15 September 2016
EMA/664198/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Parsabiv

International non-proprietary name: etelcalcetide

Procedure No. EMEA/H/C/003995/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	absorption, distribution, metabolism, excretion
AMG 416	Etelcalcetide
AUC	area under the concentration-time curve
BDC	bile duct cannulated
BSAP	bone specific alkaline phosphatase
CaSR	calcium-sensing receptor
cCA	corrected calcium
cCa x P	corrected calcium-phosphorus product
CI	confidence interval
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
CPP	Critical process parameter
CQA	Critical quality attribute
CTX	collagen C-telopeptide
DOPPS	Dialysis Outcomes and Practice Patterns Study
EAP	efficacy assessment period
EC	European Commission
EMA	European Medicines Agency
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
ESRD	end-stage renal disease
EU	European Union
EVOLVE	EValuation Of Cinacalcet Therapy to Lower CardioVascular Events, Study 20050182
FGF-23	fibroblast growth factor-23
FMEA	Failure mode effects analysis
FMoc	Fluorenylmethyloxycarbonyl
GC	Gas Chromatography
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
SHPT	Secondary Hyperparathyroidism
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IV	Intravenous
JP	Japanese Pharmacopoeia
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
KF	Karl Fischer titration
LE	Long Evans
MedDRA	Medical Dictionary for Regulatory Activities
NMR	Nuclear Magnetic Resonance
NOAEL	no observed adverse effect level
NOE	Nuclear Overhauser Effect
P	Phosphorus
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan

PK	Pharmacokinetics
PRO	patient reported outcome
PTG	parathyroid gland
PTH	parathyroid hormone
PVC	Poly vinyl chloride
QbD	Quality by design
QD	once daily
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
RH	Relative Humidity
RTU	ready to use
SAP	statistical analysis plan
SAPC	serum albumin peptide conjugate
SC	Subcutaneous
SD	Sprague Dawley
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities Queries
TFA	trifluoroacetic acid
TIW	three times a week
TK	Toxicokinetics
USP	United States Pharmacopoeia
UV/Vis	Ultraviolet/visible spectroscopy
WFI	Water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 2 September 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Parsabiv, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2014.

The applicant applied for the following indication:

Parsabiv is indicated for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy.
Parsabiv may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that etelcalcetide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0259/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0259/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance etelcalcetide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the following country: United States.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 2 September 2015.
- The procedure started on 1 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 December 2015.
- PRAC rapporteur's assessment report was circulated on 4 January 2016.
- During the meeting on 28 January 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2016.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - GCP inspections at two investigator sites, located in Poland and USA (inspection dates: 18 – 22 January 2016 and 01 – 05 February 2016, respectively) and one sponsor site in USA (inspection dates: 8 – 12 February 2016). The final integrated inspection report of the inspection carried out was issued on 11 April 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 May 2016.
- PRAC RMP Advice and assessment overview, adopted on 9 June 2016.
- During the CHMP meeting on 23 June 2016, the CHMP agreed on a list of outstanding issues by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 September 2016.The Rapporteurs circulated the updated Joint Assessment Report to all CHMP members on 8 September 2016.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing

Authorisation to Parsabiv.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Background of the disease

Secondary Hyperparathyroidism (HPT) is common among patients with Chronic Kidney Disease (CKD) (USRDS, 2009). Secondary HPT is characterized by persistently elevated levels of parathyroid hormone (PTH) in blood caused by the ongoing release of excess amounts of PTH from enlarged parathyroid glands (Goodman and Quarles, 2008; Parfitt, 1997) due to low calcium serum levels. Secondary HPT is a chronic, progressive disease that develops early during the course of CKD, worsens as kidney function decreases over time, and affects a majority of patients with advanced kidney disease.

The development of secondary HPT among subjects with CKD represents an early adaptive response that serves initially to maintain calcium homeostasis as kidney function declines leading to a decreased ability to resorb calcium. As CKD progresses and associated metabolic disturbances become more pronounced, enlargement of the parathyroid glands due to tissue hyperplasia contributes to disease progression and severity (Goodman and Quarles, 2008).

European countries that are part of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry reported over 450,000 patients with ESRD who were receiving renal replacement therapy with most patients receiving dialysis (Pippias et al, 2015). Worldwide, the number of patients with CKD receiving dialysis exceeds 1 million. The large majority of these individuals receive haemodialysis as renal replacement therapy (USRDS, 2014). Secondary HPT is a major burden for the large number of patients with CKD receiving dialysis.

For patients with CKD receiving dialysis, important clinical consequences of secondary HPT and the accompanying metabolic disruptions in calcium and phosphorus homeostasis include pathological changes in bone, reductions in bone mass, increased risk of skeletal fracture, soft-tissue and vascular calcification, left ventricular hypertrophy, and a greater risk for cardiovascular events (USRDS, 2009; Moe, 2001; Alem et al, 2000; Block and Port, 2000; Diaz-Corte and Cannata-Andia, 2000; Slatopolsky et al, 1980).

Therapeutic options

Several therapeutic strategies have been used to lower elevated PTH levels and manage the disturbance in calcium and phosphorus homeostasis among patients with secondary HPT and CKD (KDIGO, 2009; Saliba and El-Haddad, 2009; Locatelli et al, 2008). Traditionally, most therapeutic regimens have employed treatment with vitamin D sterols such as calcitriol or synthetic vitamin D analogues.

While vitamin D sterols may reduce PTH levels, they are limited by the development of hypercalcaemia and hyperphosphatemia due to enhanced gastrointestinal absorption. These agents are contraindicated in patients with pre-existing hypercalcaemia. The product labels also include cautionary statements regarding the risk of vascular or metastatic calcification as well as potential toxicity of hypercalcaemia.

An alternative approach to treating secondary HPT is to enhance signal transduction through the calcium-sensing receptor (CaSR) in parathyroid tissue. Calcimimetics target the CaSR in parathyroid tissue (Brown and Hebert, 1996; Brown et al, 1993). Cinacalcet is the only calcimimetic currently approved for the treatment of secondary HPT in patients with CKD undergoing dialysis. It is a recommended intervention for reducing elevated PTH levels among patients with CKD receiving dialysis as stated in clinical practice guidelines developed by the International Society of Nephrology Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO, 2009). Cinacalcet is a small molecule, available in tablet form for oral administration once daily (QD).

Problem statement

Because of its oral route of administration, cinacalcet is susceptible to suboptimal medication adherence, a common problem in CKD patients who have a high daily pill burden (Chiu et al, 2009).

Given the effectiveness of calcimimetics in reducing PTH, there is a medical need for a calcimimetic that can be administered by the i.v. route of administration during or after haemodialysis treatment, thereby addressing the adherence problem associated with oral cinacalcet in patients with a large pill burden.

