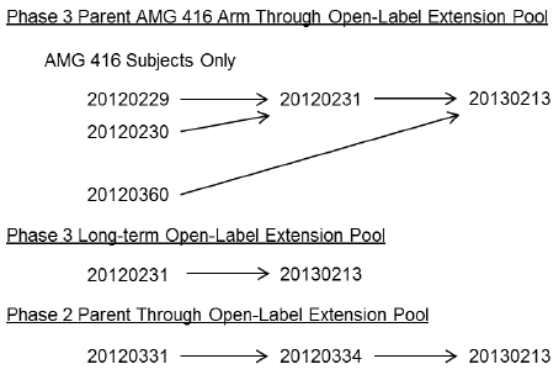


Table 33 Number of Subjects in the Safety Population by Clinical Study

		Number of Subjects Included in the Safety Set			
Study ID	Phase	AMG 416	Placebo	Cinacalcet	Total
Placebo-controlled studies					
20120330	2a	40	38	-	78
20120229	3	251	254	-	505
20120230	3	252	259	-	511
Active-controlled studies					
20120360	3	338	-	341	679
Other studies					
20120331	2b	37	-	-	37
20120359	3	148	-	-	148
Open-label extension studies					
20120334[a]	2	30	-	-	30
20120231[b]	3	890	-	-	890
20130213[c]	3	538	-	-	538

[a] Parent study was 20120331.
[b] Parent studies were 20120229, 20120230, and 20120359. Data presented are from an interim a-lysis with a data cut-off date of 15 January 2015.
[c] Parent studies were 20120231, 20120360, and 20120334. Data presented are from an interim a-lysis with a data cut-off date of 15 January 2015.

Source Table 2 Summary of Clinical Safety

Across the entire clinical development program 1704 subjects received at least 1 dose of etelcalcetide. In phase 2 and phase 3 clinical studies, a total of 1655 subjects (1253 subject-years) received at least 1 dose of etelcalcetide with 1199 (72.4%) for > 24 weeks, and 499 (30.2%) for > 52 weeks. The most frequent dose at which a subject spent the most time was 40.0% 5 mg, 16.9% 2.5 mg, 16.1% 10 mg, 10.0% 15 mg, 6.8% 7.5 mg, 5.8% 0 mg, and 3.5% 12.5 mg.

Table 34 Summary of Drug Exposure

	All Subjects (N = 1655)	6-Month Placebo-Controlled Pool (N = 503)	Phase 3 Long-Term OLE Pool (N = 1289)	Phase 2 Parent through OLE Pool (N = 37)	Phase 3 Parent AMG 416 through OLE Pool (N = 841)
Most frequent dose – n (%)					
0 mg	96 (5.8)	31 (6.2)	99 (7.7)	0 (0.0)	57 (6.8)
2.5 mg	280 (16.9)	47 (9.3)	347 (26.9)	8 (21.6)	94 (11.2)
5 mg	662 (40.0)	151 (30.0)	450 (34.9)	12 (32.4)	351 (41.7)
7.5 mg	112 (6.8)	48 (9.5)	95 (7.4)	2 (5.4)	64 (7.6)
10 mg	266 (16.1)	101 (20.1)	144 (11.2)	7 (18.9)	135 (16.1)
12.5 mg	58 (3.5)	36 (7.2)	43 (3.3)	1 (2.7)	31 (3.7)
15 mg	166 (10.0)	82 (16.3)	103 (8.0)	3 (8.1)	101 (12.0)
17.5 mg	2 (0.1)	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)
20 mg	2 (0.1)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)
22.5 mg	1 (0.1)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)
Duration of exposure – n (%)					
≥ 1 dose	1655 (100.0)	503 (100.0)	1289 (100.0)	37 (100.0)	841 (100.0)
≥ 1 dose to ≤ 12 weeks	267 (16.1)	40 (8.0)	231 (17.9)	8 (21.6)	74 (8.8)
> 12 weeks to ≤ 26 weeks	325 (19.6)	458 (91.1)	247 (19.2)	4 (10.8)	189 (22.5)
> 26 weeks to ≤ 52 weeks	564 (34.1)	5 (1.0)	690 (53.5)	8 (21.6)	225 (26.8)
> 52 weeks to ≤ 78 weeks	443 (26.8)	0 (0.0)	121 (9.4)	3 (8.1)	311 (37.0)
>78 weeks	56 (3.4)	0 (0.0)	0 (0.0)	14 (37.8)	42 (5.0)

Source Table 5.1 ISS

Medical Officer's comments-

The level of exposure is well above the minimum requirements of 300 to 600 patients at 6 months and 100 patients at 1 year recommended by the ICH E1 guidelines for chronically administered medications, which the Division agreed to with the sponsor at the 14 Feb. 2012 Type C meeting.

8.2.2. Relevant characteristics of the safety population:

The demographics of the pivotal trials were previously shown in Tables 6 through 9 and described in more detail in section 6.1.2. The baseline demographics of gender, race, ethnicity, age, BMI, and baseline labs of iPTH, serum calcium and serum phosphorous were in general similar between the placebo and treatment groups, as were the proportion of subjects taking concomitant medications of interest and general medical histories including incidence of hypertension, diabetes and dyslipidemia.

8.2.3. Adequacy of the safety database:

The safety population was adequate for the proposed indication. Approximately half of the subjects enrolled in the pivotal trials 20120229 & 20120230 were from the United States, and about ¼ of the subjects in the active control trial 201202360 were also from the United States.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review.

8.3.2. Categorization of Adverse Events

- The applicant's definitions of AEs and serious adverse events (SAEs) in the protocol(s) were accurate.

- Treatment emergent adverse events (TEAEs) referred to adverse events that occurred after the first dose of the investigational product was administered or that was seen prior to the start of the first dose of investigational product but increased in severity after treatment, regardless of whether or not they were considered drug related.

- The Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0 was used to code all AEs in pivotal studies 20120229 and 20120230, and Version 17.1 was used for the active control study 20120360.

- The investigator was required to follow reported adverse events until stabilization or reversibility. All adverse events were followed until resolution or for a minimum of 30 days after last dose of study drug administration. However, if the investigator became aware of a serious adverse event after this protocol-required reporting period, they were still required to report the event to Amgen within 24 hours following their knowledge of the event.

- Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject were to be reported in the CRF.

- Adverse events were assessed by frequency (i.e., events per patient) or by total number of patients with each individual AE which were appropriate.

- Severity categorization (e.g., mild, moderate, severe, maximal/life-threatening) of AEs by the Applicant was appropriate.

- Verbatim terms were included in the data files and in general were appropriately categorized in the AEDECOD (dictionary-derived term) data file. For example there were 139 different AETERMS related to decreased or low blood calcium that were all coded by the AEDECOD term "Blood calcium decreased" and 18 different AETERMS related to increased or high blood calcium that were all coded by the AEDECOD term "Blood calcium increased". In addition, there appeared to be no splitting of higher level terms

as all AEs related to abnormal serum calcium levels were coded under the single AEHLT term “Mineral and electrolyte analyses” and the single AEHLGT term “Water, electrolyte and mineral investigations”. That said the small number of cases of “hypocalcemia” and “worsening hypocalcemia” were lumped in with the majority of cases of decreased or low blood calcium under the AEDECOD term of “Blood calcium decreased”.

In conclusion, the applicant’s process for recording, coding, and categorizing AEs, as well as their approach to safety analyses was reasonable and appropriate.

8.3.3. Routine Clinical Tests

Blood samples were drawn three times per week prior to hemodialysis. In the placebo-controlled pivotal studies, 20120229 & 20120230, serum albumin, calcium and phosphorous were measured weekly. Serum calcium levels were corrected for serum albumin using the formula:

Corrected calcium (mg/dL) = Total Ca (mg/dL) + (4 – albumin [g/dL])*0.8.

Serum iPTH was measured on Weeks 1 and 2 and then every other week, on even numbered weeks, until the EAP when it was measured weekly from Weeks 20 through 27. Serum iPTH was also measured at the follow-up visit 30 days after drug discontinuation and prior to early termination in those subjects who discontinued that study prematurely. See Table 2 Schedule of Assessments for a listing of assessments for all other specific lab tests performed in studies 20120229 & 20120230.

In the active-controlled study 20120360 serum calcium and iPTH were measured every 2 weeks from week 2 through week 26, and on Weeks 27, 30 and end of treatment. Serum phosphorous was measured every 4 weeks from week 4 through week 24, and on weeks 26, 27, 30 and end of treatment. See Table 20 Schedule of Assessments for a listing of assessments for all other lab tests performed in study 20120360.

8.4. Safety Results

8.4.1. Deaths

Placebo-controlled Pivotal 6-month studies 20120229 & 20120230

Slightly more subjects in the placebo groups in the combined data from the two pivotal trials 20120229 & 20120230 had fatal events 15 subjects (2.9%) vs. the etelcalcetide group 11 subjects (2.2%). Two placebo patients died from CHF and two placebo patients died from sepsis. Otherwise all other causes of death occurred in no more than a single subject. The causes of death in both treatment arms were consistent with what would be expected from CKD patients on chronic dialysis (e.g. cardiac events and septic events).

Only in 1 case (22965007001), a 73-year-old female treated with etelcalcetide, was the fatal outcome assessed by the clinical investigator as related to investigational product. The event was listed as death-cause unknown. During the second week of treatment on the night after her latest hemodialysis and after her fifth dose of etelcalcetide, the patient while on aspirin and lansoprazole developed severe vomiting of "dark contents" and diarrhea, and progressive lethargy and weakness. She was seen by her general practitioner the following morning who felt she had gastroenteritis and was well enough to avoid hospitalization. However, later that day her condition worsened she developed a distended abdomen, and slurred speech. EMS was called and observed the subject to vomit coffee ground emesis with subsequent aspiration and rapid deterioration. The subject was successfully intubated and CPR was initiated but was unsuccessful. Autopsy confirmed mucosal stress ulcers in the GI system, with terminal congestion and edema in the lungs. It is this medical officer's assessment that the case probably resulted from a combination of blood loss from a GI bleed and aspiration of the contents resulting is a respiratory arrest. Given that nauseas and vomiting are two of the most common AEs associated with the use of calcimimetics it is clearly possible that etelcalcetide may have contributed to the fatal event. That said GI bleeds are known to be more common in patients with end stage renal disease than in the general population.

Four additional subjects (1 placebo, 3 etelcalcetide) had fatal events that occurred during the follow-up period of 30 days after the last dose of study treatment. The cause of death in the placebo patient was cardiac valve disease (Subject 22966089005). The causes of death in the etelcalcetide patients were: chronic renal failure (Subject 22966017001), sudden cardiac death (Subject 22966049003), and gastrointestinal hemorrhage (Subject 23066026008). These cases are not unusual in this study population. However, the case of GI hemorrhage will be described in more detail given that there was also one death in a patient with similar GI symptoms described above (22965007001).

> Subject 23066026008 was a 75 y/o black male with a history of gastroesophageal reflux disease on Prilosec, prednisolone and heparin who had his study medication discontinued on week 17 (1 Oct. 2013) for "sponsor's decision". The narrative mentions that the subject had coffee ground vomit at an unknown date and nausea and abdominal distension that lasted one week. It is not clear if this was the reason for the study drug discontinuation or if it occurred after the study drug was already discontinued. The narrative also mentions that on (b) (6), about (b) (6) weeks after study drug discontinuation that the subject had an upper GI bleed while in a nursing home and required hospitalization. Endoscopy at the time showed severe esophagitis, hiatal hernia, Mallory Weiss tear and gastritis. He received Protonix, IV fluids, Zofran and pain medication. One week later on (b) (6) he became hypotensive. The ECG was showed lateral ischemia with ST and T wave abnormalities. He died later the same day from a cardiac arrest despite being coded in the ICU. It was noted that his hematocrit

had decreased from 33% to 29% at that time and he had vomited blood during the code consistent with a persistent GI bleed.

Medical Officer's comments-

According to the sponsor this subject was prematurely discontinued from the study at week 17 because the principle investigator at the site retired unexpectedly. The applicant stated that this subject's past history included GE reflux but that there was no other report of GI pathology in this patient. Normally an event that occurs (b)(6) weeks after drug discontinuation could be considered not to be related to the study drug. For example, it would be unlikely that nausea and vomiting which can be associated with calcimimetics would have still caused such symptoms (b)(6) weeks after drug discontinuation. Whether it may have contributed to worsening of the subjects GI disease/Mallory Weiss tears while the subject was being treated for 17 weeks cannot be ruled out. It is however, concerning that one other patient (22965007001) died during treatment with etelcalcetide from what was officially described as unknown cause but by history sounds like it too was related to an upper GI bleed.

Active-controlled 6 month study 20120360

Slightly more subjects died during the 6 month study in the etelcalcetide treatment group 9 subjects (2.7%) compared to the cinacalcet treatment group 6 subjects (1.8%). Two additional subjects died in the 30 day study follow up period, one from each treatment group. Similar to what had been seen in the placebo-controlled studies the causes of death in both treatment arms were consistent with what would be expected from CKD patients on chronic dialysis (e.g. cardiac events and septic events).

Phase 3 Pooled Open-label Extension studies 20120231 and 20130213

A total of 47 subjects (3.6%; 5.1 per 100 subject-years) in the phase 3 long-term open-label extension combined dataset had treatment emergent fatal adverse events (ISS Table 6.61). Fatal events were again mostly related to cardiac events and septic events.

- cardiac arrest (9 subjects [0.7%]; 1.0 per 100 subject-years),
- sepsis (3 subjects [0.2%]; 0.3 per 100 subject-years),
- sudden death (3 subjects [0.2%]; 0.3 per 100 subject-years),
- ventricular fibrillation (3 subjects [0.2%]; 0.3 per 100 subject-years),
- cardiac failure (2 subjects [0.2%]; 0.2 per 100 subject-years),
- cardio-respiratory arrest (2 subjects [0.2%]; 0.2 per 100 subject-years),
- cerebral hemorrhage (2 subjects [0.2%]; 0.2 per 100 subject-years), and
- septic shock (2 subjects [0.2%]; 0.2 per 100 subject-years).

No other adverse event led to death for more than 1 subject each.

Phase 2 Pooled Open-label Extension studies 20120331, 20120334 and 20130213
A total of 7 subjects (18.9%; 12.8 per 100 subject-years) in the phase 2 parent through open-label extension combined dataset had treatment emergent fatal adverse events. No adverse event was the cause of death in more than one patient. Similar to what had been seen in the placebo-controlled studies and Phase 3 open-label studies the causes of death in both treatment arms were consistent with what would be expected from CKD patients on chronic dialysis (e.g. cardiac events and septic events). That said, there was also another case of a death related to a gastrointestinal bleed.

> Subject 0517-1547 in Phase 2 study 20120331 was a 54 y/o white diabetic male with a history of CHF, peripheral edema, and intermittent nausea, vomiting, due to GE reflux disease while on aspirin, heparin, metoclopramide and ranitidine who had an acute subendocardial MI on study Day 33 resulting in his hospitalization. Etelcalcetide was discontinued at that time. Ten days later on Study Day 43 he had a GI bleed resulting in cardiogenic shock and death. The investigator considered the events not related to the investigational medication.

Medical Officer's comments-

While it is concerning that there are now 3 deaths related to GI bleeds in patients treated with etelcalcetide, GI hemorrhage is more common in the hemodialysis population and these cases were confounded by multiple factors, including medical history of GE reflux/Mallory Weiss tears/ulcers/gastritis/intermittent nausea and vomiting, concomitant medication including aspirin, heparin, and steroids, and acute cardiac events that likely increased patient stress.

This medical reviewer used JMP software to identify the number of patients with preferred term AEs included under the AEHGLT term of "gastrointestinal ulceration and perforation" by treatment group in the placebo-controlled studies 20120229 & 20120230.

AEDECOD	Etelcalcetide	Placebo
Duodenal ulcer	1	2
Duodenal ulcer haemorrhage	0	1
Gastric ulcer	1	1
Gastritis erosive	3	0
Oesophageal ulcer haemorrhage	1	0
Total	6	4
From 20120229 & 20120230 ADAE datasets for AESDY>0, and AEHGLT= Gastrointestinal ulceration and perforation		

There were a slightly higher number of cases in the etelcalcetide group (6 vs. 4). However, using the AEHGLT term of "Gastrointestinal haemorrhages NEC" resulted in slightly higher results in the placebo group (9 vs. 7).

AEDECOD	Etelcalcetide	Placebo
Gastrointestinal haemorrhage	0	3
Haematemesis	1	1
Haematochezia	0	2
Large intestinal haemorrhage	1	0
Lower gastrointestinal haemorrhage	2	0
Rectal haemorrhage	1	2
Upper gastrointestinal haemorrhage	2	1
Total	7	9
From 20120229 & 20120230 ADAE datasets for AESDY>0, and AEHGLT= Gastrointestinal haemorrhages NEC		

Therefore the net result was that there was no clear net difference between treatment groups from the placebo-controlled data. Similar results were seen if the AEHGLT terms of "Gastrointestinal ulceration and perforation" and "Gastrointestinal haemorrhages NEC" were combined and focus was placed on only the severe and life threatening adverse events (etelcalcetide=6 vs placebo=5) or on only the serious adverse events (etelcalcetide=6 vs placebo=6).