2.1.2. About the product

Product type and proposed mechanism of action

Etelcalcetide (also sometimes referred to as AMG 416 throughout the text, also formerly identified as KAI 4169) is a calcimimetic being developed for the treatment of secondary HPT in patients with CKD receiving haemodialysis. Etelcalcetide is a synthetic peptide comprised of 7 D-amino acids linked to an L-cysteine via a disulfide bond that acts as an allosteric activator of the CaSR. It binds directly to the extracellular domain and activates the receptor at a site which is distinct from the calcium activating site. This suppresses secretion of PTH due to an increased sensitivity of the CaSR receptor to calcium, leading to a decrease in calcium levels.

Dose recommendation

Etelcalcetide (AMG 416) is the only calcimimetic formulated for i.v. administration. The recommended initial dose of etelcalcetide is 5 mg. Etelcalcetide is administered TIW as a bolus dose at the end of the haemodialysis treatment during rinseback or i.v. after rinseback. Parsabiv should be titrated so that doses are individualised between 2.5 mg and 15 mg.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 2.5, 5.0 or 10.0 mg of etelcalcetide (as hydrochloride salt) as active substance.

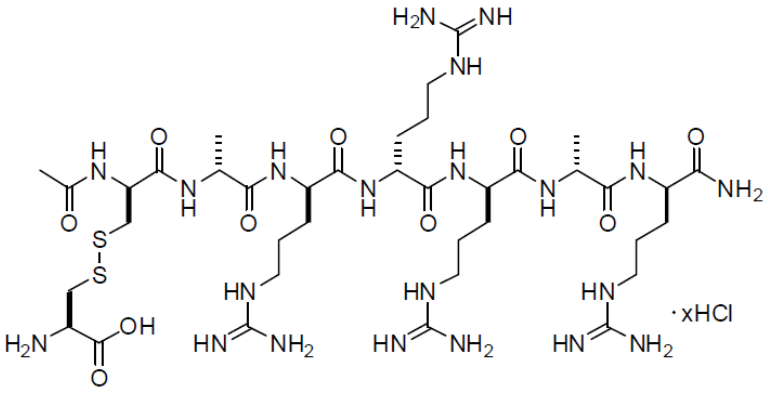
Other ingredients are sodium chloride, succinic acid, water for injection, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in type I glass vials with fluoropolymer laminated elastomeric stoppers and aluminium seals with flip-off dust covers as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of etelcalcetide hydrochloride is *N*-acetyl-D-cysteinyl-*S*-(L-cysteine disulfide)-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-alanyl-D-argininamide hydrochloride corresponding to the molecular formula $C_{38}H_{73}N_{21}O_{10}S_2$.xHCl (4≤x≤5) and a relative molecular mass of 1208.7 g/mol (where x = 4.4). It has the following structure:



The structure of etelcalcetide was inferred from the synthetic process and starting materials and confirmed using a combination of amino acid analysis, elemental analysis, mass spectrometry, ^{1}H-, ^{13}C- and ^{15}N-NMR spectroscopy (1D, 2D and NOE), chiral amino acid analysis and UV/Vis spectroscopy.

The active substance is a very hygroscopic, white to off-white, amorphous solid, freely soluble in aqueous media and polar organic solvents. The aqueous solubility ensures complete dissolution on formulation.

Etelcalcetide contains eight chiral centres. Enantiomeric purity is controlled by optical rotation. Any racemisation during the synthetic process would result in diastereomers, the most common of which are separable by the HPLC method.

Etelcalcetide is amorphous and no crystalline form has as yet been identified. The amorphous nature of the active substance is ensured by the final lyophilisation process.

Etelcalcetide is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives and salts have ever been active substances in products authorised in Europe.

Manufacture, characterisation and process controls

A single manufacturer carries out the entire process. Etelcalcetide hydrochloride is synthesized in five main steps using commercially available, well-defined starting materials with acceptable specifications. Standard solid phase peptide synthesis is used and the active substance is built from protected amino acids on amide resin. Following cleavage from the resin, the cysteine residue is coupled, followed by several chromatographic purification steps which ensure impurities are removed to acceptable levels. The final step is formation of the hydrochloridesalt and lyophilisation.

The process was developed using a QbD approach although no design space or other regulatory flexibility is requested. Risk assessments were carried out, building on prior process knowledge and using tools such as failure mode effects analysis (FMEA) to identify critical steps in the process. Critical process parameters (CPPs) and critical quality attributes (CQAs) of the active substance were identified. Based on this work, adequate in-process controls (IPCs) are applied during the synthesis. Impurities formed in step 1, from impurities in the starting materials, truncated peptides, or diastereomers all carry through to later stages since they are all attached to the resin and can't be purged. By contrast, the removal of all reagents and their by-products can be assured by sufficient washing of the resin after each completed reaction.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A thorough evaluation of impurities was carried out. Potential and actual impurities, including mutagenic impurities, were identified and strategies to prevent their formation or ensure their purge have been implemented. The active substance itself is AMES positive, although subsequent *in vivo* studies showed it is not mutagenic. Related impurities are considered to have equivalent toxicity by analogy. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are in line with the detailed knowledge of the process. The levels of impurities are controlled in the active substance specification.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced during development are minor, consisting of changes to solvents and reagents. A comparability exercise was carried out, demonstrating that the changes have no impact on CQAs of the active substance. The quality of the active substance used in the various phases of the development is therefore considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in low density polyethylene bag closed with a cable tie inside a heat-sealed aluminium bag. The materials comply with the relevant requirements of the Ph. Eur. and EC Regulation 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (solid and in solution), identity (MS, HPLC, amino acid analysis), assay (HPLC), impurities (HPLC), specific optical rotation (polarimetry), water content (KF), chloride content (titration), trifluoroacetic acid content (IC), residual solvents (GC), elemental impurities (ICP-MS), bacterial endotoxins (Ph. Eur.) and microbiological quality (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 18 batches of the active substance throughout the whole development programme are provided. Manufacturing scales ranged from early lab scale batches, to pilot scale, culminating in 4 full production scale batches. The batches were used for toxicological, clinical, stability and validation studies. The results are within the specifications at the time of testing and consistent from batch to batch, taking into account the changes in manufacturing process.

Stability

Stability data on 7 batches of active substance at >10% of the stated production scale from the proposed manufacturer stored in the intended commercial package (although smaller scale) for up to 24 months (1 batch for 36 months) under long term conditions (-20 ± 5 ºC) and for up to 24 months under accelerated conditions (5 ± 3°C) according to the ICH guidelines were provided. Supportive data over 36 months on an additional pilot scale batch was provided. Samples were tested for appearance, assay, impurities and water content. The analytical methods used were the same as for release and are stability indicating. No trends to appearance, assay and impurities were noted. Water content increased over time but remained within specification.

Photostability testing following the ICH guideline Q1B was performed on one batch. An increase in impurities with an associated reduction in assay was observed, along with an increase in water content.