8.4.2. **Serious Adverse Events**

The event rate for serious AEs was similar between etelcalcetide 130 subjects (25.8%) and placebo 149 subjects (29.0%) in the pooled data from the pivotal studies and between etelcalcetide 85 subjects (25.1%) and cinacalcet 93 subjects (27.3%) in the active controlled study 20120360.

Table 35 Serious Adverse Events Occurring in ≥1% of Subjects in Pivotal Studies 20120229 and 20120230 and Active-controlled Study 20120360

	Total placebo-controlled studies		20120360	
Preferred Term	Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)	Cinacalcet (N = 341) n (%)	AMG 416 (N = 338) n (%)
Number of subjects reporting serious treatment emergent adverse events	149 (29.0)	130 (25.8)	93 (27.3)	85 (25.1)
Hyperkalaemia	2 (0.4)	10 (2.0)	5 (1.5)	1 (0.3)
Pneumonia	14 (2.7)	10 (2.0)	1 (0.3)	1 (0.3)
Angina pectoris	3 (0.6)	7 (1.4)	1 (0.3)	1 (0.3)
Fluid overload	7 (1.4)	6 (1.2)	1 (0.3)	2 (0.6)
Atrial fibrillation	5 (1.0)	5 (1.0)	2 (0.6)	0 (0.0)
Cardiac failure congestive	5 (1.0)	5 (1.0)	1 (0.3)	0 (0.0)
Sepsis	4 (0.8)	4 (0.8)	4 (1.2)	3 (0.9)
Vascular graft thrombosis	5 (1.0)	3 (0.6)	3 (0.9)	0 (0.0)
Arteriovenous fistula thrombosis	5 (1.0)	2 (0.4)	1 (0.3)	1 (0.3)
Gangrene	2 (0.4)	2 (0.4)	0 (0.0)	4 (1.2)
Anaemia	5 (1.0)	1 (0.2)	4 (1.2)	0 (0.0)

Total placebo-controlled studies: Studies 20120229 and 20120230.
Safety analysis set: all subjects in the combined dataset who received at least one dose of IP.
Coded using MedDRA version 17.1
Source: ISS Table 6.7
Source Table 18 Summary of Clinical Safety

Medical Officer's comments-

These Serious AEs are common in the hemodialysis population. No AE was more frequent in the etelcalcetide group in both the placebo and active controlled studies, or occurred at a rate of >2% in the etelcalcetide group relative to either comparator group.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to discontinuation from the pooled data from the placebo-controlled studies were slightly more frequent in the placebo group (n=13, 2.5%) compared to the

etelcalcetide group (n=9, 1.8%). The most common AE was blood calcium decreased which was seen in 5 subjects 1.0% of patients in the etelcalcetide group compared to 0 subjects in the placebo group. Other AEs seen in the etelcalcetide group seen in only one subject each (0.2%) were nausea, vomiting, drug hypersensitivity, chest discomfort, GI malformation, hemiparesis and hyperhidrosis. There were no patients who discontinued from the placebo group with these same AEs.

Adverse events leading to discontinuation from the total active-controlled study were slightly more frequent in the etelcalcetide group (n=19, 5.6%) compared to the cinacalcet group (n=16, 4.7%). The most frequent AEs leading to discontinuation in the etelcalcetide group and occurring in 2 or more subjects were:

vomiting (n=3, 0.9%) in the etelcalcetide group vs. (n=1, 0.3%) in the cinacalcet group
nausea (n=2, 0.6%) in the etelcalcetide group vs. (n=3, 0.9%) in the cinacalcet group
dermatitis (n=2, 0.6%) in the etelcalcetide group vs. (n=0) in the cinacalcet group

Other AEs of interest occurring only once in the etelcalcetide group were oesophageal haemorrhagic, hepatic enzyme increased, muscular weakness, myocardial ischemia, cardiac arrest, calciphylaxis, and bronchospasm (source, Table 6.9 ISS).

Medical Officer's comments-

The AEs leading to discontinuation are mostly related to cardiovascular disease, gastrointestinal symptoms and hypersensitivity.

8.4.4. Significant Adverse Events

Adverse reactions were characterized as mild, moderate, severe, and maximal/life-threatening. A review of adverse reactions with the same AEDECOD listing in each patient and the same level of severity identified mostly mild and moderate severity adverse reactions as more common in the etelcalcetide treatment group compared to placebo in the pivotal placebo-controlled studies (see Table 36). A MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the combined severe and life threatening events did not find any Preferred Terms that resulted in a p-value less than 0.05. The most frequent terms identified were related to cardiovascular events which are common in this study population. The most frequent severe and maximal/life-threatening adverse events of interest which were also more common in the etelcalcetide group vs. placebo in order of frequency were: gastroenteritis 3 vs. 0, blood calcium decreased 2 vs. 1, lower GI hemorrhage 2 vs. 0, acute hepatic failure 1 vs. 0, hepatic enzyme increased 1 vs. 0, oesophageal ulcer hemorrhage 1 vs. 0, upper GI hemorrhage 1 vs. 0, and vomiting 1 vs. 0.

Table 36 Number of Subjects with Adverse Reactions by Preferred Term (AEDECOD) and AE Severity (AESEV) in Placebo-Controlled Studies 20120229 and 20120230

	Total AE Preferred Terms AEDECOD/USUBJID/AESEV	Mild	Moderate	Severe	Life threatening
AMG 416	2358	1313	821	200	24
PLACEBO	1806	941	630	213	22

Source JMP analysis, Pts with a specific preferred term with the same level of severity were only counted once.

Medical Officer's comments-

Most of the AEs which were more common in the etelcalcetide treatment group compared to placebo were mild and moderate in severity, with no large increase in severe and life threatening AEs. While most of the severe and life threatening were cardiovascular events common in this study population, there does appear to be a signal for significant GI events including GI bleeds which although rare seem to be more common in the etelcalcetide treatment group.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Etelcalcetide vs. Placebo-

Treatment Emergent AEs that occurred in ≥5% of subjects in either combined treatment arm in the pivotal trials and the combined pooled data are shown in Table 37 in order of frequency of occurrence in the etelcalcetide group pooled data. Given that the two pivotal trials, 20120229 and 20120230, had similar designs and enrolled similar study populations it is not surprising that the event rates for blood calcium decreased and hypocalcemia, AEs that are likely to be drug related are similar in the individual studies and the pooled study data. Other AEs that were consistently higher in the etelcalcetide group compared to placebo and likely to be drug related include muscle spasms which can be triggered by low serum calcium levels, and nausea and vomiting which have been seen with the other calcimimetic, cinacalcet.

Table 37 Number of Subjects Reporting Treatment AEs Occurring in ≥5% of Subjects in Either Treatment Arm in Placebo-Controlled Studies 20120229 & 20120230

	20120229		20120230		Total placebo-controlled studies	
	Placebo (N = 254) n (%)	AMG 416 (N = 251) n (%)	Placebo (N = 259) n (%)	AMG 416 (N = 252) n (%)	Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)
Number of subjects reporting treatment emergent adverse events	200 (78.7)	230 (91.6)	210 (81.1)	231 (91.7)	410 (79.9)	461 (91.7)
Blood calcium decreased	21 (8.3)	153 (61.0)	31 (12.0)	168 (66.7)	52 (10.1)	321 (63.8)
Muscle spasms	18 (7.1)	30 (12.0)	16 (6.2)	28 (11.1)	34 (6.6)	58 (11.5)
Diarrhoea	18 (7.1)	18 (7.2)	26 (10.0)	36 (14.3)	44 (8.6)	54 (10.7)
Nausea	13 (5.1)	31 (12.4)	19 (7.3)	23 (9.1)	32 (6.2)	54 (10.7)
Vomiting	18 (7.1)	26 (10.4)	8 (3.1)	19 (7.5)	26 (5.1)	45 (8.9)
Headache	20 (7.9)	18 (7.2)	11 (4.2)	20 (7.9)	31 (6.0)	38 (7.6)
Hypocalcaemia	1 (0.4)	18 (7.2)	0 (0.0)	17 (6.7)	1 (0.2)	35 (7.0)
Hypertension	17 (6.7)	12 (4.8)	12 (4.6)	19 (7.5)	29 (5.7)	31 (6.2)
Hypotension	10 (3.9)	16 (6.4)	16 (6.2)	14 (5.6)	26 (5.1)	30 (6.0)
Arteriovenous fistula site complication	14 (5.5)	13 (5.2)	12 (4.6)	16 (6.3)	26 (5.1)	29 (5.8)
Arthralgia	10 (3.9)	10 (4.0)	16 (6.2)	11 (4.4)	26 (5.1)	21 (4.2)
Upper respiratory tract infection	10 (3.9)	8 (3.2)	16 (6.2)	13 (5.2)	26 (5.1)	21 (4.2)

This combined dataset includes data from the 2 placebo-controlled studies 20120229 and 20120230.
Safety analysis set: all subjects in the combined dataset who received at least 1 dose of investigational product.
Coded using MedDRA version 17.1
Source: ISS Table 6.4

Source Table 7 Clinical Overview

The applicant analyzed the top seven treatment emergent AEs from Table 37 by duration of exposure to etelcalcetide. Incidence rates that were greater than seen with placebo at each study dose are highlighted in Table 38. While these data do not yield clear dose responses relationships, at doses above 2.5mg the event rate are consistently above what is seen with placebo or the 0mg dose pointing to the possibility that they are likely to be drug-related.

Table 38 Exposure Duration Adjusted Incidence of the Seven Most Common Treatment AEs by Dose Level Taken from Table 37

	Placebo (N = 513)		0 mg (N = 419)		2.5 mg (N = 127)		5 mg (N = 502)		7.5 mg (N = 137)		10 mg (N = 276)		12.5 mg (N = 63)		15 mg (N = 112)		AMG 416 (N = 503)	
Preferred Term	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r
Blood calcium decreased	49	23.1	1	3.1	3	15.5	142	262.4	26	146.8	78	261.3	20	248.9	50	287.5	320	269.1
Muscle spasms	33	15.2	2	6.2	5	25.5	24	33.0	4	19.3	13	32.3	3	29.3	6	23.9	57	27.0
Nausea	29	13.2	1	3.1	2	10.2	24	32.3	7	34.1	8	19.7	2	18.8	7	28.8	51	23.9
Diarrhoea	43	19.9	1	3.1	5	25.9	16	21.6	4	19.4	15	37.3	2	18.6	7	28.8	50	23.4
Vomiting	25	11.3	2	6.2	2	10.1	15	20.3	6	29.7	8	19.8	5	46.9	3	12.2	41	19.0
Headache	29	13.1	3	9.3	2	10.0	16	21.5	3	14.3	8	19.7	2	18.4	2	8.0	36	16.5
Hypocalcaemia	1	0.4	0	0.0	1	5.0	19	25.7	3	14.2	8	19.5	1	9.2	3	11.9	35	16.1
Hypertension	26	11.8	1	3.1	3	15.0	15	20.2	4	19.2	5	12.2	1	9.2	2	7.9	31	14.1

This combined dataset includes data from the 2 placebo-controlled studies 20120229 and 20120230.
N = The number of subjects in safety analysis set, N for each dose level is the number of subjects who have ever received the dose.
r = exposure adjusted incidence rate per 100 subject year.
The dose is the dose level a subject was receiving on the onset date for a treatment emergent adverse event. The first occurrence was used to determine the dose level, if a subject had multiple occurrences of a treatment emergent adverse event.
For subjects who had dose withheld or did not receive dose on the day of the adverse event, the previous dose level within 7 days was assigned. If there was no active dose within 7 days, 0 mg was assigned.
Adverse events that occurred during the 30 day follow up period are excluded.
Coded using MedDRA version 17.1
Source: ISS Table 6.34

Source Table 40 Summary of Clinical Safety, Highlighted values > placebo

A MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the data from the pivotal trials was performed by this medical reviewer, looking at AEs that occurred after study Day 1 (AESDY>0) and were associated with actual drug treatment during the trial (TRT01A). The analysis sorted in order of lowest p-value for p-values < 0.05 is shown in Table 39. This analysis confirms the much higher event rates for blood calcium decreased, muscle spasms and hypocalcemia seen in the sponsor's analysis but also identifies other AEs likely to be related to low serum calcium levels including paresthesias and myalgias not seen in the sponsor's table because of their lower event rates 4.8% and 1.6%, respectively (see items in red text). Of note "convulsions" which can also be related to hypocalcemia were seen at an equal rate in both treatment groups at 0.8%, and "ECG QT prolonged" was only slightly higher in the etelcalcetide group at 0.8% vs. 0.6%. This analysis also shows the AEs of nausea and vomiting are likely to be drug related. In addition, a new AE of hypophosphatemia which may be related to lowering of serum PTH levels is also identified, even though it occurred at a low event rate of only 1.4%.

Table 39 MAED Analysis of Pooled Data from Pivotal Studies 20120229 & 20120230 with p-values < 0.05

Sorted by p-value	AMG 416 (N = 503)			PLACEBO (N = 513)			AMG 416 vs. PLACEBO			
PT	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Relative Risk	RR 95% CI lower	RR 95% CI upper	p-value
Blood calcium decreased	540	321	63.8	61	52	10.1	6.3	4.8	8.2	0
Hypocalcaemia	36	35	7.0	1	1	0.2	35.7	4.9	259.6	0
Paraesthesia	39	24	4.8	5	3	0.6	8.2	2.5	26.9	0
Sinusitis	10	9	1.8	1	1	0.2	9.2	1.2	72.2	0.011
Muscle spasms	83	58	11.5	46	35	6.8	1.7	1.1	2.5	0.012
Nausea	66	54	10.7	43	32	6.2	1.7	1.1	2.6	0.013
Blood calcium increased	10	8	1.6	1	1	0.2	8.2	1.0	65.0	0.02
Myalgia	9	8	1.6	1	1	0.2	8.2	1.0	65.0	0.02
Vomiting	49	45	9.0	32	27	5.3	1.7	1.1	2.7	0.027
Hypophosphataemia	7	7	1.4	1	1	0.2	7.1	0.9	57.8	0.037

Source MAED Analysis using ADSL and ADAE datasets for AEDECOD, AESDY>0 and TRT01A
AEs likely to be associated with low serum calcium levels are listed in red text.

The same MedDRA analysis sorted in order of highest relative risk with etelcalcetide vs. placebo for Relative Risk-values > 6 is shown in Table 40. This analysis shows AEs that are much more common in the etelcalcetide group (i.e. > 6-fold) but because of low frequency may have p-values above 0.05. In this table items with p-values <0.05 are listed in red text and are similar to the items identified in Table 39. But additional items of interest include a series of items likely to be related to allergy and drug reactions including: sinusitis, asthma, drug hypersensitivity, erythema and seasonal allergy which are listed in blue text. It is possible that these items represent similar conditions but because of how the investigator chose to code them no single Preferred Term was frequent enough to generate a p-value < 0.05.

In addition, the term “hepatic enzyme increased” is observed which will be discussed in more detail under Lab Findings in Section 8.4.6, and “gastric erosive”, which may correlate with the small number of cases of GI bleeding seen in the etelcalcetide group (see section 8.4.4 Significant Adverse Events) some of which resulted in fatal outcomes (see section 8.4.1 Deaths). Of note glandular stomach erosion was seen in a few rats in the nonclinical toxicity studies at

mid and high doses (see Section 4.4 Nonclinical Pharmacology/Toxicology) pointing to the fact that such cases may be drug related.

Of note the Preferred Terms of "cardiac failure" and "cardiac failure congestive" were both slightly higher in the etelcalcetide group, n=3 (0.6%) vs. n=1 (0.2%) and n=8 (1.6%) vs. n=6 (1.2%), respectively but both p-values were well over 0.05 at 0.37 and 0.60, respectively, demonstrating no clear increased risk with the treatment of etelcalcetide in the placebo-controlled studies. In contrast to this medical reviewer's analysis the applicant chose to combine and adjudicate these cases and focused on confirmed cases requiring hospitalization, which resulted in the same number of total patients in the etelcalcetide group n=11 (2.2%) vs. one fewer case in the placebo group n=6 (1.2%), which they considered potentially significant.