Forced degradation studies were conducted in the solid state and on the active substance in solution under thermal and humid conditions and in solution exposed to acid, base, oxidant and light. Etelcalcetide degrades to an extent under all conditions, to the greatest extent under warm humid conditions, but significantly so under all solution conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at -20 ± 5 ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Parsabiv is a sterile, single-use preservative-free solution for intravenous (IV) injection available in 3 strengths containing 2.5, 5 or 10 mg of active substance respectively containing the following excipients: sodium chloride; succinic acid; water for injection; hydrochloric acid sodium hydroxide.

A liquid formulation was selected for development since it provides an easy to use dosage form, suitable for administration in the planned clinical setting. Excipients were chosen with stability and osmolarity of the formulation in mind. Succinic acid was selected as the optimum buffering agent. A range of tonicity agents were evaluated and sodium chloride was found to give the least amount of degradation at room temperature. The stability of etelcalcetide in solution is also dependent on its concentration. The amounts of the various excipients were then optimised and the robustness of the optimal formulation assessed by DoE, examining the impact of variation in concentration, pH and NaCl content on assay and osmolarity over time under both long term (2-8 ^{o}C) and accelerated (25 ^{o}C) conditions. At the lower temperature, the formulation is robust with respect to minor variations in composition. At the higher temperature, variation in pH had the largest impact on stability. Although multivariate experiments were carried out, no design space is claimed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Phase 1-3 clinical trials were carried out using a lyophilised formulation which was reconstituted before injection with sterile water for injections (WFI). The lyophilised powder contains a different tonicity agent and once reconstituted, is less acidic. Concentration, stability and osmolarity are similar between the two

formulations. Since both lyophilised and liquid formulations share the same IV route of administration, have comparable batch analyses and the active substance shows no sign of secondary or higher order aggregates, a bioequivalence study was not deemed necessary. The more practical liquid formulation was introduced into the phase 3 open label extension study and is intended for commercialisation.

Etelcalcetide degrades significantly on heating and terminal sterilisation was therefore determined not to be appropriate. Following compounding, the formulated solution is sterile filtered and filled aseptically into glass vials. Some manufacturing parameters and the vial dimensions were modified on transfer of the process from one manufacturer to another during development without any impact on finished product quality. Batches from both manufacturers were used in clinical and stability studies.

A holding study was carried out in order to assess the impact of prolonged contact between the formulated product and materials of the manufacturing vessels, piping and filters. No significant impact on product quality was observed: metal ion contact did not increase significantly and any organic leachables were below the levels of toxicological concern. Maximum processing times were defined for each step of the process. Given that the product is stored in a refrigerator, the applicant carried out fragmentation tests at low temperature to demonstrate that the rubber stopper can be pierced cold without compromising its integrity.

Compatibility studies were carried out with siliconised polypropylene syringes and PVC tubing for dialysis to be used in the clinical setting. The results indicate no compatibility issues.

The primary packaging is type I glass vials with fluoropolymer laminated elastomeric stoppers and aluminium seals with flip-off dust covers. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: dissolution and mixing of the excipients and active substance; sterile filtration; aseptic filling and capping. Formulation and sterile filtration were deemed critical steps appropriate limits for the IPCs have been set. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process (formulation, filtration and aseptic filling) have been validated using a bracketing approach. Two batches each (one at maximum vessel fill, one at minimum) of the 2.5 mg and 10 mg strengths were used. It was therefore deemed acceptable not to validate the 5 mg strength. Filter validation investigated membrane compatibility, extractables content and microbial retention with all results meeting the desired criteria. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (MS, HPLC), assay (HPLC), impurities (HPLC), sub-visible particles (USP), pH (Ph. Eur.), osmolarity (Ph. Eur.), deliverable volume (Ph. Eur.), container closure integrity (vacuum decay), sterility (Ph. Eur.) and endotoxins (Ph. Eur.).

The specified impurities have been toxicologically qualified although tighter limits are set in the specification in line with batch data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches of the 2.5 and 10 mg strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. In addition, batch results were provided for five pilot scale batches of the 2.5 mg strength and ten of the 10 mg strength, as well as results from eleven batches of the lyophilised formulation. All batches complied with the specifications in place at the time of release. No batch results from the 5 mg strength were presented which is considered acceptable since it is an intermediate strength made using the same process.

Stability of the product

A bracketing approach to stability was adopted, with only vials of the highest and lowest strength used for the stability study. The design is considered acceptable as the 5 mg presentation is an intermediate strength made using the same manufacturing process.

Stability data from three pilot scale batches each of the 2.5 and 10 mg strengths as well as two production scale batches of each strength stored for up to 24 months under long term conditions (2-8 ^{o}C) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of Parsabiv are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Results from an additional batch of each strength manufactured at a different site stored for up to 24 months under long term and accelerated conditions were also provided. Vials were stored either in an upright or inverted orientation.

Samples were tested for appearance, assay, impurities, pH, sub-visible particles, container closure integrity and sterility. No significant changes to any parameters other than assay and impurities were observed. An increase in impurities with an associated drop in assay occurred over time, relatively small under long term conditions but more pronounced at higher temperature, although results remained within the proposed specifications under both conditions.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Parsabiv is photosensitive and degrades when the vials are exposed to light. It was demonstrated that the outer carton provides adequate protection from light. An additional photostability study was carried out in order to assess the impact of lighting conditions likely to be encountered in a clinical setting. Results indicate that Parsabiv does degrade under such conditions but statistical analysis supports an in-use exposure of up to four hours outside the outer carton in a clinical setting.

Stressed stability studies were also carried out under conditions of heat and exposure to acid, base, neutral pH and oxidant. Degradation was observed under all conditions, more so under basic conditions and high temperature.

A transportation study was also carried out with vials exposed to vibration, pressure and shock events at 2-8 ^{o}C. Temperature cycling between -20 and 30 ^{o}C was also carried out. No impact on the measured parameters in either study was observed over the duration of the study.

Based on available stability data, the proposed shelf-life of 24 months at 2-8 ^{o}C in the outer carton protected from light as stated in the SmPC (section 6.3) is acceptable. Once removed from the refrigerator, Parsabiv should not be exposed to temperatures higher than 25 ^{o}C and must be used within 7 days if stored in the outer carton, or within 4 hours if removed from the outer carton.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Terminal sterilization is not feasible due to the instability of the active substance at high temperature which mandated the choice of sterile filtration. Since the process is considered non-standard, the process was validated prospectively using a bracketing approach.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Nonclinical pharmacology studies consisted of in vitro cell signalling studies to characterize the molecular pharmacology and target specificity of etelcalcetide on the CaSR. In vivo pharmacology studies utilized healthy dogs and rats and uremic rat models to characterize primary effects on PTH lowering and secondary effects on the complications of HPT.

Primary pharmacology - In vitro

Etelcalcetide is a calcimimetic that activates the CaSR signalling pathway both in HEK293T expressing CaSR and in isolated rat parathyroid gland. Potency of etelcalcetide in ex vivo isolated parathyroid gland is 25-60x

higher than potencies estimated by EC50 in an heterologous CaSR expression system. CaSR was abundantly expressed in the chief cells of the parathyroid gland, to a lesser extent in kidney tubules adjacent to glomeruli and in pancreatic islets of Langerhans, glandular cells of the stomach and small intestine, and to the least extent in thyroid parafollicular cells. Low expression in rat testis and rodent bone was only detected with the more sensitive methods. The similarity of CaSR expression across species supports the pharmacological relevance of the animal models.