Table 40 MAED Analysis of Pooled Data from Pivotal Studies 20120229 & 20120230 with Relative Risk of Etelcalcetide/Placebo > 6-fold

Sorted by Relative Risk	AMG 416 (N = 503)			PLACEBO (N = 513)			AMG 416 vs. PLACEBO			
PT	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Relative Risk	RR 95% CI lower	RR 95% CI upper	p-value
Hypocalcaemia	36	35	7.0	1	1	0.2	35.7	4.9	259.6	0
Procedural hypertension	4	4	0.8	0	0	0	9.2	0.5	170.0	0.06
Sinusitis	10	9	1.8	1	1	0.2	9.2	1.2	72.2	0.011
Blood calcium increased	10	8	1.6	1	1	0.2	8.2	1.0	65.0	0.02
Myalgia	9	8	1.6	1	1	0.2	8.2	1.0	65.0	0.02
Paraesthesia	39	24	4.8	5	3	0.6	8.2	2.5	26.9	0
Aortic valve stenosis	3	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Asthma	5	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Drug hypersensitivity	4	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Erythema	4	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Gastritis erosive	3	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Hepatic enzyme increased	3	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Hyponatraemia	3	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Hypophosphataemia	7	7	1.4	1	1	0.2	7.1	0.9	57.8	0.037
Seasonal allergy	3	3	0.6	0	0	0	7.1	0.4	137.9	0.121
Blood calcium decreased	540	321	63.8	61	52	10.1	6.3	4.8	8.2	0

Source MAED Analysis using ADSL and ADAE datasets for AEDECOD, AESDY>0 and TRT01A
AEs with p-values < 0.05 are listed in red text. AEs associated with potential allergic components are listed in blue text.

A MedDRA analysis of these same data using narrow SMQ search terms identified "gastrointestinal nonspecific inflammation and dysfunctional conditions" and "gastrointestinal nonspecific symptoms and therapeutic procedures" as more common in the etelcalcetide group with p-values < 0.05. While these GI adverse reactions are common in the hemodialysis population occurring at rates of 21 to 23% in the placebo group, they appear about 7% more frequent in the etelcalcetide group occurring at rates of 28 to 30% occurring with a relative risk of 1.3 fold in the etelcalcetide population.

Table 41 MAED Analysis of Pooled Data from Pivotal Studies 20120229 & 20120230 using Narrow Search SMQs

SMQ (Narrow Search)		AMG 416 (N = 503)			PLACEBO (N = 513)			AMG 416 vs. PLACEBO			
Level 1	Level 2	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Relative Risk	RR 95% CI lower	RR 95% CI upper	p-value
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	243	140	27.8	210	108	21.1	1.3	1.1	1.6	0.013
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions		273	150	29.8	228	118	23.0	1.3	1.1	1.6	0.015

Source MAED Analysis using ADSL and ADAE datasets for AEDECOD, AESDY>0 and TRT01A

Other narrow SMQs of interest with higher p-values include: "hypersensitivity" etelcalcetide 4.6% vs. placebo 3.7%, p-value=0.53; "Torsade de pointes/QT prolongation" etelcalcetide 1.2% vs. placebo 0.6%, p-value=0.34; "cardiac failure" etelcalcetide 3.2% vs. placebo 2.7%, p-value=0.71; and "Convulsions" etelcalcetide 0.8% vs. placebo 1%, p-value=1.0.

Etelcalcetide vs. Cinacalcet-

A MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the data from the active controlled trial 20120360 was performed by this medical reviewer, looking at AEs that occurred after study Day 1 (AESDY>0) and were associated with actual drug treatment during the trial (TRT01A). The analysis sorted in order of lowest p-value for p-values < 0.05 is shown in Table

42. This analysis demonstrates that the rates for "blood calcium decreased", are higher with etelcalcetide compared to cinacalcet, consistent with the greater efficacy seen with etelcalcetide with respect to PTH lowering. Hypotension although much less frequent than the cases of "blood calcium decreased" was also more common with etelcalcetide compared to cinacalcet which may be associated with low blood calcium. Pruritus while not specifically seen in the MAED analysis of the placebo-controlled trials (Table 39 & Table 40) may represent an allergic/drug reaction symptom which were more common with etelcalcetide in the placebo-controlled trials MAED analysis (see Table 40).

Table 42 MAED Analysis of Data from the Active Controlled Study 20120360 with p-values < 0.05

	AMG 416 (N = 338)			Cinacalcet (N = 341)			AMG 416 vs. Cinacalcet			
	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Relative Risk	RR 95% CI lower	RR 95% CI upper	P-value
Bronchitis	5	5	1.5	19	17	5.0	0.3	0.1	0.8	0.015
Blood calcium decreased	378	234	69.2	350	205	60.1	1.2	1.0	1.3	0.016
Hypotension	34	23	6.8	11	10	2.9	2.3	1.1	4.8	0.021
Pruritus	17	15	4.4	5	5	1.5	3.0	1.1	8.2	0.024
Iron deficiency	7	5	1.5	0	0	0	11.1	0.6	199.9	0.03
Urinary tract infection	1	1	0.3	8	8	2.4	0.1	0.02	1.0	0.038

Source MAED Analysis using ADSL and ADAE datasets for AEDECOD, AESDY>0 and TRT01A

The same MedDRA analysis sorted this time in order of AEs occurring in most subjects in the etelcalcetide group is shown in Table 43. This analysis shows AEs that are most common in the etelcalcetide group irrespective of their frequency in the cinacalcet group. In addition to "Blood calcium decreased" which had a p-value <0.05 as seen previously in Table 42, "hypocalcemia" occurred at almost twice the rate in the etelcalcetide treatment group compared to cinacalcet, 5.0% vs 2.4%, although the p-value was above 0.05 at 0.069.

Table 43 MAED Analysis of Data from the Active Controlled Study 20120360 with Etelcalcetide Subjects >16, Sorted by Etelcalcetide Events

	AMG 416 (N = 338)			Cinacalcet (N = 341)			AMG 416 vs. Cinacalcet			
	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Relative Risk	RR 95% CI lower	RR 95% CI upper	P-value
Blood calcium decreased	378	234	69.2	350	205	60.1	1.2	1.0	1.3	0.016
Nausea	148	61	18.1	173	77	22.6	0.8	0.6	1.1	0.153
Vomiting	73	44	13.0	103	47	13.8	0.9	0.6	1.4	0.822
Hypertension	34	23	6.8	28	24	7.0	1.0	0.6	1.7	1
Hypotension	34	23	6.8	11	10	2.9	2.3	1.1	4.8	0.021
Diarrhoea	25	22	6.5	48	35	10.3	0.6	0.4	1.1	0.096
Headache	32	22	6.5	35	25	7.3	0.9	0.5	1.5	0.763
Muscle spasms	29	22	6.5	34	21	6.2	1.1	0.6	1.9	0.876
Anaemia	20	18	5.3	19	15	4.4	1.2	0.6	2.4	0.597
Pain in extremity	20	18	5.3	19	15	4.4	1.2	0.6	2.4	0.597
Hypocalcaemia	19	17	5.0	9	8	2.4	2.1	0.9	4.9	0.069

Source MAED Analysis using ADSL and ADAE datasets for AEDECOD, AESDY>0 and TRT01A
AEs likely to be associated with low serum calcium levels are listed in red text.

A MedDRA analysis of these same data using narrow SMQ search terms identified only "cardiac failure" as more common in the etelcalcetide group compared to cinacalcet with p-values < 0.05. While cardiac failure is common in the hemodialysis population, the narrow SMQ identified 10 subjects in the etelcalcetide group compared to only 2 subjects in the cinacalcet group for relative event rates of 3% vs. 0.6% or a relative risk of 5-fold, p=0.021.

Medical officer's comments-

Treatment emergent adverse reactions that were more common in the etelcalcetide treatment group compared to placebo can be grouped into several categories including:

- *Low serum calcium (blood calcium decreased, and hypocalcemia) and increased neuromuscular symptoms related to low serum calcium (paresthesias, muscle spasms, and myalgia),*

- *GI symptoms (nausea, vomiting, erosive gastritis, and hepatic enzyme increased)*
- *Allergic symptoms (drug hypersensitivity, erythema, sinusitis, asthma, and seasonal allergy)*
- *Hypophosphatemia*

It is this medical reviewer's assessment that given the mechanism of action of etelcalcetide at lowering PTH levels and the fact that many of these symptoms have also been seen with the other currently approved calcimimetic, cinacalcet, that many of these AEs are likely to be drug related.

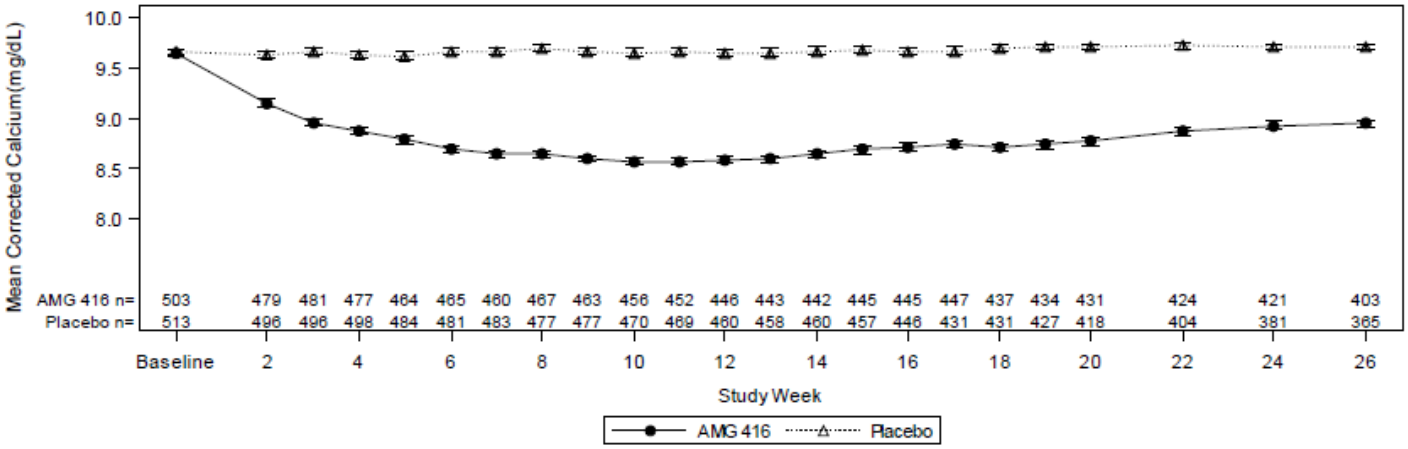
When comparing etelcalcetide to cinacalcet it appears that the risk of hypocalcemia and low blood calcium is greater with etelcalcetide which probably reflects the fact that it is more effective at lowering PTH levels. Given that etelcalcetide is administered intravenously it was initially considered that it might be less likely to cause GI symptoms compared to cinacalcet which is given orally and might locally irritate the GI tract. However, assuming that some of the GI symptoms are directly due to low serum calcium levels the fact that etelcalcetide is more likely to lower serum calcium levels may have limited that observed benefit as etelcalcetide was only slightly less likely to cause nausea than cinacalcet and there was no real difference in the rate of the vomiting between both drugs.

The higher rate of "cardiac failure" seen with etelcalcetide compared to cinacalcet using the MedDRA Analysis narrow SMQ search may be related to the increased frequency of hypotension seen with etelcalcetide compared to cinacalcet which also generated low p-values less than 0.05 in the Preferred Term MedDRA Analysis (see Table 42 & Table 43). That said the finding of increased cardiac failure was unexpected in this application as in the large 5 year outcome trial EVOLVE, cinacalcet, another calcimimetic, showed a reduction in the secondary endpoint of "heart failure" compared to placebo: 10.6% vs. 12.2% p=0.034. While it is not possible to draw conclusions between different trials, it is possible that the higher event rate seen in the active-controlled study with etelcalcetide compared to cinacalcet may reflect treatment benefit associated with the use of cinacalcet and not necessarily increased risk associated with the use of etelcalcetide; that would go along with why this medical reviewer identified no significant evidence of increased risk for all events of cardiac failure with etelcalcetide compared to placebo in the pivotal placebo-controlled trials, even though the applicant thought the difference while small was potentially concerning.

8.4.6. Laboratory Findings

SERUM CALCIUM-
In the placebo-controlled pivotal trials, 20120229 and 20120230, mean corrected serum calcium levels decreased from a baseline of 9.6mg/dL to about 8.6mg/dL by week 10 of treatment and then slightly drifted back up to 8.9mg/dL by the end of treatment at week 26. This is in contrast to no change from baseline in the placebo group. (b) (4) .

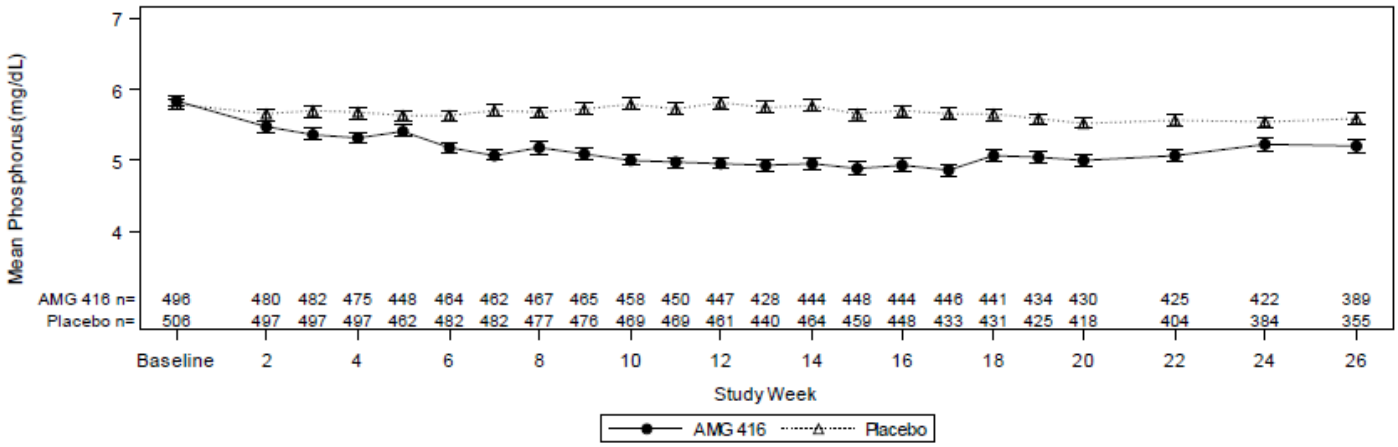
Figure 26 Mean (SE) Corrected Calcium (mg/dL) by Study Week during the 6-month Placebo Controlled Period (Pooled Safety Data from Studies 20120229 & 20120230)



Source Fig. 3 Summary of Clinical Safety

SERUM PHOSPHOROUS-
In the placebo-controlled pivotal trials, 20120229 and 20120230, mean serum phosphorous levels decreased from a baseline of 5.9mg/dL to about 5.0mg/dL between weeks 10 and 16 of treatment and then slightly drifted back up to 5.2mg/dL by the end of treatment at week 26. This is in contrast to a slight decrease of 0.2mg/dL from baseline to week 26 in the placebo group (b) (4)

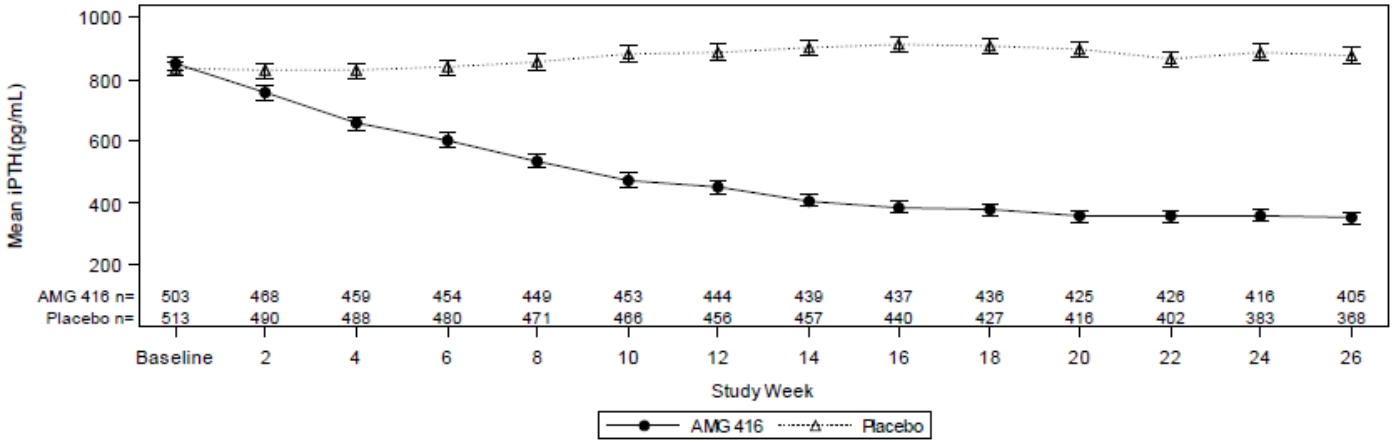
Figure 27 Mean (SE) Corrected Phosphorous (mg/dL) by Study Week during the 6-month Placebo Controlled Period (Pooled Safety Data from Studies 20120229 & 20120230)



Source Fig. 4 Summary of Clinical Safety

SERUM IPTH-
In the placebo-controlled pivotal trials, 20120229 and 20120230, mean serum iPTH levels decreased from a baseline of 847pg/mL to 374pg/mL by the end of treatment at week 26 ($p<0.001$), for a mean decrease of 56% from baseline. This is in contrast to a slight increase of from a baseline of 836pg/mL to 930pg/mL by week 26 in the placebo group, for an increase of 13%. Therefore the net placebo subtracted difference in serum iPTH from baseline to the end of treatment was 69%.