Etelcalcetide did not block or potentiate binding of the ligand to any of a panel of class III GPCR receptors. This supports specificity of binding of etelcalcetide to the CaSR when compared to a panel of receptors, ion channels and transporters. The requirement of the amino terminal D-cysteine in etelcalcetide, and the dependence on the interaction of the D-cysteine with the CaSR-cysteine on position 482 in the hinge region for agonist activity was established. None of the other members of the class III GPCR family that share this hinge segment have a cysteine in this region. Together this suggests specific allosteric activity of etelcalcetide for CaSR.

Primary pharmacology - In vivo

In healthy dogs, etelcalcetide potentiates the calcium mediated activation of CaSR when administered at sufficiently high concentrations. In a 1K1C rat model of acute renal insufficiency rapid, reversible and dose dependent reductions in plasma PTH regardless of the degree of renal function or baseline PTH levels were observed upon etelcalcetide treatment. Consistent with a reduction in PTH, a dose-dependent reduction in serum calcium was also observed.

In a rat model of chronic renal insufficiency (5/6 Nephrectomy) etelcalcetide treatment effectively reduced PTH, prevented soft tissue calcification (aorta and heart), kidney mineralization and parathyroid gland hyperplasia in these uremic rats. Treatment with etelcalcetide also has a positive impact on the expression of the CaSR, VDR and FGFR1 when dosed for six weeks, and may have a positive effect on gland function in the background of chronic kidney disease. In addition, etelcalcetide treatment appeared effective in decreasing PTH levels and PTG weight, reducing bone turnover and normalizing mineralization in a rat model of secondary HPT due to renal insufficiency.

In 5/6 nephrectomy rats, that were fed a high phosphate (0.9%) and low calcium (0.6%) diet etelcalcetide decreased PTH levels, PTG weight, Ki67stained chief cells count and FGF23 levels. Cortical porosity, bone mineral density (femur diaphysis) bone strength endpoints such as maximal bone load, energy to failure and toughness trended power were all improved upon etelcalcetide treatment. However, none of the measured factors improved to the level of the control rats.

Etelcalcetide in uremic rats, in which uremia was induced by addition of 0.75% (w/w) adenine in a base diet, prevented development of increased PTG-weight, increased average Ki-67-stained parathyroid chief cell count and increase of the aortic calcium content.

Secondary pharmacology

An extensive discussion of literature, non-clinical and clinical data of etelcalcetide indicates that etelcalcetide is likely protective of bone health in secondary HPT patients due to normalization of high bone turnover in these patients. Long term animal studies and emergent clinical data do not indicate a propensity for Adynamic Bone Disease. Etelcalcetide carries no evident risk of carcinogenesis in various tissues. Nonclinical data indicate that etelcalcetide does not have a direct effect on cardiac morphology. There is no in vivo evidence of immune related sequelae from CaSR activation. The risk of etelcalcetide impacting the occurrence of Alzheimer Disease and Pulmonary Arterial Hypertension (PAH) in secondary HPT patients is considered

negligible. Overall, non-clinical and clinical data fit well with the data present in published literature on CaSR and calcimimetics**.**

Safety pharmacology

There was no significant change in hERG current up to the highest concentration tested (10 µg/mL), which is at least 42-fold greater than the estimated human Cmax (unbound) and 100 fold greater then clinical exposure at the maximum clinical dose of 15 mg. However, the originally submitted hERG channel test was regarded not - GLP compliant. With the responses the applicant has submitted a new hERG channel test, conducted under GLP compliance, from which results can be concluded that Parsabiv is not an inhibitor of the hERG channel.

Upon a single IV dose of 1.5 mg/kg etelcalcetide the pharmacological effect that was observed was a decrease in plasma PTH associated with a decrease in serum calcium and magnesium and an increase in serum phosphorus. A slight QTc prolongation, increased body temperature, heart rate and blood pressure were detected. These changes are considered secondary to hypocalcaemia and/or stress associated with adverse hypocalcaemia. QTc prolongation in patients is further discussed in the clinical AR and is included in the RMP.

Pharmacodynamic Drug Interactions

The potential for additive or synergistic effects on CaSR signalling with co-administration of cinacalcet and etelcalcetide was evaluated in two HEK293T cell lines stably transfected with the human CaSR. Co-administration of cinacalcet and etelcalcetide turned to be additive with respect to CaSR activation.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of etelcalcetide has been investigated upon single dose intravenous (IV) administration in rat and dog. Multiple dose toxicokinetics (TK) was examined upon IV administration, which is the intended clinical route, in rat, dog and pregnant rabbit. Subcutaneous multiple dose toxicokinetics was examined in rat and mouse only.

Methods of analysis

A liquid chromatography (LC) method with mass spectrometric detection (LC-MS/MS) was used for bioanalysis of etelcalcetide in plasma from the TK and PK studies. Validation reports for the analytical methods used, demonstrating the suitability of the methods for the purpose of analysis of etelcalcetide and its related products were provided. Metabolite profiling was performed by LC separation followed by ^{14}C and high resolution mass spectrometric (HRMS) detection. Structure assignments of etelcalcetide biotransformation products were based on comparison to authentic standards, calculated elemental composition of the products based on HRMS data, the ^{12}C and ^{14}C isotopic peak pattern, prior knowledge of retention times, and interpretation of the collision induced dissociation fragmentation data.

Absorption

Pharmacokinetics (PK) studies were performed in as single dose in species, strains and formulation(s) used in the pharmacology and toxicology studies. The intended clinical route of etelcalcetide is by IV administration; therefore, the kinetics of absorption upon delivery by a non IV route was not studied.

The PK of etelcalcetide was studied following IV bolus administration to Sprague Dawley (SD) rats with normal renal function or varying degrees of renal insufficiency, and after IV bolus administration to beagle dogs with normal kidney function. Plasma exposure of etelcalcetide was dose proportional over the dose-range tested. Etelcalcetide clearance was strongly dependent on renal function. Removal of both kidneys in rats (BN rats) resulted in a 3-fold reduction in etelcalcetide clearance and in a 3-fold increase in exposure compared to rats with normal kidney function. The volume of distribution was 0.5 L/kg in normal rats and 0.7 L/kg in BN rats, indicating good tissue penetration. Elimination was fast in rats with normal kidney function (~1.3 h) and moderate to slow (~6.7 h) in BN rats. In dogs, with normal kidney function, similar pharmacokinetics were found with a CL of 0.4 L/h/kg, a volume of distribution of 4 L/kg and a terminal elimination of 10 h. In humans similar pharmacokinetics was found upon IV administration to CKD patients, having a 5-fold higher exposure and 6-fold higher terminal elimination half life (3 – 5 d).