Figure 28 Mean (SE) iPTH (pg/mL) by Study Week during the 6-month Placebo Controlled Period (Pooled Safety Data from Studies 20120229 & 20120230)



Source Fig. 2 Summary of Clinical Safety

LIVER TESTS-
In general the rate of significant abnormalities in liver testing was low. In the placebo-controlled trials there were two subjects (0.4%) in the etelcalcetide treatment group with ALT levels > 3X ULN compared to 3 subjects (0.6%) in the placebo group, and two subjects (0.4%) in the etelcalcetide treatment group with AST levels > 3X ULN compared to 1 subject (0.2%) in the placebo group.

In the placebo-controlled trials there was one subject (0.2%) in the etelcalcetide treatment group with BILI levels > 2X ULN compared to 2 subjects (0.4%) in the placebo group.

None of these subjects met the definition of Hy's Law. The two subjects with elevated transaminases in the etelcalcetide treatment group were both from study 20120230:

23066006028 was a 58 year old Asian female who developed peak ALT 588U/L and peak AST

1002 U/L on Study Week 5 while in the etelcalcetide treatment group. Etelcalcetide was temporarily withheld but the work up did not find a cause for the elevated liver transaminases. Etelcalcetide was restarted on Study Week 10 and continued until week 26 when it was discontinued for iPTH < 100pg/mL.

23066010003 was a 35 year old black male who developed symptoms of nausea, vomiting and diarrhea, cough, fever and chills for several days during Study Week 17 while in the etelcalcetide treatment group and was hospitalized with a diagnosis of "acute hepatitis", peak ALT 748 U/L and peak AST 710 U/L, and low serum calcium at 6.5mg/dL with albumin at 3.1mg/dL. Etelcalcetide was discontinued but the work up did not identify a cause for the elevated liver transaminases. The subject was discharged 4 days later on a course of azithromycin with a diagnosis of acute hepatitis of unknown etiology. Etelcalcetide was not restarted after discharge from the hospital.

The one subject with elevated bilirubin in the etelcalcetide treatment group 22966169001 had metastatic biliary cancer and died during the follow up period after completing the study.

In the active-controlled study 20120360 no subjects in either treatment group had ALT > 3XULN and one subject in the cinacalcet group (0.3%) had an AST value > 3X ULN, but there was limited liver test monitoring in this study as liver tests were performed for most patients only at screening and the follow up visit at the end of the study. In addition the lab dataset did not include results obtained during an ER visit or hospitalization. Therefore they did not include one subject in this trial who had a serious AE of hepatic enzyme increased. Subject 36066073001 was a 40 year old white woman with a history of diabetic gastroparesis, erosive oesophagitis, GI haemorrhage and impaired gastric emptying who on Study Day 18 developed abdominal pain and hematemesis with coffee ground blood, while on 5mg etelcalcetide TIW. In the ER her blood glucose was > 600 mg/dL so she was started on an insulin drip, and received ondansetron, metoclopramide and hydromorphone for the pain and nausea. Labs at that time included ALT=762 U/L, AST=1461 U/L, total bili=0.5mg/dL, direct bili=0.1mg/dL, blood pH 7.17, bicarbonate 15 mmol/L, sodium 121 mmol/L, and potassium=6.4 mmol/L. She was diagnosed with diabetic gastroparesis, increased hepatic enzymes, and diabetic ketoacidosis with hyperkalemia. Abdominal ultrasound revealed mild ascites, edematous gallbladder with thickened wall, coarse liver echotexture suggestive of chronic liver damage. She improved and was discharged on Study Day 29. On Study Day 34 etelcalcetide was restarted. On study Day 50 repeat labs were AST=24 U/L (ULN=34 U/L), ALT=58 U/L (ULN=34 U/L), and total bili= 5.13 micromol/L (ULN=20.52 micromol/L). The study drug was discontinued due to repeat elevated liver tests. Follow up tests on Study Day 65 were back to normal AST=15 U/L, ALT=15 U/L, total bili=3.42 micromol/L. The applicant commented that this case of a positive rechallenge test was confounded by the findings of the ultrasound which suggest the patient had chronic liver disease.

In the open label extension study 20130213 there was one patient (22921001001) a 67 year old man from the Czech Republic who developed elevated transaminases (ALT 324 U/L, AST 259 U/L, bili 0.4mg/dL) suspected to be due to liver injury 3 weeks after starting etelcalcetide. Etelcalcetide was discontinued and the liver test returned to normal. Despite the abnormal tests he was asymptomatic. The hospital work up could not identify a cause for the abnormal liver tests (e.g. normal abdominal US, viral hepatitis tests, CMV, ANA, CRP). There were no other co-suspect medications. According to the "Additional Info from (b) (6) in the CSR Case Narrative he was given a decreased dose resulting in further increase in liver tests, so the investigational drug was discontinued. This medical reviewer initially mistook the increase in liver tests following the decreased dose as a rechallenge, however the applicant confirmed that the lower dose occurred only two days after the initial enzyme elevation was noted and as such so was too soon to permit normalization of the liver tests to consider the lower dose a true rechallenge test.

In open label extension study 20120231 there was one patient (23066004003) a 59 year old black man whose dose was down titrated to 2.5mg TIW on Study Day 222 due to low iPTH < 100pg/mL, then 36 days later on Study Day 258 he presented to the ER with confusion, hypotension, due to acute hepatitis, encephalopathy and a non-ST elevation MI. Labs at the time included ALT=1176 U/L, AST=3211 U/L, total bili=2.5 (no units given). Etelcalcetide was discontinued and liver tests improved so the subject was discharged to a rehab facility on Study Day 264. On Study Day 276 he was formally diagnosed with cryptogenic cirrhosis (cirrhosis of unknown etiology) and hypotension which were ongoing.

Medical officer's comments-

The isolated cases in the etelcalcetide treatment group in the placebo-controlled studies do not point to a specific increased hepatic risk. That said there continued to be a small number of patients with hepatic enzyme elevations during treatment with etelcalcetide during the open-label extensions, one case of a positive rechallenge test and one case of persistent liver test abnormalities despite lowering the etelcalcetide dose suggesting possible drug-related injury. In response to these findings the applicant emphasized that there was no evidence of liver toxicity in the nonclinical studies, etelcalcetide is not a substrate, inhibitor, or inducer of CYP-450 liver enzymes and not a substrate or inhibitor of liver transporters, and there is only very minor hepatic elimination in CKD patients on hemodialysis. Therefore they concluded that given "the safety and efficacy of etelcalcetide have not been evaluated in subjects with impaired liver function as such subjects were excluded from the clinical studies, there is currently no strong evidence that etelcalcetide poses additional risk to patients with active liver disease".

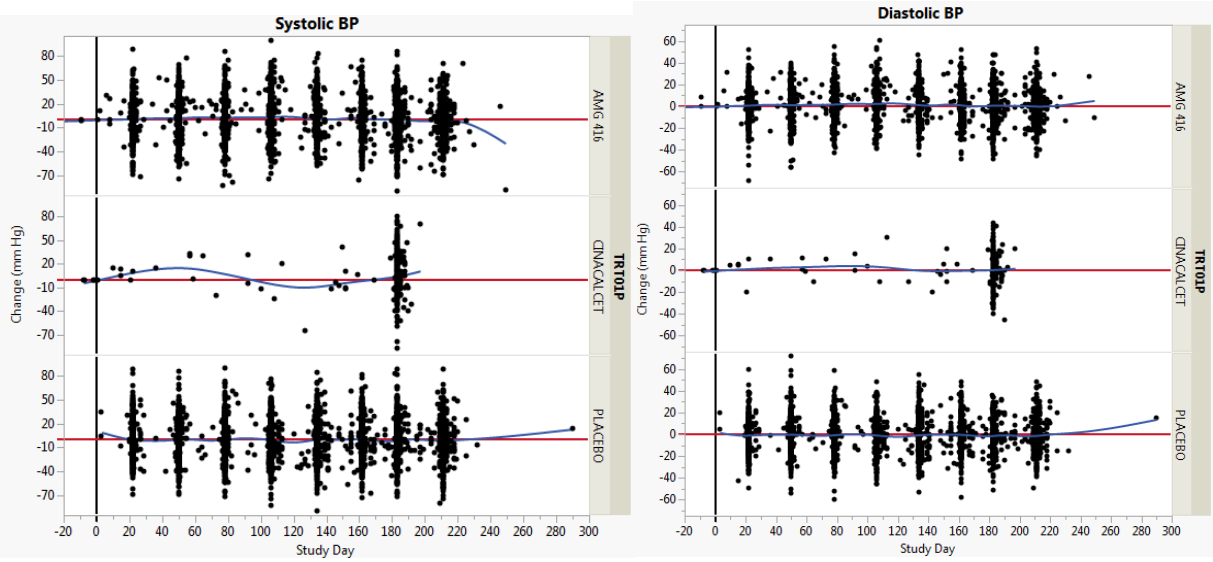
OTHER LAB VALUES-
No significant changes were noted in other serum chemistry or hematology parameters.

8.4.7. **Vital Signs**

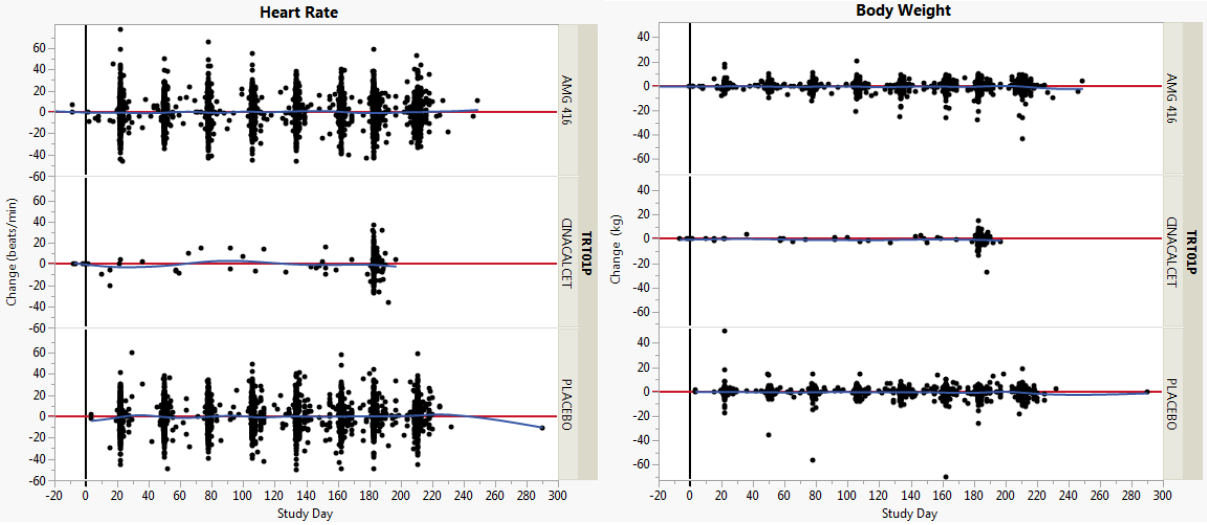
Hypertension and hypotension are both listed as AEs in Table 37 occurring in > 5% of subjects in either treatment arm of the placebo-controlled studies. In study 20120229 hypertension was slightly more common in the placebo group (6.7% vs. 4.8%) while in study 20120230 it was slightly more common in the etelcalcetide group (7.5% vs. 4.6%). In study 20120229 hypotension was slightly more common in the etelcalcetide group (6.4% vs. 3.9%) while in study 20120230 it was slightly more common in the placebo group (6.2% vs. 5.6%). Therefore there was no consistent pattern for either hypertension of hypotension in these trials and the small differences likely relate to normal variability in the hemodialysis population.

The mean change to week 24 in the placebo-controlled dataset for systolic BP was 2.5mm Hg and 1.8 mm Hg in the etelcalcetide and placebo groups, respectively (ISS Table 7.27). The mean change to week 24 in the placebo-controlled dataset for diastolic BP was 1.1mm Hg and 0.2 mm Hg in the etelcalcetide and placebo groups, respectively (ISS Table 7.28). The mean change in heart rate was 0.6 beats/min and -0.3 beats/min in the etelcalcetide and placebo groups, respectively (ISS Table 7.28.1).

Similarly looking at the individual systolic and diastolic BP values over time showed no change from baseline over the course of the treatment in any of the treatment arms in the pivotal placebo-controlled and active-controlled studies. Similar results were seen with HR and body weight.



ISS ADVS dataset Systolic BP and Diastolic BP CHG vs. ADY by TRT01P



ISS ADVS dataset Heart rate and Body Weight CHG vs. ADY by TRT01P

8.4.8. **Electrocardiograms (ECGs)**

In the clinical development program, 12-lead electrocardiogram (ECG) assessments were performed prior to dialysis and at 10 to 30 min post dose at baseline, weeks 5, 13 and 26 in the placebo-controlled trials 20120229 and 20129230. ECGs were also performed prior to dialysis at baseline and weeks 12 and 27 in the active controlled study 20120360. All recordings were performed in triplicate approximately 2 min apart. Given that hypocalcemia is known to increase the QTc interval, an integrated ECG analysis was conducted to assess the potential for etelcalcetide to affect prolongation of QT intervals (see section 8.4.9).

8.4.9. **QT**

The QT-IRT had previously reviewed and agreed to a QT waiver request submitted by sponsor under IND 109773 for the following rationales:

> "A thorough QTc study cannot be safely conducted with KAI-4169 in healthy subjects because hypocalcemia was observed following a single 10 mg dose, limiting the exposure that can be safely achieved in healthy volunteers. In addition, a thorough QTc study in either healthy volunteers or hemodialysis subjects will produce results that are confounded by the direct effect of reductions in serum calcium on QTc, making any meaningful interpretation difficult. Furthermore, a significant number of hemodialysis subjects have prolonged QTc (i.e., > 450 ms) at baseline, so the inclusion of a positive control to assess assay sensitivity may not be acceptable in this population."

The ECG summary report and proposed labeling were reviewed by Jiang Lu of the CDER DCRP QT Interdisciplinary Review Team. The review determined that administration of etelcalcetide was associated with reductions in serum calcium, and a reduction in serum calcium was associated with QTc interval prolongation in both nonclinical and clinical studies. Also the estimated difference in the mean change from baseline in predialysis QTc interval between etelcalcetide and placebo was above the threshold of regulatory concern for thorough QT studies (i.e. mean difference > 5 ms with an upper bound of the 95% confidence interval [CI] of > 10 ms).

Electrocardiogram categorical analyses shown in Table 44 indicate that the etelcalcetide treatment group had a higher subject incidence of post baseline increases of > 60msec in QTc interval compared with the placebo group.

Table 44 QTcF Interval Maximum Post-baseline and Maximum Increase from Baseline Categories (6-month Placebo-controlled Pooled Safety Data)

	20120229		20120230		Total placebo-controlled studies	
QTcF	Placebo (N = 254) n (%)	AMG 416 (N = 251) n (%)	Placebo (N = 259) n (%)	AMG 416 (N = 252) n (%)	Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)
Baseline – n (%)						
≤ 450 msec	210 (82.7)	179 (71.3)	199 (76.8)	198 (78.6)	409 (79.7)	377 (75.0)
> 450 to 480 msec	25 (9.8)	46 (18.3)	31 (12.0)	36 (14.3)	56 (10.9)	82 (16.3)
> 480 to 500 msec	6 (2.4)	6 (2.4)	14 (5.4)	7 (2.8)	20 (3.9)	13 (2.6)
> 500 msec	4 (1.6)	2 (0.8)	2 (0.8)	0 (0.0)	6 (1.2)	2 (0.4)
Maximum post-baseline – n (%)						
≤ 450 msec	176 (69.3)	123 (49.0)	173 (66.8)	133 (52.8)	349 (68.0)	256 (50.9)
> 450 to 480 msec	49 (19.3)	72 (28.7)	47 (18.1)	71 (28.2)	96 (18.7)	143 (28.4)
> 480 to 500 msec	13 (5.1)	14 (5.6)	15 (5.8)	22 (8.7)	28 (5.5)	36 (7.2)
> 500 msec	4 (1.6)	14 (5.6)	6 (2.3)	10 (4.0)	10 (1.9)	24 (4.8)
Maximum increase from baseline – n (%)						
≤ 30 msec	221 (87.0)	167 (66.5)	223 (86.1)	178 (70.6)	444 (86.5)	345 (68.6)
> 30 to 60 msec	16 (6.3)	46 (18.3)	13 (5.0)	53 (21.0)	29 (5.7)	99 (19.7)
> 60 msec	0 (0.0)	4 (1.6)	0 (0.0)	2 (0.8)	0 (0.0)	6 (1.2)

QTcF = QT interval using Fridericia's correction
This pool includes data from the 2 placebo-controlled Studies 20120229 and 20120230.
On-treatment approach: data collected on or before the last nonmissing dose of investigational product were included.
The observations with the following diagnoses or findings were excluded from the analyses: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.
Source: Modified from ISS Table 7.44

Source Table 5 ECG Summary report

In the 6-month placebo-controlled combined dataset the incidence of adverse events in the SMQs of ventricular tachyarrhythmias (0.4% etelcalcetide; 0.8% placebo) and Torsade de pointes/QT prolongation (1.2% etelcalcetide; 0.6% placebo) was low and similar in both treatment groups (Applicant's Summary of Clinical Safety Table 20). In Study 20120360, only 1 subject had an adverse event in the SMQs of ventricular tachyarrhythmias or Torsade de

pointes/QT prolongation (1 etelcalcetide subject [0.3%] with an event of electrocardiogram QT prolonged).