The repeated dose PK profile of etelcalcetide was obtained from toxicokinetic studies only and determined in rat, rabbits and dogs following IV infusion and in rat and mouse upon SC administration. Subcutaneous administration was only studied in repeated dose TK studies. Overall, on multiple dosing, over the dose range examined, plasma concentrations and exposure generally increased in proportion to dose and there was no evidence of gender differences or appreciable accumulation (< 2-fold) with repeat IV or SC dosing for up to 6 - 9 months in normal rats or dogs. As observed in single dose studies, after multiple dosing in rat or dog, by IV administration, a rapid initial decline in plasma levels from maximum concentration was observed followed by a slower elimination phase, indicating good distribution into the tissues. Subcutaneous pharmacokinetics showed a relatively fast absorption phase with peak concentrations occurring at the first time point measured (usually 15-30 min) after dosing in rats and mice. Thereafter, the PK profile followed a similar profile as observed upon IV dosing.

Distribution

The vivo tissue distribution of [^{14}C]-etelcalcetide was determined in male and female SD rats and in male Long Evans (LE) rats by quantitative whole body autoradiography. No sex- or strain-dependent differences in tissue distribution of etelcalcetide-related radioactivity were observed. In general, for most tissues, the highest tissue concentration of radioactivity was found 1 h post-dose, declining thereafter with the exception of kidney and liver having a tissue Cmax at 12h post dose. The highest total tissue exposure over plasma exposure ratio was observed in the kidney (630x), liver (68x), cartilage (intervertebral (58x), hyaline (176x) and articular (26x)), epiphyseal plate (53x), spleen & bone marrow (61x), and lymph nodes (54x). Between 2 to 84 days tissue levels declined slowly. The ^{14}C-radioactivity half-life in tissues was generally longer than in plasma (140 h). Etelcalcetide-related radioactivity was even still present 84 days after dosing in bone marrow, cartilage, eye, kidney, lymph node, small intestine, spleen, thymus and thyroid. Longest ^{14}C half life was found in the thyroid (>84 d), which may be related to its pharmacological target, the CaSR in the parathyroid. In the 6 month toxicity study a cytoplasmic eosinophilia was found in the parathyroid gland. This was considered reflective of increased chief cell activity related to etelcalcetide pharmacology. The lowest levels were detected in the brain and bone. When comparing SD and the pigmented Long Evans rats in the whole body autoradiography, the distribution profile was similar although a higher exposure and slower decline was found in the eye (~17 fold) as compared to the SD rat. In toxicology studies, however, no toxicological findings were reported for the (pigmented) eye in dog, suggesting that melanin binding apparently has no toxicological consequences. Of the tissues with moderate to high concentration of etelcalcetide-related radioactivity, cartilage (intervertebral, hyaline, and articular), and epiphyseal plate are of interest as literature suggests that the CaSR has a functional role in cartilage and bone regulating skeletal homeostasis.

The in vitro / in vivo protein binding studies of etelcalcetide in rat and human showed substantial protein binding, which was a combination of a reversible covalent binding (40%-70%) mainly to albumin, and of a non-covalent plasma protein binding in animals and humans of the resulting etelcalcetide.

The covalent binding to form serum albumin peptide conjugate (SAPC) from etelcalcetide in human whole blood was fast reaching steady state by 3 hr. Non-covalent binding of etelcalcetide to plasma proteins was low to moderate, similar across species (fraction unbound range: 0.53 to 0.77) and was independent of concentration of albumin. This means that free etelcalcetide levels are about 1.2 and 1.5 fold higher in rat and dog, respectively, than in humans. It should be noted that etelcalcetide bioanalysis method uses protein precipitation, which means that the covalently albumin bound etelcalcetide (SAPC) is not included in the reported exposure levels.

Blood to plasma (B/P) ratio of etelcalcetide in blood from rat, healthy humans, and humans with CKD was 0.52, 0.53, and 0.66, respectively indicating no preferential partitioning of etelcalcetide into red blood cells but retaining in the plasma compartment.

Placental transfer studies of etelcalcetide were investigated in rats upon IV administration. The observed mean percent of fetal plasma to maternal plasma concentration at 1-2h after dosing was 3 % on GD 21, indicating low placental transfer of etelcalcetide. In the rat fetal development study no toxicological effects were found upon etelcalcetide dosing.

Transfer of etelcalcetide to the milk was investigated in rats upon IV administration. [^{14}C]-etelcalcetide-derived radioactivity was excreted in milk at concentrations similar to those in plasma. Cmax in milk was reached at 8 h after administration, at which time the milk/plasma ratio was 3.3 fold.

Metabolism

In vitro metabolism of [^{14}C]-etelcalcetide, which was studied in hepatocytes, liver and kidney metabolizing fractions and rat and human whole blood, appeared relatively fast. Etelcalcetide was predominantly biotransformed via replacement of the L-cysteine moiety of etelcalcetide, whereas the D-amino acid backbone of the molecule remained intact. A similar metabolizing profile was found in rat and human whole blood. Overall, the evidence demonstrated that the biotransformation of etelcalcetide was predominantly the result of disulfide exchange rather than via metabolism by conventional metabolizing enzymes such as proteases or cytochromes P450.

The in vivo biotransformation of etelcalcetide was only assessed following IV dosing in bile duct cannulated (BDC) rats with intact kidney function and in bilaterally nephrectomised rats. A substantial proportion of the plasma radioactivity was covalently bound to plasma proteins via a disulfide link to the D-amino acid peptide portion of etelcalcetide, mostly as serum albumin peptide conjugate (SAPC, 42% of plasma AUC in normal rats and 19% in BN rats as compared to 59% and 71% in whole blood of rat and human). Biotransformation, as shown in vitro, was predominantly via replacement of the L-cysteine moiety; the D-amino acid backbone of the molecule remained intact. The most abundant non-protein adducted circulating components in rats with intact kidney function included [^{14}C]-etelcalcetide (21.4-44.1%), M10 (22.3-28.0%) and M1 (2.6-6.7%). The plasma metabolic profile was slightly different in bilaterally nephrectomised male rats wherein the proportion of M1 (22.5%) was slightly higher. These metabolites were also observed in human plasma.

Urine of rats with normal kidney function contained mainly intact drug (37%-47%) or the biotransformed products M1, M3, M2b. Overall renal elimination was minimal in bilaterally nephrectomised rats and therefore not studied. Excretion into faeces and bile was minor, and therefore these matrices were also not profiled for metabolite presence.

The kinetics of etelcalcetide and SAPC was characterized in vitro in healthy human whole blood. The metabolism of etelcalcetide by disulfide exchange with endogenous thiols in blood (e.g., L-glutathione) was relatively fast leaving 50% of intact etelcalcetide after 1h and yielding equilibrium after 3-4 h. SAPC was the predominant product formed, composing approximately 60% of all etelcalcetide related products, when etelcalcetide was incubated in whole blood. The disulfide exchange was reversible. The reverse reaction wherein etelcalcetide was formed from SAPC was 18-fold slower. Similarly, the disulfide exchanges that resulted in the formation of the aggregate of all non-protein biotransformed products from etelcalcetide were 2-fold faster than the reverse reactions.

Excretion

The excretion of etelcalcetide was determined following a single IV administration of [^{14}C]-etelcalcetide in bile cannulated rats with normal and no kidney function. The results showed renal elimination was the predominant in vivo clearance pathway for etelcalcetide in rats with normal kidney function (80%). The [^{14}C]-etelcalcetide was not eliminated by non-renal pathways in the nephrectomised rats. There was minor excretion in faeces (< 4%) and bile (< 1%). Excretion in other preclinical species, such as dog, was not assessed.

The dialysis properties of [^{14}C] etelcalcetide-derived radioactivity were determined in an in vitro study. Intact etelcalcetide was readily dialyzed by a clinical dialyzer, and etelcalcetide related components were readily removed by dialysis but was significantly attenuated when etelcalcetide was preincubated for 3 hr in bovine whole blood to form SAPC. These in vitro study results indicate administration of etelcalcetide during haemodialysis would result in a significant loss of non-protein bound etelcalcetide.

These data are in line with data in humans, where the urine is the major route of elimination, while a lower percentage of radioactivity was recovered from faeces. In CKD patients in urine and faeces combined only 7% of the dose was excreted, while dialysis contained 60%.

2.3.4. Toxicology

Single dose toxicity

Such studies were not conducted with etelcalcetide, consistent with ICH M3(R2).

Repeated dose studies

In rats, etelcalcetide was well-tolerated up to 1 mg/kg/day after up to six months exposure. Observed effects were similar over studies, including concordance of effect types and severity in the two six-month studies performed. A dose-dependent decrease of serum PTH and serum calcium was observed at all doses, from 5 minutes after dosing. Eight to 24 hours after dosing these parameters were returned to baseline levels. At doses higher than 1 mg/kg/day, the level of hypocalcaemia was considered adverse and was accompanied by characteristic stress responses. These included body weight and food consumption decreases as well as clinical signs, such as tremors, convulsions, prostration, decreased activity, lethargy, dyspnoea and dehydration. In addition, thymus, spleen and adrenal gland weight were decreased, accompanied by lymphoid depletion in the thymus and a reduction in splenic red pulp. Also neutrophils were increased and white blood cells decreased. After recovery, no adverse findings were detected and serum PTH, calcium and phosphorus levels were returned to normal. The rat/human exposure ratio at the rat NOAEL was between 0.22 and 0.82, therefore, there are no safety margins.

In dogs, etelcalcetide was well-tolerated in one month studies up to 0.3 mg/kg/day, in the combined 3 and 9 month study up to 0.5 mg/kg/day and a NOAEL was not reached in the 6 month study (LOAEL 0.2 mg/kg/day). Observed effects were comparable over studies, including concordance of effect types (e.g. decreased body weight, decreased food consumption, QTc prolongation, decreased activity, prostration, lethargy and salivation among others) and severity in the combined non-GLP 3 and 9 month study and the GLP six-month study. However, adverse effects were observed at a lower exposure in the 6 month study (body weight and QTc prolongation) compared to the combined 3 and 9 month study. The dog/human exposure ratio at the NOAEL was 0.5 for the 3 and 6 month study. At the LOAEL the dog/human exposure ratio was 1.0 for the 3 and 6 month study and 0.12 for the 6 month study.

In mice, etelcalcetide was well-tolerated at a dose of 1.5 mg/kg/day in treatment up to a month. Serum calcium was decreased and serum phosphorus increased at all doses tested, but was only considered adverse at doses 1.5 mg/kg/day in males and at 3.0 mg/kg/day in females. This is agreed. At higher doses, mortality was observed (6 mg/kg) accompanied by clinical signs, which are related to hypocalcaemia and related stress, including tremors, ataxia and effects on activity (≥3 mg/kg/day in males and ≥6 mg/kg/day in females). Redness, haemorrhage, and inflammation at the injection site of females was observed at high dose. The NOAEL for the mouse was 1.5 mg/kg/day for males and 3 mg/kg/day for females, with etelcalcetide exposure 0.17-0.25 times the exposure to humans at the MRHD.

Toxicokinetic profiles were comparable between sexes for rat, dog, mouse and rabbit. Overall, on multiple dosing, over the dose range examined, plasma concentrations and exposure generally increased in proportion to dose and there was no evidence of gender differences or appreciable accumulation (< 2-fold) with repeat IV or SC dosing for up to 6 - 9 months in normal rats or dogs. Due to overt hypocalcaemia related adverse effects in healthy animals, the exposure at the NOAEL in animals was consistently lower compared to human exposure at the MRHD.

Genotoxicity

Etelcalcetide was found positive in two Salmonella strains (TA100 and TA1535) in the bacterial mutagenicity assay and was found negative in the chromosomal aberration test in vitro and in vivo, negative in gene mutation tests (CHO and CHL cells) and negative in the Muta Mouse assay.

A further thorough investigation of the positive results in the bacterial mutagenicity assay was performed. In following experiments it was excluded that positive results were induced by free amino acids or impurities.

Additional mechanistic studies were performed to understand the mechanism behind the positive response in the bacterial mutagenicity assay. Structurally related peptides were tested and removal of the D-cysteine from the peptide backbone completely eliminated mutagenic activity. This observation suggests that a thiol (RSH) or thiolate anion (RS-) is important for mutagenic activity of etelcalcetide. Further investigation showed that biotransformation of etelcalcetide is limited to disulphide exchange with the D-cysteine, that the peptide backbone is stable in S. typhimurium and that it is unlikely that free L-cysteine is mediating the mutagenic activity of etelcalcetide in TA1535. Furthermore, it was found that TA1535 is sensitive to known oxidative mutagens, which suggests that TA1535 may be susceptible to ROS-mediated mutagenesis. This was confirmed by co-administration of an oxidant with anti-oxidants and iron-chelators in strain 1535, which showed that TA1535 is sensitive to free radical-mediated mutation under certain oxidant conditions, and that etelcalcetide may be inducing mutations via ROS formation. Other thiol-containing peptides and amino acids have been shown to be mutagenic in the bacterial mutagenicity assay, including L-cysteine, glutathione (GSH), N-acetyl cysteine, and cysteinyl glycine.

Carcinogenicity

In a six-month carcinogenicity study in Tg.rasH2 mice and a two-year carcinogenicity study in rats, no etelcalcetide related (non)-neoplastic microscopic changes or increased tumour incidence was observed. Both species were treated subcutaneously due to the technical limitations of dosing mice and rats by the IV route daily for the study duration.

Because of decreasing survival in high dose groups and vehicle controls, groups were terminated early. This is agreed, as it is in accordance with OECD guidance 416, the EMA Note for Guidance on Carcinogenic Potential (CPMP/SWP/2877/00) and termination plans approved by FDA's Executive Carcinogenesis Assessment Committee (ECAC).