The applicant's proposed labeling:

> (b) (4) In the combined placebo-controlled studies, (b) (4) patients (b) (4) [PARSABIV] (b) (4) a maximum increase from baseline of > 60 msec in the QTcF interval (1.2% [PARSABIV], 0% placebo). The (b) (4) incidence of maximum post-baseline predialysis QTcF > 500 msec in the [PARSABIV] and placebo groups was 4.8% and 1.9%, respectively.

was acceptable from IRT's perspective.

8.4.10. **Immunogenicity**

The immunogenicity data submitted by the applicant was reviewed by Bruce Huang, Ph.D. in the Division of Biotechnology Research and Review II. The review concluded that the SPR-based immunogenicity assay was properly validated with reasonable binding and confirmatory cut points, sensitivity, specificity and resistance to onboard drug concentration, and was suitable for evaluation of the potential presence of anti-etelcalcetide antibodies in patient sera. Binding antibodies to etelcalcetide were detected in 71 out of 995 total patients (7.1%). However, 80.3% of the 71 patients with positive anti-etelcalcetide antibodies had pre-existing anti-drug antibodies in their sera. Therefore only 13 patients (1.5% of all pts) developed anti-drug antibodies during 6 months of exposure to etelcalcetide. According to the review the applicant conducted sufficient in vitro experiments to show that a cell-based neutralizing antibody assay was impractical since even high affinity antibodies raised against etelcalcetide did not have blocking ability with regards to the drug activity, therefore no neutralizing antibody data was submitted.

There was no significant impact of anti-etelcalcetide antibodies on the concentration of etelcalcetide in the trial subjects over time, irrespective of whether they had pre-existing anti-drug antibodies or developed them over the course of the clinical trials. There was no impact of the presence of negative, pre-existing or developing anti-drug antibodies on change from baseline in iPTH during the EAP. Nor were patients receiving the highest doses of etelcalcetide more likely to develop anti-drug antibodies. While hypersensitivity and infusion-reactions were noted using a hypersensitivity SMQ in 4.7% of antibody negative patients the rate was lower in subjects with anti-drug antibodies (e.g. 2.3% due to one subject with preexisting anti-drug antibodies and 0% due to no subjects with developing anti-drug antibodies, see Table 6.32 ISS). Among patients treated with etelcalcetide there was no clear association with anti-drug antibodies and specific adverse reactions in subjects with anti-drug antibody data. In

conclusion, there is no evidence that the pre-existing or developing anti-etelcalcetide antibodies affected the PK, efficacy or safety profile of etelcalcetide.

8.5. Analysis of Submission-Specific Safety Issue

8.5.1. HYPOCALCEMNIA

The rate of AEs related to low serum calcium levels measured in the 6-month placebo-controlled trials was substantially greater in the etelcalcetide treatment group compared to placebo: "blood calcium decreased" (64% vs. 10%) and "hypocalcemia" (7.0% vs. 0.2%). The rate of AEs related to low serum calcium levels measured in the 6-month active-controlled study compared to cinacalcet was also greater with etelcalcetide although the difference between the comparator groups was much smaller: "blood calcium decreased" (69% vs. 60%) and "hypocalcemia" (5.0% vs. 2.3%). Most events of symptomatic hypocalcemia and asymptomatic blood calcium decreased were mild or moderate in severity (see Table 45). Cases which were coded as serious or severe occurred at similar rates between etelcalcetide and the comparator groups in these studies.

Table 45 Number of Subjects with AEs of Blood Calcium Decreased or Hypocalcemia by Seriousness, Severity and Treatment Group in Studies 20120229, 2010230 and 20120360

Study	AESER	AESEV	AMG416	Placebo
20120229	N	Mild	116	18
20120229	N	Moderate	66	4
20120229	N	Severe	0	1
20120230	N	Mild	141	21
20120230	N	Moderate	66	10
20120230	N	Severe	2	0
Study	**AESER**	**AESEV**	**AMG416**	**Cinacalcet**
20120360	N	MILD	194	156
20120360	N	MODERATE	68	83
20120360	N	SEVERE	5	4
20120360	Y	MODERATE	1	0
20120360	Y	SEVERE	0	1

Source ISS ADAE dataset; AESER=Y refers to serious cases, AESEV -severity

Looking at the lowest serum calcium recorded per patient during the 6-month placebo-controlled studies showed that most of the difference between treatment groups was in CTCAE grades 1 and 2, 7.0 to 8.3mg/dL range (71%-20%=51%), although there were also slightly more patients with serum calcium levels below 7.0mg/dL (CTCAE grade 3) in the etelcalcetide group compared to placebo (6%-2%=4%).

Table 46 Number of Subjects with Their Lowest Corrected Serum Calcium Below the Lower Limit of Normal by CTCAE Grade and Treatment Group for Studies 20120229 & 20120230

CTCAE Grade	Lowest Serum Ca	229 placebo N=254		230 placebo N=260		229 AMG 416 N=254		230 AMG 416 N=255		Total % difference AMG416-placebo
		n	%	n	%	n	%	n	%	%
1	8.0-<8.4	23	9	31	12	38	15	41	16	5
2	7.0-<8.0	24	9	26	10	138	54	147	58	46
3	6.0-<7.0	4	2	6	2	13	5	17	7	4
4	<6.0	3	1	3	1	3	1	5	2	0
	total	54	21	66	25	192	75	210	82	55

ADLB 229 & 230, PARAMCD=CCAC, ADY>0, TRT01A, AMG 416=etelcalcetide

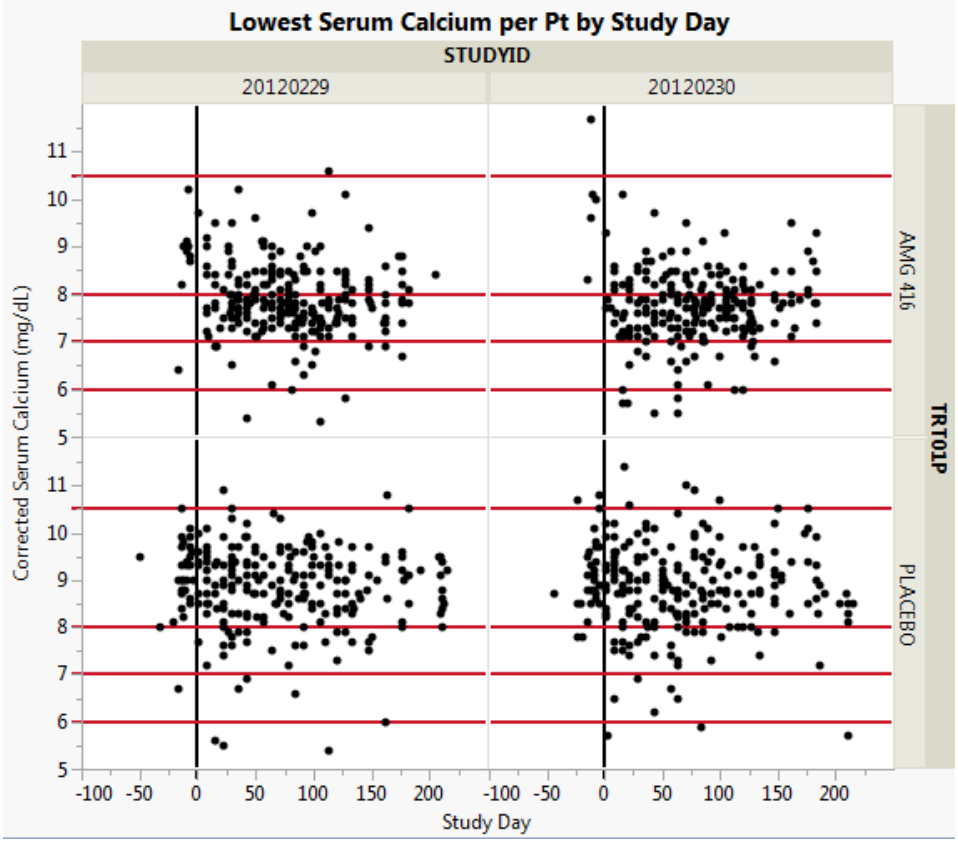
Looking at the lowest serum calcium recorded per patient during the 6-month active-controlled study using cinacalcet as the comparator showed again that there were slightly more patients with low calcium levels with etelcalcetide in CTCAE grades 1 & 2, 7.0 to 8.3mg/dL range (76%-64%=12%) compared to the comparator, with no real difference in the rates with serum calcium levels below 7.0mg/dL (CTCAE grades 3 &4).

Table 47 Number of Subjects with Their Lowest Corrected Serum Calcium below the Lower Limit of Normal by CTCAE Grade and Treatment Group for Study 20120360

CTCAE Grade	Lowest Serum Ca	360 AMG 416 N=340		360 Cinacalcet N=343		Total % difference AMG416-cinacalcet
		n	%	n	%	%
1	8.0-<8.4	69	20	52	15	5
2	7.0-<8.0	190	56	169	49	7
3	6.0-<7.0	21	6	26	8	-2
4	<6.0	9	3	6	2	1
	total	289	85	253	74	11

ADLB 360, PARAMCD=CCAC, ADY>0, TRT01A

Figure 29 Lowest Serum Calcium per Patient by Treatment group for Placebo-controlled Studies



Source ADLB from studies 229 & 230 each patient supplies only their lowest single value

A plot of the lowest serum calcium level per patient for the placebo-controlled pivotal studies demonstrates that there were more calcium values above the upper limit of normal 10.5 mg/dL in the placebo groups. Calcium values are evenly distributed across the normal range between 8 and 10.5mg/dL in the placebo groups while most of the values in the etelcalcetide group are packed into the lower half of the normal range, and there is also a clear increase in values between 7 and 8mg/dL below the lower limit of normal in the etelcalcetide group compared to placebo. Note also that there are values below 7mg/dL prior to Study Day 1 suggesting that there is a low rate of hypocalcemia in this study population even before investigational drug administration.

No subjects in the placebo-controlled studies, 20120229 and 20120230, or the active-controlled study, 20120360, had a serious adverse event of hypocalcemia. Hypocalcemia rarely led to discontinuation of etelcalcetide. In the 6-month placebo-controlled combined dataset, 5 (1%) etelcalcetide subjects discontinued investigational product due to an event of hypocalcemia compared to no subjects in the placebo group. The rates of events potentially associated with

increased neuromuscular irritability secondary to low calcium were also higher in the etelcalcetide group compared to placebo with paresthesia (4.8% etelcalcetide; 0.6% placebo), hypoesthesia (1.8% etelcalcetide; 0.8% placebo), and myalgia (1.6% etelcalcetide; 0.2% placebo) (ISS Table 6.13). In the active-controlled study 20120360, no subjects in the etelcalcetide arm and 2 (0.6%) subjects in the cinacalcet arm had hypocalcemia adverse events that led to discontinuation of investigational product.

Medical officer's comments-

Low blood serum calcium levels and hypocalcemia are known risks associated with the use of calcimimetics. Most of the events in the clinical trials were classified as CTCAE grades 1 and 2 and when they were associated with AEs they were classified mostly as mild or moderate in severity. That said low serum calcium levels were seen despite a greater increase in the use of vitamin D sterols (31% vs. 10%) and calcium supplements (50% vs. 9%) in the etelcalcetide treatment arms compared to placebo, and there is always the potential for more severe outcomes in real use settings with less stringent safety monitoring. Labeling will recommend against initiating dosing in subjects with serum calcium levels below the lower limit of normal and will include information on symptoms of hypocalcemia to aid healthcare professionals to identify cases of concern. Given that etelcalcetide appears somewhat more effective at lowering PTH levels than cinacalcet it is not unexpected that it might result in a slightly higher incidence of hypocalcemia.

8.5.2. **HYPOPHOSPHATEMIA**

There were 7 (1.4%) patients with AEs of hypophosphatemia in the 6-month placebo-controlled trials with etelcalcetide compared to only 1 (0.2%) patient in the placebo group. None of the cases were considered severe. Of the 7 cases, 4 were considered mild in severity and 3 were considered moderate, and none required discontinuation of the study medication.

There were 2 patients (0.6%) with AEs of hypophosphatemia in the 6-month active-controlled trials with etelcalcetide compared to 1 patient (0.3%) in the cinacalcet group with 2 events. The single case in the cinacalcet treatment group was considered serious and required the drug dose to be interrupted and eventually discontinued.

Looking at the lowest serum phosphorous level recorded per patient during the 6-month placebo-controlled studies showed that there was a small increase in the lowest observed phosphorous levels in the etelcalcetide group compared to placebo in CTCAE grades 1, 2, and 3 of 9%-5%=4%, 13%-7%=6% and 13%-6%=7% respectively (see Table 48).

Table 48 Number of Subjects with Their Lowest Serum Phosphorous Level below the Lower Limit of Normal by CTCAE Grade and Treatment Group for Studies 20120229 & 20120230

CTCAE Grade	Lowest Serum PO4	229 placebo N=254		230 placebo N=260		229 AMG 416 N=254		230 AMG 416 N=255		Total % difference AMG 416-placebo
		n	%	n	%	n	%	n	%	%
1	2.5 -<2.8	10	4	19	7	30	12	17	7	4
2	2.0-<2.5	19	7	19	7	31	12	36	14	6
3	1.0-<2.0	13	5	16	6	25	10	41	16	7
4	<1.0	0		0		0		0		0
	total		16		20		34		37	17

ADLB 229 & 230, PARAMCD=PHOSC, ADY>0, TRT01A, AMG 416=etelcalcetide

Looking at the lowest serum phosphorous level recorded per patient during the 6-month active-controlled studies showed that there was a also a small increase in the lowest observed phosphorous levels in the etelcalcetide group compared to cinacalcet in CTCAE grades 1, 2, and 3 of 9%-5%=4%, 9%-8%=1% and 11%-7%=4% respectively.

Table 49 Number of Subjects with Their Lowest Serum Phosphorous below the Lower Limit of Normal by CTCAE Grade and Treatment Group for Study 20120360

CTCAE Grade	Lowest Serum PO4	360 AMG 416 N=340		360 Cinacalcet N=343		Total % difference AMG416-cinacalcet
		n	%	n	%	%
1	2.5 -<2.8	29	9	16	5	4
2	2.0-<2.5	29	9	27	8	1
3	1.0-<2.0	37	11	23	7	4
4	<1.0	0	0	0	0	0
	total		29		20	9

Medical officer's comments-

Low blood serum phosphorous levels are a known risk associated with the use of calcimimetics which lower serum PTH. Most of the events in the clinical trials were classified as CTCAE grades 1, 2 or 3. None of the cases in the etelcalcetide treatment group were considered serious and all of the cases were mild or moderate in severity. Serum phosphorous levels will need to be monitored regularly during treatment with etelcalcetide. Low phosphorous levels can generally be treated with changes to diet or concomitant medications without need for interrupting the dose of the calcimimetic.