An increased incidence of fibrosis (rat) and inflammation and haemorrhage (mice) at the injection site was observed in vehicle control and etelcalcetide injected animals, but was not observed in the saline control group. These effects are considered vehicle related.

Exposure at the high dose in both rat and mice studies was relatively low, with an animal/human exposure ratio of 0.4 for both rat and mice compared to human at the MRHD. This is due to the increased sensitivity of animals with normal renal function to the hypocalcaemic effects of PTH lowering.

Reproductive toxicity

Etelcalcetide did not induce malformations in offspring of rats and rabbits at exposure marginally above the intended human exposure (animal/human exposure ratios of 1.6 in rat and 4.3 in rabbit). Distribution studies showed limited placental transfer in the rat (2.9%), but exposure in the rat foetuses was observed (20 ng/mg).

In rats, etelcalcetide induced effects associated with hypocalcaemia at the high dose during gestation and lactation. There was a small delay in parturition and reduced pup weight at the mid and high dose, in addition to an increased incidence of dehydration in the pups and pup mortality at high dose. The effects of etelcalcetide on pre-weaning pup weights continued into the post-weaning period in the F1 generation males. The NOAEL for F0 and F1 was 0.75 mg/kg/day at end of rat gestation, this corresponded to a rat/human exposure ratio of 0.46.

Studies in juvenile animals were not conducted as etelcalcetide is developed for the treatment of secondary HPT in adult patients (18 years of age and older) with CKD on haemodialysis.

Local tolerance

No haemolytic potential was observed for etelcalcetide in human blood cells and IV and para-venous injection of a single dose etelcalcetide 15 mg/injection was well-tolerated in Beagle dogs.

Other toxicity studies

There is no evidence that etelcalcetide is immunogenic in animals.

Dependence is not expected based on lack of chemical or pharmacological similarity with other drugs, very limited CNS distribution, lack of behavioural observations in safety pharmacology and repeat dose studies, and no off-target binding to receptors linked with abuse potential.

In accordance with regulatory guidance ICH M3(R2), studies on metabolites were not conducted.

The impurity isopropyl hydrogen sulphate was evaluated for mutagenicity in a bacterial reverse mutation assay and was not found mutagenic. One month repeated dose studies in rat and dog showed that impurities do not present an additional risk compared to etelcalcetide.

Studies or information on phototoxicity of etelcalcetide or its metabolites/degradation products are not necessary according the note for guidance of photo-safety testing (EMA/CHMP/SWP/336670/2010) as the MEC for etelcalcetide < 1000 L mol-1 cm-1.

2.3.5. Ecotoxicity / environmental risk assessment

Because the compound is a synthetic peptide, no further ERA is necessary. Therefore etelcalcetide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In vitro primary pharmacology studies sufficiently show specificity of etelcalcetide for interaction with CaSR evoking an allosteric stimulation in absence, but more efficiently in the presence of low levels of calcium, both in *in vitro* and *ex vivo* test systems.

In vivo primary pharmacology of etelcalcetide has been sufficiently studied. Several models of secondary HPT were generated in rats by feeding a special diet and / or removing (parts of) the kidney(s). Treatment with etelcalcetide restored PTH and subsequent calcium levels, prevented PTG hyperplasia, high bone turnover, mineralization of aorta, heart and kidneys and a decrease in bone strength. Also FGF23 levels and VDR, CaSR and FGFR1 expression were restored. Dependent on the model the above mentioned parameters restored near to normal or completely to normal levels.

Secondary pharmacology has been extensively discussed and is regarded sufficient. The specificity of the peptide for its target and the absence of any toxicity signals, other than caused by exaggerated pharmacology, that point towards off target effects of the peptide, does not warrant studies addressing secondary pharmacology.

Safety pharmacology studies included an *in vitro* hERG channel test and one *in vivo* test in beagle dog to address potential effects of the compound on CNS, respiratory and cardiovascular systems. From the results of the newly submitted hERG channel test, conducted under GLP compliance, it can be concluded that Parsabiv is not an inhibitor of the hERG channel. The applicant attributed the QTc prolongation that was observed to decreased calcium levels, which is related to the primary pharmacology of etelcalcetide in healthy animals. As reflected in the RMP, cardiovascular function of patients treated with etelcalcetide will be monitored.

One pharmacodynamic drug interaction study was conducted with etelcalcetide and cinacalcet showing that activities of both calcimimetics on CaSR were simply additive.

In summary, the package of studies investigating the pharmacology of etelcalcetide was sufficient.

Toxicology

Stress responses are identifiable for many routinely evaluated clinical and anatomic pathology parameters (Everds et al. 2013). Etelcalcetide induced effects on organ weights (decreased thymus and spleen weight

and increased adrenal gland weight) and concurrent pathological changes (lymphoid depletion in thymus, altered leukocyte counts and stomach erosion) are secondary effects due to stress. In addition, haematological and histopathological findings of stress only occurred at doses where evidence of stress and hypocalcaemia was observed. These stress related effects are described thoroughly in ICH S8 annex 1.4 Interpretation of Stress Related changes and in the article of Everds et al (2013). Therefore, these adverse effects can be related to stress and thus are probably not relevant for the human situation.

Intra-cytoplasmic golden-brown pigment in the proximal tubules were observed in rat in the 6-month study at high dose only and in dogs in all dose groups of the 3, 6 and 9 month studies. After recovery this was fully reversible in rats, but in dogs the pigment was present with reduced severity at high dose, suggesting ongoing reversibility. The identity of the pigment and mechanism of increase is uncertain. Possible explanations are an increase in etelcalcetide or serum albumin peptide conjugates due to efficient tubular reabsorption of peptides or albumin. Alternatively it may reflect an increase in lipofuscin, a common background finding in the kidney of dogs, however this is less likely, as this effect was also observed in rat. The finding is considered non-adverse as no associated degenerative microscopic changes in the kidney were observed.

Etelcalcetide induced a slight increase in QTc interval in both male and female dogs at most doses. QTc changes were anticipated due to decrease in serum calcium (Scheidegger and Drop, 1979). In dog safety pharmacology studies, it was additionally shown that QTc interval increase was directly associated with decreased serum calcium levels and not with a decrease in PTH. QTc changes have also been observed in patients and therefore monitoring of QTc has been included in the RMP.

It is acknowledged that healthy animals are more sensitive to the hypocalcaemic effects of etelcalcetide compared to disease model animals with a decreased kidney function. Etelcalcetide induced pharmacological effects (decreased PTH and serum calcium and increased phosphorus) were observed at relatively low exposure, without any adverse signs, in healthy animals compared to human exposure in patients. Because of the wide bio-distribution of etelcalcetide (see PK section) with higher levels of etelcalcetide exposure in most tissues compared to serum levels, it can be reasoned that AUC is not a representative measure of exposure. On the other hand, it can be argued that bio-distribution in animal and human will be comparable, in which case etelcalcetide serum levels are a valid means to compare animal to human exposure.