8.5.3. **ADYNAMIC BONE DISEASE**

Adynamic bone disease is a term coined to represent low bone turnover as evidenced by a low bone formation rate (BFR) without osteoid accumulation (osteomalcia) and without fibrosis (mixed uremic osteodystrophy). On bone biopsy there are few or no osteoblasts without evidence of fibrosis or excess unmineralized osteoid. Adynamic bone disease is associated with the decreased ability to repair microdamage in bone which places subjects at higher risk of fracture and also is associated with vascular calcifications[3] probably due to the decreased buffering capacity of the abnormal bone. While there is an association with low PTH levels and adynamic bone disease in hemodialysis patients, a diagnosis of adynamic bone disease can only be made by biopsy. So the fact that there were no subjects diagnosed with an adverse event of adynamic bone disease during the placebo-controlled trials is not reassuring given that bone biopsies were not included in the study protocols. Current KDIGO guidelines recommend titrating iPTH levels to 2 to 9 times the upper limit of normal of the iPTH assay (e.g. 130 to ~600pg/mL) to avoid the risk for adynamic bone disease. In a study of 175 hemodialysis patients who had bone biopsies without evidence of aluminum toxicity, low BFRs were seen in 80% of subjects with iPTH levels < 100pg/mL[4]. Consistent with this the European Renal Best Practice Work Group suggests a PTH threshold of < 100 pg/mL for evidence of low bone turnover. According to Wang et al. the predictive value of the low PTH can be increased by also looking for low Bone Specific Alkaline Phosphatase (BSAP) as low bone turnover disease is unlikely with BSAP $\geq$20ng/mL. A bone histomorphometry study of long term treatment with cinacalcet (BONAFIDE) in 77 dialysis patients with secondary hyperparathyroidism identified two subjects (3%) with adynamic bone disease, with low bone formation rate per tissue area and other histomorphometric findings of adynamic bone disease after 12 months of treatment with cinacalcet[5]. In one patient PTH levels went from 331pg/mL at screening to persistently below 150pg/mL during the study, and BSAP decreased from 21.5 to 14.6ng/mL. In the other patient PTH decreased from 711 to 236pg/mL during the study but was seen as low as 106pg/mL and BSAP decreased from 63.2 to 9.3ng/mL. Note in these two cases there were marked changes in iPTH from baseline but neither was consistently below 100pg/mL and yet they developed adynamic bone disease. The authors mention that BSAP levels $\leq$10 ng/mL may provide an additional biomarker of adynamic bone disease in addition to low serum PTH.

The applicant's pooled analysis of the iPTH data in response to the 15 July Information Request

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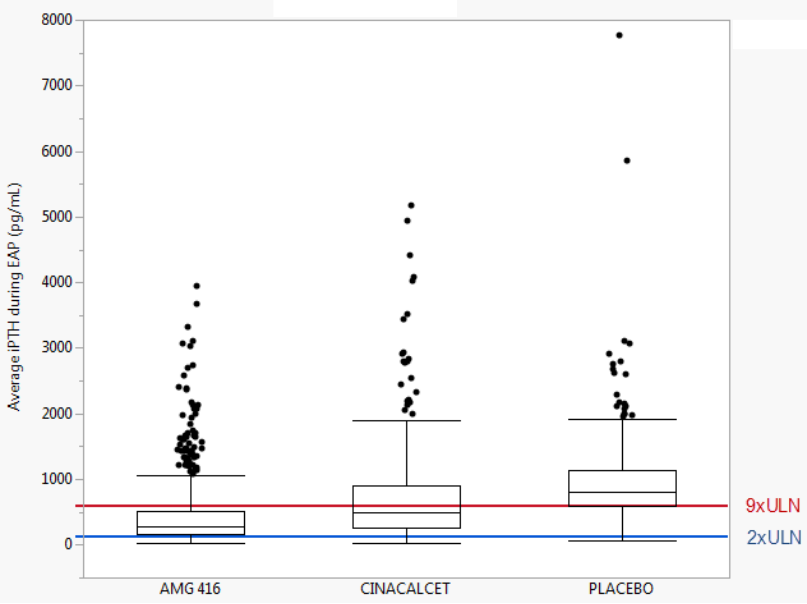
[3] **Bover J1, Ureña P2, Brandenburg V3, Goldsmith D4, Ruiz C5, DaSilva I5, Bosch RJ5.** Adynamic bone disease: from bone to vessels in chronic kidney disease. Semin Nephrol. **2014 Nov;34(6):626-40**

[4] **Wang M1, Hercz G, Sherrard DJ, Maloney NA, Segre GV, Pei Y**. Relationship between intact 1-84 parathyroid hormone and bone histomorphometric parameters in dialysis patients without aluminum toxicity. Am J Kidney Dis. 1995 Nov;26(5):836-44.

[5] **Behets GJ, Spasovski G, Sterling LR, Goodman WG, Spiegel DM, De Broe ME, D'Haese PC**. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015 Apr;87(4):846-56

confirmed that a much larger % of subjects in the pivotal trials had iPTH levels < 100pg/mL in etelcalcetide treatment groups 40% compared to placebo 4.7%. This resulted in at least one dose suspension due to two consecutive iPTH levels < 100pg/mL in 25% of the etelcalcetide patients. While it can be argued that appropriate labeling can be used to limit the risk of low iPTH and it is only chronically low iPTH levels that lead to adynamic bone disease, this medical reviewer is concerned that a significant number of subjects in the etelcalcetide treatment groups continued to have low iPTH levels < 100pg/mL during the EAP at weeks 20 to 27 well after dose titration was complete, as the applicant states that most patients were already on what were considered stable doses at 9 to 10 weeks into the study. Figure 30 shows average iPTH levels for patients during the EAP at the end of treatment from pooled data from the placebo-controlled pivotal trials, 20120229 and 20120230 and the active-controlled trial 20120360. More subjects reached the recommended iPTH range of 2 to 9X ULN with treatment with etelcalcetide compared to cinacalcet or placebo, consistent with the greater efficacy of the new calcimimetic.

Figure 30 Average iPTH during the EAP for Studies 20120229, 20120230 and 20120360



Source PTHIAVG from ADLB2 from ISS, JMP outlier boxplot-line median 50%, ends of box 25th and 75th percentiles

However looking at only the lowest iPTH levels it becomes clear that a significant % of the patients in the etelcalcetide group are being over titrated even though the dosing guidelines in all of these studies recommended suspending the dose for two consecutive iPTH values <100pg/mL. In Figure 31 values <100 pg/mL are **bolded**. There are many more patients with low iPTH values < 100 pg/mL in the etelcalcetide treatment group 52/754=6.9% compared to cinacalcet 10/310=3.2% and placebo 2/456=0.4%. Looking at the last BSAP values in these 64 subjects showed that more patients had both low iPTH values < 100 pg/mL and low BSAP < 10

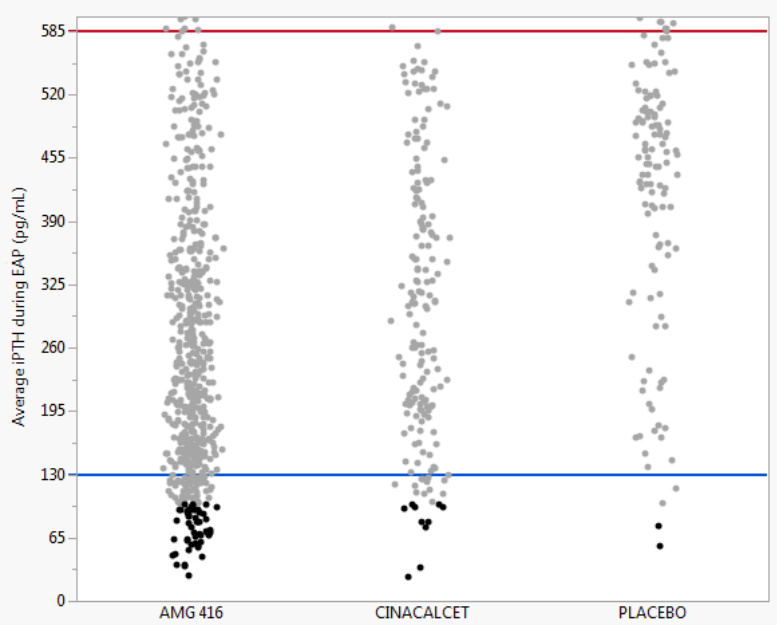
µg/L in the etelcalcetide treatment group 18/754=2.4% compare to cinacalcet 3/310=1.0% and placebo 1/456=0.2%, suggesting that subjects treated with etelcalcetide were at greater risk of developing adynamic bone disease.

Medical Officer's comments-

While the subset of etelcalcetide subjects with both iPTH levels < 100 pg/mL and low BSAP < 10 µg/L is small at 2.4% these conditions were chosen as a worst case scenario and it is possible that subjects with slightly higher levels of iPTH levels up to 2X ULN (e.g. iPTH <130 pg/mL) and BSAP levels up 20 µg/L may still be at risk. This would correspond to 96/754=12.7% of subjects in the etelcalcetide treatment group compared to 14/310=4.5% in the cinacalcet group and 3/456=0.7% on placebo.

Given that the titration conditions were similar in these trials (e.g. dose suspension for two consecutive iPTH values < 100 pg/mL) for the different study treatments it is not clear why etelcalcetide should have resulted in so many more subjects with very low iPTH levels compared to cinacalcet during the EAP. One possibility is the fact that plasma accumulation of etelcalcetide beyond the first few months of treatment was not expected by the treating physicians and they did not adequately down titrate the dose near the end of the 6 month study period. Figure 22 demonstrates that there was some dose down titration between months 2 and 6 in the placebo controlled studies, but it may not have been adequate to prevent over treatment in some cases. An alternative possibility is that the lowest available dose of 2.5mg TIW may still be too high for some patients and that dose adjustments may need to be titrated more precisely rather than simply as multiples of the 2.5 and 5.0 mg available vials. That said given that the dosage form is a solution of known concentration healthcare professionals should be able to perform appropriate dose adjustments with the recommended regular monitoring of iPTH and serum calcium as long as the package insert gives appropriate recommendations.

Figure 31 Average iPTH during the EAP for Studies 20120229, 20120230 and 20120360 Low Values below 600pg/mL



Source PTHIAVG from ADLB2 from ISS, AMG 416=etelcalcetide, **values < 100pg/mL are bolded**.

8.6. Safety Analyses by Demographic Subgroups

The applicant compared SMQs of cardiac failure, convulsions, hypersensitivity, hypocalcemia, Torsade de pointes-QT prolongation, ventricular tachyarrhythmias, and AEs of interest of hypophosphatemia, and infusion reaction by the following subgroups: gender; age (< 65, ≥65, ≥75); race (black, white/other); region (North America, Europe, Other), mode of dialysis (hemodialysis, hemodiafiltration); dialysis vintage (≤1 yr, >1 yr ≤5 yr, >5 yr); screening iPTH <600pg/mL, >600 ≤1000pg/mL, >1000pg/mL); enrollment into open label extension 20120231 (yes, no); baseline dialysate calcium (< 2.5mEq/L; ≥ 2.5mEq/L); baseline vitamin D status (yes, no); baseline calcium-containing phosphate binders or calcium supplement use (yes, no).

Differences were seen in the following categories:

Gender-
There was a higher frequency of “blood calcium decreased” (66% vs. 60%) and “hypocalcemia” (8.1% vs. 5.1%) in men than women treated with etelcalcetide.

Age-(< 65, ≥65, ≥75)
There was a higher frequency of "blood calcium decreased" (68% vs. 57%) and "hypocalcemia" (8.6% vs. 4.0%) in subjects treated with etelcalcetide by age < 65 years vs. > 65 years, respectively, while the rate was intermediate for age > 75 at (65%) for "blood calcium decreased" and (6.9%) for "hypocalcemia" showing there was no clear trend with respect to age.

There was a lower frequency of "heart failure" (2.1% vs. 5.1% vs. 5.6%) in subjects treated with etelcalcetide by age < 65 years vs. > 65 years, vs. > 75 years, respectively. This would be expected as elderly subjects are more likely to develop cardiac disease.

Race- (black, white/other)
There was a higher frequency of "blood calcium decreased" (68% vs. 53%), "hypocalcemia" (8.2% vs. 3.7%) and infusion reactions (21% vs. 16%) in white subjects compared to black subjects treated with etelcalcetide.

Region-(North America, Europe, Other)
Subjects in other regions had the highest subject incidence of blood calcium decreased (83%) and hypocalcemia (18%), followed by subjects in Europe (67% blood calcium decreased and 7.0% hypocalcemia) and subjects in North America (58% blood calcium decreased and 4.7% hypocalcemia).

Subjects in Europe had the highest subject incidence of infusion reactions (27%), followed by subjects in other regions (18%) and subjects in North America (16%).

Mode of Dialysis-(hemodialysis, hemodiafiltration)
Subjects on hemodialfiltration were less likely to have cardiac failure (1.4% vs. 3.5%), hypersensitivity (1.4% vs. 4.8%), and hypocalcemia (5.8% vs. 7.1%), but were more likely to have blood calcium decreased (70% vs. 63%), and infusion reactions (30% vs. 18%) than subjects on standard hemodialysis.

Dialysis Vintage-(≤1 yr, >1 yr ≤5 yr, >5 yr);
Subjects with the greatest dialysis vintage >5years had the least incidence of cardiac failure (2.0%) vs. subjects with < 1 year of vintage (3.4%) and 1 to 5 years of vintage (4.1%).

Subjects with the greatest dialysis vintage >5years had the least incidence of blood calcium decreased (55%) vs. subjects with < 1 year of vintage (68%) and 1 to 5 years of vintage (71%).

Subjects with the intermediate 1 to 5 years of vintage had the least incidence of infusion reactions (17%) vs. subjects with >5year of vintage (21%) and < 1 year of vintage (27%).

Screening iPTH- (< 600pg/mL, >600 ≤1000pg/mL, >1000pg/mL)
Subjects with the lowest screening iPTH (< 600pg/mL) had the highest incidence of hypersensitivity (6.5%) vs. subjects with intermediate screening iPTH (>600 ≤1000pg/mL) with (4.1%) and those with the highest screening iPTH (>1000pg/mL) at (1.8%).

Subjects with the lowest screening iPTH (< 600pg/mL) had the lowest incidence of blood calcium decreased (55%) and hypocalcemia (4.1%) vs. subjects with intermediate screening iPTH (>600 ≤1000pg/mL) with 67% and 9.0%, respectively, and those with the highest screening iPTH (>1000pg/mL) with 70% and 7.1%, respectively.

Enrollment into open label extension 20120231 (yes, no)-
Subjects not enrolled into the open label extension did not have a higher incidence of "blood calcium decreased" 52%, no vs. 67%, yes, but they did have a slightly higher incidence of "hypocalcemia" 7.6%, no vs. 6.8%, yes.

Subjects not enrolled into the open label extension had a slightly higher incidence of "infusion reactions" 24% vs. 18%, "Torsade de pointes-QT prolongation (SMQ)" 2.5% vs. 0.8% and "Ventricular tachyarrhythmias (SMQ)" 1.7% vs. 0%.

Baseline Dialysate Calcium (< 2.5mEq/L; ≥ 2.5mEq/L)-
Subjects with baseline dialysate < 2.5mEq/L did not have a higher incidence of "blood calcium decreased" 60% vs. 64% but they did have a slightly higher incidence of "hypocalcemia" 8.1% vs. 6.1%.

Baseline Vitamin D status (yes, no)-
Subjects on vitamin D analogs at baseline had a lower incidence of "blood calcium decreased" 59% vs. 76% and "hypocalcemia" 5.5% vs. 10.3%.

Baseline Calcium-Containing Phosphate Binders or Calcium Supplement Use (yes, no)-
Subjects on calcium binders or supplements at baseline had a higher incidence of "blood calcium decreased" 70% vs. 60% and "hypocalcemia" 10.2% vs. 5.0%.

Medical Officer's comments-

Taken together these data point to the greatest risk of low blood calcium and hypocalcemia in young, white males, living outside North America, with a baseline iPTH level < 600pg/mL and receiving calcium supplements, but not vitamin D sterols at baseline.

Infusion reactions were more likely in European subjects, subjects on hemodiafiltration, and subjects on dialysis for less than one year.

Elderly subjects were more likely to have heart failure, while subjects with infusion reactions, or evidence of QT-prolongation or V-tach arrhythmias were more likely not to be enrolled into the open label extension, both of which would have been expected findings.

8.7. Specific Safety Studies/Clinical Trials

None

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There were 7 neoplasms reported in the 6-month placebo-controlled pivotal studies in the etelcalcetide treatment group similar to 7 neoplasms in the placebo group. The only neoplasm seen in more than one patient was basal cell carcinoma seen in the placebo group. Looking at all neoplasms identified in the clinical program ISS database in subjects treated with etelcalcetide for any period of time identified an additional 18 neoplasms. Only two types of neoplasms were seen in more than one patient: Melanocytic nevus (n=2) and squamous cell carcinoma of the skin (n=2). Of note, there was also no evidence of a predisposition for specific drug-related neoplasms in the nonclinical data (see section 4.4).

AEDECOD	ETELECALCETIDE	PLACEBO
Adenoma benign	1	0
Basal cell carcinoma	0	2
Biliary cancer metastatic	1	0
Bladder adenocarcinoma stage unspecified	1	0
Bone giant cell tumour benign	0	1
Laryngeal cancer	1	0
Lung neoplasm	1	0
Malignant melanoma	1	0
Oesophageal adenocarcinoma	0	1
Ovarian cancer	1	0
Papilloma	0	1
Prostate cancer	0	1
Renal cancer metastatic	0	1

Source ADAE studies 229 and 230 AEBODSYS= Neoplasms benign, malignant and unspecified.

8.8.2. Human Reproduction and Pregnancy

There were four pregnancies reported in the clinical program in which subjects were administered etelcalcetide during pregnancy: 3 cases of maternal exposure and 1 case of paternal exposure. Of the 3 cases of maternal exposure, 2 subjects had a spontaneous abortion, and 1 subject had an elective termination. The outcome of the case of paternal exposure is unknown. There were no reports in which a lactating subject was exposed to etelcalcetide. In conclusion, there is limited data to identify any safety signal associated with the use of etelcalcetide during pregnancy or with breast feeding.

8.8.3. Pediatrics and Assessment of Effects on Growth

The applicant submitted an iPSP requesting a waiver for pediatric studies in preterm and newborn infants less than (b) (4) days old, and a partial deferral of the pediatric clinical studies (b) (4) (b) (4) (1 month to < 2 years), children (2 to 11 years) and adolescents (12 to < 18 years) under the Pediatric Research Equity Act until safety and efficacy profile in adults has been established.

(b) (4)

The applicant proposes to extrapolate efficacy data obtained in adults to the pediatric population. They plan to perform a comparative PK and PD modelling and simulation study in adults to enable extrapolation and support the selection of safe and efficacious doses of etelcalcetide in the pediatric population. They propose to perform a single 26-week, Phase 3, randomized, multiple-dose titration study comparing etelcalcetide to cinacalcet to assess safety and further characterize pharmacokinetics, pharmacodynamics, and the exposure response to etelcalcetide in children.

Medical Officers' comments-

Given that this drug has to be given intravenously and is proposed for TIW dosing this limits the number of pediatric patients that may be available for recruitment into the etelcalcetide pediatric program. According to the 2011 NAPRTCS annual report[6] <3% of pediatric hemodialysis patients age 0 to 18 years are under 2 years of age, as these younger children are primarily treated with peritoneal dialysis. Therefore, it is very likely that the applicant is correct that they will have difficulty recruiting subjects < 2 years of age for a pediatric trial. According to the same report, most pediatric patients with chronic kidney disease are treated with peritoneal dialysis (63%), and so would not be available for recruitment for a pediatric study with etelcalcetide which has to be given intravenously. Even though pediatric studies using this formulation are likely to have difficulty with

[6] 2011 NAPRTCS annual report https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf

recruitment given the small patient population, this medical reviewer believes that the applicant should still make a reasonable attempt to study etelcalcetide in the pediatric hemodialysis population.

During the evaluation of the pediatric program with cinacalcet the clinical investigators concluded that part of the difficulty with using cinacalcet safely in children and adolescents in the original double-blind, placebo-controlled study centered about their inability to be able to distinguish lack of efficacy from poor compliance and inconsistent dosing versus inadequate dose titration. Partially for this reason, the initial placebo-controlled study was changed to an open-label study to help investigators to single out subjects with inadequate efficacy to more closely ascertain if they were being compliant with their medication prior to increasing their dose in order to avoid running the risk of inducing hypocalcemia. Given this concern a drug with a definite advantage in terms of compliance, which could be clearly monitored, would be a significant benefit assuming it did not carry any additional safety concerns. However, the increased risk of hypocalcemia seen in the adult trials with etelcalcetide compared to cinacalcet, the increased risk of adynamic bone disease, which has been associated with stunted growth in children, and the slightly higher potential for liver tissue injury make the benefit-risk assessment more difficult. The higher risk of hypocalcemia is especially concerning given that there was a pediatric death due to hypocalcemia during the pediatric trials with cinacalcet. This single death was complicated by dose escalation in the face of inadequate monitoring without evidence of poor compliance contributing to the outcome. In the end the decision as to whether etelcalcetide provides a sufficient clinical advantage compared to cinacalcet to warrant studying it in the pediatric population requires clinical judgment. This medical reviewer would support initiation of such studies in an open-label program assuming there is strict oversight of the potential complications. However, it is recommended that a low threshold for stopping any clinical studies be implemented and in case there is any clear evidence of a serious safety concern with etelcalcetide compared to cinacalcet in the pediatric program that the study should be halted, and that use of etelcalcetide in the pediatric population not be recommended.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Etelcalcetide has been administered in single doses up to 60 mg and multiple doses up to 22.5 mg three times per week to hemodialysis subjects with secondary hyperparathyroidism without evidence of overdose according to the applicant. That said chronic high doses of etelcalcetide can lead to hypocalcemia with or without clinical symptoms and adynamic bone disease. Hypocalcemia can lead to paresthesias, muscle spasms, prolonged QTc/arrhythmias, hypotension and seizures. Etelcalcetide can be cleared by hemodialysis, but the rate of elimination is likely to be affected by covalent and noncovalent binding to plasma proteins and

the rate of redistribution to other tissue compartments.

Calcimimetics are unlikely to be abused. There is no evidence of drug withdrawal or rebound hypercalcemia after drug discontinuation.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing data are available as etelcalcetide has not been previously marketed in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

Since patients with significant ongoing cardiac disease (e.g. CHF NYHA class III & IV, or history of MI, angioplasty or CABG in the past 6 months), poorly controlled seizures requiring treatment in the past 12 months or active liver disease were excluded from the clinical program use in these populations in the postmarket setting may result in the identification of increased drug-related risk.

Given that etelcalcetide must be given by chronic intravenous therapy and is likely to be less effective in subjects with normal or only limited loss in renal function off-label use for other conditions associated with hyperparathyroidism such as the following is unlikely:

- predialysis subjects with secondary hyperparathyroidism due to Stage 3 or 4 chronic kidney disease,
- patients with hypercalcemia due to hyperparathyroidism due to a parathyroid carcinoma,
- patients with primary hyperparathyroidism for whom thyroidectomy would be indicated on the basis of serum calcium but who are unable to undergo parathyroidectomy and
- renal transplant patients with tertiary hyperparathyroidism that has not yet responded adequately following transplant surgery

8.10. Additional Safety Issues From Other Disciplines

None

8.11. Integrated Assessment of Safety

Toxicity associated with the use of calcimimetics is primarily related to the risk of hypocalcemia, which can result in symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, and cardiac arrhythmias (torsades de pointes & ventricular tachycardia). Of less concern are hypophosphatemia, which is less likely to result in serious adverse reactions, and adynamic bone disease which occurs due to chronic over suppression of PTH and so is much less likely to present in short term trials with acute symptoms.

Hypocalcemia and Related AEs-
Etelcalcetide significantly lowered mean corrected serum calcium levels from a baseline of 9.6mg/dL to about 8.6mg/dL by week 10 of treatment in the pivotal placebo-controlled studies in contrast to no change from baseline in the placebo group (see Figure 26). Analyzing the individual patient data in the placebo-controlled studies by CTCAE grade (1, 8.0-<8.4mg/dL; 2, 7.0-<8.0 mg/dL; 3, 6.0-<7.0 mg/dL; and 4, <6.0 mg/dL), looking at the lowest corrected serum calcium levels for each patient showed that most of the difference in the number of subjects with low serum calcium levels between the etelcalcetide treatment group and placebo were in CTCAE grades 1 and 2 (7.0 to 8.3mg/dL) accounting for 51% of the difference, with only about 4% of the difference in patients with serum calcium levels below 7.0 (CTCAE grade 3) (see Table 46). Similarly in the active-controlled study 20120360 most of the subjects with low serum calcium levels in the etelcalcetide treatment group compared to cinacalcet were also in CTCAE grades 1 and 2 (12%), with no real difference in patients with serum calcium levels below 7.0 (CTCAE grades 3 & 4, see Table 47).

Again consistent with the findings that most of the low serum calcium levels were of low CTCAE grade most of the AEs of blood calcium decreased or hypocalcemia seen in the etelcalcetide treatment group were graded as mild or moderate (99%) with only 2 cases (0.4%) graded as severe in the placebo-controlled studies, 20120229 and 20120230, and 5 cases (1.5%) graded as severe in the active-controlled study, 20120360. That said none of the cases, even those graded as severe, were considered Serious AEs. In the 6-month placebo-controlled dataset only 5 subjects (1%) discontinued etelcalcetide treatment due to an event of hypocalcemia, and 1 subject (0.2%) discontinued due to nausea, while no subjects discontinued due to other symptoms potentially associated with hypocalcemia such as muscle spasms, myalgias, paresthesias, convulsions or hypotension. In the active-controlled study 20120360, no subjects in the etelcalcetide group and 2 subjects (0.6%) in the cinacalcet group discontinued due to the AE of blood calcium decreased. In addition, in the etelcalcetide group 3 subjects (0.9%) discontinued due to vomiting, 2 subjects discontinued due to nausea (0.6%), and 1 subject (0.3%) discontinued with each of the following calciphylaxis, bronchospasm, feeling abnormal, decreased appetite, muscular weakness, and somnolence.

A MedDRA-Based Adverse Event Diagnostics (MAED) analysis of the data from the pivotal placebo-controlled studies performed by this medical reviewer identified much higher event

rates for blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), hypocalcemia (7% vs. 0.2), paresthesias (5% vs. 1%) and myalgias (2% vs. 0.2%) in the etelcalcetide treatment group compared to placebo, all with p-values < 0.05. Of note "convulsions" which can also be related to hypocalcemia were seen at an equal rate in both treatment groups at 0.8%, and hypotension (6% vs. 5%) and "ECG QT prolonged" (0.8% vs. 0.6%) were only slightly higher in the etelcalcetide group. The analysis also showed that AEs of nausea (11% vs. 6%) and vomiting (9% vs. 5%) which are likely to be drug related were higher in the etelcalcetide treatment group compared to placebo even though the p-values were > 0.05. A MAED analysis of the active-controlled study 20120360 which compared etelcalcetide to cinacalcet also identified blood calcium decreased (69% vs. 60%, p=0.016) as more common in the etelcalcetide treatment group, suggesting that etelcalcetide has a higher risk of inducing low blood calcium levels than the currently approved calcimimetic. Of note hypotension which may be related to hypocalcemia was also more common in the etelcalcetide treatment group in this study (7% vs. 3%, p=0.021).

In conclusion low blood serum calcium levels and hypocalcemia are known risks associated with the use of calcimimetics, but the risk appears slightly higher with etelcalcetide compared to the currently approved calcimimetic, cinacalcet. That said most cases associated with the use of etelcalcetide were mild or moderate in severity and did not lead to discontinuation of treatment, although they did result in increased dosing with vitamin D sterols (31% vs. 10% placebo) and calcium supplements (50% vs. 9% placebo). Other AEs that may be related to hypocalcemia and occurring infrequently including muscle symptoms, paresthesias, and possibly hypotension and QT prolongation are potentially monitorable events. Labeling to recommend against dosing in subjects with serum calcium levels below the lower limit of normal and including information on symptoms of hypocalcemia to aid healthcare professionals to identify cases of concern should provide adequate risk management.

Hypophosphatemia-

Etelcalcetide significantly decreased mean serum phosphorous levels from a baseline of 5.9mg/dL to about 5.0mg/dL by week 10 of treatment in the placebo-controlled pivotal trials, compared to a slight decrease of 0.2mg/dL from baseline to end of treatment in the placebo group.

Analyzing the individual patient data in the placebo-controlled studies by CTCAE grade (1, 2.5-<2.8mg/dL; 2, 2.0-<2.5mg/dL, 3, 1.0-<2.0mg/dL; and 4, <1.0mg/dL) looking at the lowest serum phosphorous levels for each patient showed that most of the difference in the number of subjects with low serum phosphorous levels between the etelcalcetide treatment group and placebo were small: CTACAE grade 1, 4%; 2, 6%; 3, 7%; and 4, 0%. Similar results were seen in the active-controlled study versus cinacalcet where the differences by CTCAE grade were: 1,

4%; 2, 1%; 3, 4%; and 4, 0%.

There were 7 patients (1.4%) with AEs of hypophosphatemia in the 6-month placebo-controlled trials with etelcalcetide compared to only 1 patient (0.2%) in the placebo group. Of the 7 cases in patients treated with etelcalcetide, 4 were considered mild in severity and 3 were considered moderate. None of the cases were serious or required discontinuation of the study medication.

There were 2 patients (0.6%) with AEs of hypophosphatemia in the 6-month active-controlled trials with etelcalcetide compared to 1 patient (0.3%) in the cinacalcet group with 2 events. The single case in the cinacalcet treatment group was considered serious and required the drug dose to be interrupted and eventually discontinued.

In conclusion, low blood serum phosphorous levels are a known risk associated with the use of calcimimetics which lower serum PTH, but in general they are unlikely to result in severe or serious AEs. Hypophosphatemia can typically be controlled with routine monitoring and appropriate changes to diet or concomitant medications without need for interrupting the dose of the calcimimetic.

Adynamic Bone Disease-
Adynamic bone disease due to low bone turnover is associated with the decreased ability to repair microdamage in bone which places subjects at higher risk of fracture and also is associated with vascular calcifications[7] due to the decreased calcium buffering capacity of the abnormal bone. While there is an association with low PTH levels and adynamic bone disease in hemodialysis patients, a diagnosis of adynamic bone disease can only be made by bone biopsy. So the fact that there were no subjects diagnosed with an adverse event of adynamic bone disease during the placebo-controlled trials is not reassuring given that bone biopsies were not part of the study protocols. The study protocols were designed to "maintain the dose" if iPTH levels were >100pg/mL and ≤300pg/mL and to "suspend dosing" for two consecutive values < 100pg/mL in an attempt to limit the likelihood of subjects developing adynamic bone disease with chronic therapy. The European Renal Best Practice Work Group suggests a PTH threshold of < 100 pg/mL for evidence of low bone turnover[8]. Behets et al.[9] mention that BSAP levels ≤10 ng/mL may provide an additional biomarker of adynamic bone disease in addition to low serum

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[7] **Bover J, Ureña P, Brandenburg V, Goldsmith D, Ruiz C, DaSilva I, Bosch RJ.** Adynamic bone disease: from bone to vessels in chronic kidney disease. Semin Nephrol. **2014 Nov;34(6):626-40**

[8] **David J.A. Goldsmith, Adrian Covic, Denis Fouque, Francesco Locatelli, Klaus Olgaard, Mariano Rodriguez, Goce Spasovski, Pablo Urena, Carmine Zoccali, Gérard Michel London and Raymond Vanholder** Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement **Nephrol Dial Transplant (2010) 25, 3823-3831**

[9] **Behets GJ, Spasovski G, Sterling LR, Goodman WG, Spiegel DM, De Broe ME, D'Haese PC**. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 2015 Apr;87(4):846-56

PTH (see section 8.5.2 ADYNAMIC BONE DISEASE for a more detailed explanation about the risk of adynamic bone disease in subjects with low serum iPTH and BSAP levels.) Given that etelcalcetide showed superior efficacy to cinacalcet, the lab datasets were analyzed to determine if etelcalcetide was more likely to result in low levels of iPTH < 100pg/mL and BSAP≤10 ng/mL that might place subjects at increased risk of adynamic bone disease. There were many more patients with low iPTH values < 100 pg/mL during the EAP after 6-month of treatment in the etelcalcetide group 52 (6.9%) compared to cinacalcet 10 (3.2%) and placebo 2 (0.4%). Looking at the last BSAP values in these 64 subjects showed that more patients had both low iPTH values < 100 pg/mL and low BSAP < 10 ng/mL in the etelcalcetide treatment group 18/754=2.4% compare to cinacalcet 3/310=1.0% and placebo 1/456=0.2%, suggesting that subjects treated with etelcalcetide were potentially at greater risk of developing adynamic bone disease with continued treatment. In conclusion, these data point to the possibility that subjects were being over treated despite the study design to maintain iPTH levels in the 100pg/mL to 300pg/mL range. Labeling needs to emphasize the risk for adynamic bone disease with chronic over suppression of iPTH levels. Regular monitoring should be recommended to maintain iPTH levels (b) (4)

Liver Testing-

Liver test elevations are not typically associated with calcimimetics and as such were not an expected finding associated with the treatment with etelcalcetide. Marked elevations of transaminases > 3 times ULN or total bilirubin > 2 times ULN were infrequent and not necessarily greater than expected with placebo. In the placebo-controlled trials there were two subjects (0.4%) in the etelcalcetide treatment group with ALT levels > 3X ULN compared to three subjects (0.6%) in the placebo group, and two subjects (0.4%) in the etelcalcetide treatment group with AST levels > 3X ULN compared to one subject (0.2%) in the placebo group. In the placebo-controlled trials there was one subject (0.2%) in the etelcalcetide treatment group with total bilirubin levels > 2X ULN compared to 2 subjects (0.4%) in the placebo group. None of these subjects met the definition of Hy's Law. Of the two subjects with transaminase elevations > 3XULN on etelcalcetide one was rechallenged after the tests had normalized and did not have a recurrence, while the other improved after the drug was discontinued but was not rechallenged. No etiology for the elevated enzymes was identified in either patient. The single subject with the elevated bilirubin on etelcalcetide had metastatic biliary cancer as the likely cause for the elevation. In addition there were two other patients with transaminase elevations on etelcalcetide in the open label extension. One had a positive rechallenge test while the other continued to have transaminase elevations after dose reduction and so the etelcalcetide was discontinued.

In conclusion, the isolated cases in the etelcalcetide treatment group in the placebo-controlled studies do not point to a specific increased hepatic risk. That said there continued to be a small number of patients with hepatic enzyme elevations during treatment with etelcalcetide during

the open-label extensions, one case of a positive rechallenge test and one case of persistent liver test abnormalities despite lowering the etelcalcetide dose suggesting possible drug-related injury. In response to these findings the applicant emphasized that there was no evidence of liver toxicity in the nonclinical studies, etelcalcetide is not a substrate, inhibitor, or inducer of CYP-450 liver enzymes and not a substrate or inhibitor of liver transporters, and there is only very minor hepatic elimination in CKD patients on hemodialysis. Therefore they concluded that given "the safety and efficacy of etelcalcetide have not been evaluated in subjects with impaired liver function as such subjects were excluded from the clinical studies, there is currently no strong evidence that etelcalcetide poses additional risk to patients with active liver disease". This medical reviewer agrees that there is limited evidence for any serious risk and as such no extra liver test monitoring is indicated at this time unless subjects present with specific symptoms. Routine post marketing surveillance should continue to look for potential evidence of liver toxicity.

Worsening Heart Failure-

The applicant is proposing to include worsening heart failure as a WARNING AND PRECAUTION in the PI given the theoretical concern that reductions in serum calcium levels can potentiate the risk of heart failure. While subjects on hemodialysis are at increased risk of dying from cardiovascular heart disease including CHF as was evidenced in the current clinical program there was no evidence that treatment with etelcalcetide increased the risk of worsening heart failure. In the 6-month pivotal placebo-controlled studies 2 subjects on placebo and one on etelcalcetide died from CHF. In the open-label extension an additional two subjects (0.2%) died from cardiac failure for an event rate of 0.2 per 100 patients-years. The MAED analysis of preferred terms identified event rates of 0.6% on etelcalcetide vs. 0.2% for placebo for the preferred term "cardiac failure" and 1.6% on etelcalcetide vs. 1.2% for placebo for the preferred term "cardiac failure congestive" both with insignificant p-values of 0.37 and 0.60, respectively. Similarly the MAED narrow SMQ event rate for "cardiac failure" was 3.2% on etelcalcetide compared to 2.7% on placebo, p-value=0.71. However, according to the applicants analysis the subject incidence of combined adjudicated congestive heart failure requiring hospitalization in the placebo-controlled studies was slightly higher in the AMG 416 treatment group (2.2% AMG 416; 1.2% placebo). In the active-controlled study 20120360 the MAED narrow SMQ event rate for "cardiac failure" was 3% on etelcalcetide compared to 0.6% on cinacalcet with a p-value of 0.021, suggesting a difference in safety between the two calcimimetics. That said, cinacalcet had previously demonstrated a reduction in the rate of heart failure relative to placebo as a secondary endpoint in the large 5-year outcome trial EVOVLE so the higher event rate seen here with etelcalcetide compared to cinacalcet may reflect treatment benefit associated with the use of cinacalcet and not necessarily increased risk associated with the use of etelcalcetide. In conclusion, cardiac failure is a common finding in hemodialysis patients and the worsening of heart with etelcalcetide due to its potential to lower serum calcium is currently primarily a theoretical concern as there were few cases of

heart failure on etelcalcetide in the clinical program and none were associated with hypocalcemia. Therefore this medical reviewer would recommend that "worsening of heart failure" be added to potential complications of hypocalcemia in the WARNINGS AND PRECAUTIONS section of the PI and not be listed as its own separate section.

GI Hemorrhage-
There is clear evidence that etelcalcetide increases the rate of nausea (10.7% vs. 6.2%) and vomiting (8.9% vs. 5.1%) relative to placebo, which had previously been seen with the other calcimimetic, cinacalcet. These symptoms probably result from a combination of low serum calcium levels and a direct GI effect. Since nausea and vomiting can contribute to Mallory Weiss tears there is the potential that treatment with etelcalcetide may be exacerbating symptoms in patients with a predisposition to GI hemorrhage, a finding which is known to be more common in the hemodialysis population. In addition, there is evidence of glandular stomach erosion in a few rats in the nonclinical toxicity studies at mid and high doses (see Section 4.4 Nonclinical Pharmacology/Toxicology) suggesting a mechanism for drug related toxicity. In their response to the 29 July Information Request the applicant stated that they believed that the stomach erosions seen in the rodents were stress related as they were associated with reduced body weight and food consumption and were not seen in the 9 month dog study. However, such an interpretation would not be supported by the lack of stomach erosion findings in the low dose rats and the presence of emesis in the mid and high dose dog study. In addition, there is evidence that activation of the calcium sensing receptor agonist in the stomach, by cinacalcet stimulates gastrin production suggesting a potential mechanism of plausibility. Correlation of the lack of findings in healthy animals with normal renal function to human subjects with CKD may also be an issue although the doses used in the animals were much higher in the hopes of getting more comparable drug exposure.

While the number of cases of GI hemorrhage is small, similar to what was seen in the placebo group and in line with historical controls (see Response to 16 June 2016 Information Request), this reviewer was struck mainly by the severity of the cases seen in the etelcalcetide treatment group.

In total there were three deaths:

- one death (22965007001) assessed by the clinical investigator as related to the investigational product, occurred two weeks after starting treatment, but was formally listed as death of unknown cause (see pg 113 for patient narrative)
- one death (23066026008) occurred about 6 weeks after drug discontinuation on week 17 of the study in a subject who had evidence of esophagitis, gastritis, and Mallory Weiss tears on endoscopy, and was due to GI hemorrhage (see pg 113 for patient narrative)
- one death (Subject 0517-1547) occurred in the open-label extension 10 days after drug discontinuation on Study Day 33 and was due to GI hemorrhage/acute MI/cardiogenic

shock (see pg 115 for patient narrative)

The MAED analysis identified the narrow SMQ search terms “gastrointestinal nonspecific inflammation and dysfunctional conditions” (etelcalcetide 29.8% vs. placebo 23.0%) and “gastrointestinal nonspecific symptoms and therapeutic procedures” (etelcalcetide 27.8% vs. placebo 21.1%) as both more common in the etelcalcetide group with p-values < 0.05. However a JMP analysis performed by this medical reviewer using the AEHLGT terms of “Gastrointestinal ulceration and perforation” and “Gastrointestinal haemorrhages NEC” on the placebo controlled data from studies found no clear increased risk of ulcer and hemorrhage in the etelcalcetide treatment group compared to placebo.

In conclusion, given that GI bleeds are more common in the hemodialysis population and the total number of events is small and typically confounded by multiple factors such as medical history of GE reflux/Mallory Weiss tears/ulcers/gastritis/intermittent nausea and vomiting, concomitant medications including aspirin, heparin, and steroids, and acute cardiac events that likely increased patient stress, there is probably too little information to support a specific warning at this time. That said this medical reviewer would recommend that the sponsor use post marketing surveillance to see if there is evidence that subjects with a history of erosive GI symptoms are at increased risk of an event during treatment with etelcalcetide and as such chronic treatment should be avoided in these patients, or at a minimum they should be on stomach acid prophylaxis.

In summary the primary safety risks associated with the use of etelcalcetide are related to a greater risk of hypocalcemia which is typically mild to moderate but can be associated with symptoms of paresthesias, muscle spasms, myalgia, bronchospasm, increased risk of seizures, hypotension, prolongation of the QT interval, cardiac arrhythmias (torsades de pointes & ventricular tachycardia) and worsening of heart failure. The risk of hypocalcemia appears slightly greater with etelcalcetide compared to cinacalcet, but is outweighed by etelcalcetide’s greater efficacy. Labeling to recommend against dosing in subjects with serum calcium levels below the lower limit of normal and including information on symptoms of hypocalcemia to aid healthcare professionals to identify cases of concern should provide adequate risk management. There is also a small risk for hypophosphatemia which too is typically mild to moderate and can typically be controlled with routine monitoring and appropriate changes to diet or concomitant medications without need for interrupting the dose of the calcimimetic. The risk for adynamic bone disease is less clear. While no AEs of adynamic bone disease were seen during treatment with etelcalcetide, following 6 months of treatment with etelcalcetide some patients developed iPTH levels below current recommended guidelines which place these subjects at risk of future adynamic disease with chronic therapy. Strict observance to current treatment guidelines is recommended in the labeling to minimize this potential risk. There is also a small signal for liver test elevations in a small number of patients which is reversible with discontinuation of therapy. No additional liver test monitoring is recommended at this time

although typical prudence should be observed when starting any patient with active liver disease on a new medication. There is also the possibility of worsening GI bleeds in subjects with a prior history of disease, which is yet to be clearly defined. Continued post marketing product surveillance is recommended specifically focusing on this potential risk.

9 Advisory Committee Meeting and Other External Consultations

None

10 Labeling Recommendations

10.1. Prescribing Information

1 INDICATIONS AND USAGE

Revise the proposed indication to recommend treatment of "adult" patients [redacted] (b) (4)

2 DOSAGE AND ADMINISTRATION

Recommend removing [redacted] (b) (4) replacing it with the term "lower limit of normal" given that the exact lower limit of normal value will vary with the clinical laboratory used to process the samples.

4 CONTRAINDICATIONS

Contraindications should be bulleted and listed in order of severity.

5 WARNINGS AND PRECAUTIONS

Recommend that "Coadministration with Other Products" referring to the risk of hypocalcemia with concomitant administration with cinacalcet not be a separate subsection but be included under "Hypocalcemia" as that is the reason for the safety concern.

Recommend against "Worsening Heart Failure" being included as a separate subsection as it represents a theoretical risk due to hypocalcemia which was not seen in the clinical trials, and is better placed along with the other safety concerns associated with hypocalcemia including ventricular arrhythmias and seizures under "Hypocalcemia".

6 ADVERSE REACTIONS

The table of AEs should only list percentages for better clarity as the total number of patients is already listed at the top and can be used to calculate the number of patients if needed.

Recommend removing the reference to [redacted] (b) (4)

(b) (4)

(b) (4)

7 DRUG INTERACTIONS

Defer to Clin Pharm

8 USE IN SPECIFIC POPULATIONS

(b) (4)

12 CLINICAL PHARMACOLOGY

Given that the drug can continue to accumulate past 8 weeks consider adding additional information about drug accumulation out to 6 months, as it appears that there was evidence for the need for later dose reductions in the trials possibly due to continued accumulation.

14 CLINICAL STUDIES

Include more demographic information with respect to gender, race and ethnicity on the clinical trials.

Delete (b) (4) .

Delete reference to (b) (4)

Remove (b) (4)

17 PATIENT COUNSELING INFORMATION

Acceptable

10.2. Patient Labeling

There is no need for a Medication Guide for this product at this time.

10.3. Nonprescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

This medical reviewer agrees with the DRISK assessment that the primary safety issues identified in this application including hypocalcemia, hypophosphatemia, worsening heart failure, and adynamic bone disease can be adequately addressed with appropriate labeling and there is no need for a REMS for this application.

12 Postmarketing Requirements and Commitments

The sponsor submitted an iPSP for pediatric studies to be performed as part of a postmarketing requirement (see section 8.8.3).

13 Appendices

13.1. References

Behets GJ, Spasovski G, Sterling LR, Goodman WG, Spiegel DM, De Broe ME, D'Haese PC. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. **Kidney Int.** 2015 Apr;87(4):846-56

Bover J1, Ureña P2, Brandenburg V3, Goldsmith D4, Ruiz C5, DaSilva I5, Bosch RJ5. Adynamic bone disease: from bone to vessels in chronic kidney disease. **Semin Nephrol**. 2014 Nov;34(6):626-40

David J.A. Goldsmith, Adrian Covic, Denis Fouque, Francesco Locatelli, Klaus Olgaard, Mariano Rodriguez, Goce Spasovski, Pablo Urena, Carmine Zoccali, Gérard Michel London and Raymond Vanholder Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement **Nephrol Dial Transplant** (2010) 25, 3823-3831

Irfana H. Soomro and David S. Goldfarb, Dysphoria Induced in Dialysis Providers by Secondary Hyperparathyroidism, **Clin J Am Soc Nephrol** 10: 9–11, 2015

KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD) **American Journal of Kidney Diseases** 55: No 5 (May), 2010: pp 773-799
https://www.kidney.org/sites/default/files/docs/kdoqi-ckd-mbd-commentary.pdf

2011 NAPRTCS annual report
https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf

Wang M1, Hercz G, Sherrard DJ, Maloney NA, Segre GV, Pei Y. Relationship between intact 1-84 parathyroid hormone and bone histomorphometric parameters in dialysis patients without aluminum toxicity. **Am J Kidney Dis**. 1995 Nov;26(5):836-44.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 20120229

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 490		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 (2honoraria, 2 research grants, 1 student scholarship) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 20120230

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 423		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 (2honoraria, 3 research grants, 1 advisory board) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator- 1 investigator with 8275 shares of Amgen stock Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 20120360

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 588		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 (Amgen support) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator 1 investigator with 600 shares of Amgen stock worth $67,050 as of 2014 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

WILLIAM A LUBAS
08/19/2016

MARINA ZEMSKOVA
08/19/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208325 Seq0000 | **Applicant: Amgen** | **Stamp Date: August 24, 2015**

Drug Name: etelcalcetide injection | **NDA/BLA Type: 505 (b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			the narrative portion is located in section 2.7.3 and the appendices of tables, figures, and datasets are located in section 5.3.5.3. ISS
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			the narrative portion is located in section 2.7.4 and the appendices of tables, figures, and datasets are located in section 5.3.5.3. ISE
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to	X			The Phase 2a study

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: **20120330** A Phase 2a Double-blind, Randomized, Placebo-controlled Multiple Ascending Dose Study to Assess the Safety, Tolerability and Efficacy of KAI-4169 in Hemodialysis Subjects With Secondary Hyperparathyroidism Sample Size: 87 Arms: Placebo vs. AMG 416 (5-15mg) dose titration Study Number: **20120229** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis Sample Size: 508 Arms: Placebo vs. AMG 416 (5-15mg) dose titration Study Number: **20120230** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis Sample Size: 515 Arms: Placebo vs. AMG 416 (5-15mg) dose titration Location in submission: Section 5.3.5.1				showed clinically relevant reductions in PTH in the patient population. The two Phase 3 pivotal trials were designed with dose titration every 4 weeks to determine optimal dosing.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 **20120229** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis Indication: The treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis. Pivotal Study #2 **20120230** A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Hemodialysis Indication: The treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.	X			The submission includes two Phase 3, double-blind, placebo-controlled studies as well as a Phase 3 double-blind, double-dummy active controlled study against cinacalcet, the only currently approved calcium-sensing receptor agonist.

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	Content Parameter	Yes	No	NA	Comment
	Study Number: **20120360** A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism Indication: The treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			FDA agreed that the proportion of subjects with > 30% reduction from baseline in predialysis PTH was an appropriate endpoint at the EOP2 meeting
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			A thorough QTc study is not feasible and was not required as part of the AMG 416 clinical development program in accordance with ICH E14 (ICH E14, 2005). The timing of electrocardiogram (ECG) assessments in the phase 3, placebo-controlled studies, in addition to other early phase studies, was considered appropriate to evaluate the effect of AMG 416 on QTc interval and was agreed to at the EOP2

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					meeting.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			1199 exposed to AMG 416 for > 24 weeks and 499 exposed to AMG 416 for > 52 weeks
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			See Appendix 2 of ISS For narratives on all deaths (2.1), SAEs (2.2), discontinuations (2.3-2.5), subjects with symptomatic hypocalcemia (2.7), liver toxicity AEs (2.8) and cardiovascular event AEs (2.9)
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The agreed to PSP includes a waiver for studies in newborns under (b)(4) days of age and a partial deferral in older children until the safety and efficacy in adults has been established.
ABUSE LIABILITY					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Drug is unlikely to be abused.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	There were no foreign only pivotal studies. While the pivotal studies were multinational greater than 50% of the subjects were from US sites, so there is sufficient US data to look for potential geographical disparities.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

William Lubas MD, PhD	October 20, 2015
Reviewing Medical Officer	Date
Marina Zemskova MD	October 20, 2015
Clinical Team Leader	Date

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

/s/

WILLIAM A LUBAS
10/22/2015

MARINA ZEMSKOVA
10/22/2015