Taking this into account, due to the increased sensitivity of healthy animals to the hypocalcaemic effects, only exaggerated pharmacological effects related to hypocalcaemia or secondary stress are observed at exposure levels comparable to clinical levels in human (rat/human exposure margin of 2.0 at doses inducing hypocalcaemia). These exaggerated pharmacology effects are not relevant for the clinical situation, as in the clinical situation the dose will be adjusted based on levels of calcium in the blood. Theoretically, the hypocalcaemia induced adverse effects may dominate possible other adverse effects, which may be observed at higher exposure levels in animals with a decreased kidney function and in the clinical situation. Therefore, the performed studies are not able to capture possible adverse effects occurring at exposure levels relevant to human. So a large battery of toxicology tests involving many test animals has been performed with only very limited relevance for the clinical situation and thus could only be considered as supportive. Alternative studies might have provided a better understanding of possible adverse effects by etelcalcetide in the clinical situation. Although more information on the lack or presence of adverse effects at an exposure equal to the human situation would have been preferred, the current repeated-dose toxicology package shows a pharmacological effect already at relatively low exposure compared to pharmacology induced adverse effects and, in addition, shows similarity to pharmacology induced adverse effects (hypocalcaemia related) observed in human. Additionally, although less in-depth examined than species in the repeat-dose studies, in the rabbit

embryo-foetal toxicity studies no signs of toxicity were seen at more relevant higher exposures. Therefore, the toxicology package is deemed sufficient.

The investigation of genotoxicity was performed adequately.

In the two-year rat study, the Peto trend test for survival was statistically significant for female pituitary gland adenomas of the pars distalis linked to survival compared to saline and vehicle control. This was due to an outlier pituitary mortality ratio during week 89. The number of pituitary gland adenomas in male and female rats were not statistically increased compared to controls, and the incidence of pituitary gland adenomas in females was not dose/exposure dependent, and was similar to historical control. Besides, pituitary tumours generally alter the normal pituitary organ axis and induce secondary changes in pituitary axis target tissues, such as mammary tumours, which was not observed in this study. Furthermore, limited distribution of etelcalcetide in the central nervous system was observed. Therefore, the statistically significant Peto trend test for pituitary gland adenomas in females was considered neither biologically significant nor etelcalcetide-related.

Regarding immunotoxicity, based on repeat-dose toxicity studies, there is no evidence of primary etelcalcetide induced immunotoxicity in animals. Although decreases in numbers of immune cells and thymus and spleen weight have been observed in rat and dog repeated dose studies, and also a high concentration of etelcalcetide is observed in lymph nodes (see nonclinical pharmacokinetics section), there is a vast amount of evidence indicating these findings are in agreement with adverse effects associated with stress, as described in ICH S8 Annex 1.4 and by Everds et al. 2013.

2.3.7. Conclusion on non-clinical aspects

Marketing authorization for Parsabiv (etelcalcetide) may be granted from a non-clinical point of view related to pharmacology, pharmacokinetics and toxicology, as no major objections have been identified.

2.4. Clinical aspects

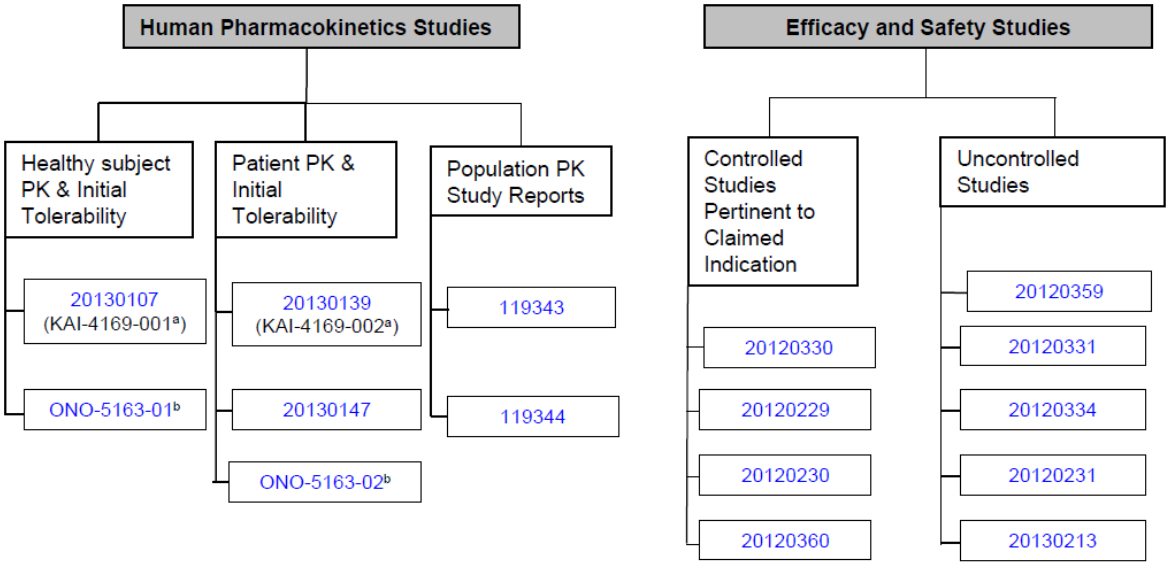
2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- overview of clinical studies



2.4.2. Pharmacokinetics

Two studies in healthy volunteers and three studies in CKD patients were submitted to support the pharmacokinetics of etelcalcetide. Furthermore, three phase II studies (studies 20120330, 20120331, and 20120334) and three phase III studies (studies 20120229, 20120230, and 20120231) in patients with chronic kidney disease receiving haemodialysis, with limited and sparse sampling data were submitted to be included in popPK and PK/PD modelling. In addition, 10 reports covering in vitro data and 1 report with population pharmacokinetic analysis were submitted.

Analytical methods

The LC-MS/MS methods applied were sufficiently validated. Validation proved that the methods were specific, precise and accurate. Stability was shown covering study sample handling and storage. During method development, plasma was acidified, as in non-acidified plasma, etelcalcetide was more sensitive to stability problems. Based upon the analytical reports, run performance was within normal criteria and ISR data showed acceptable reproducibility.

Bioequivalence

Etelcalcetide is administered as a solution for injection. Two formulations were used in the clinical studies, i.e. a lyophilized powder for reconstitution for injection and a sterile liquid for injection. Considering that both formulations are solutions for injection and taking into account the excipients, no influence on bioavailability/pharmacokinetics is expected.

Linear pharmacokinetics in AUC is observed in healthy subjects and patients on haemodialysis with secondary hyperparathyroidism. At steady state, in CKD patients, the etelcalcetide accumulation ratio was about 2- to 3-fold. Steady state was observed at about 4 weeks. The SmPC recommends to titrate the dose no more frequently than every 4 weeks, which would be in line with reaching expected steady state levels.

Etelcalcetide pharmacokinetics shows a moderate between-subject variability of about 50%. PopPK analysis indicated that the inter- and intra-individual variability in etelcalcetide distribution and elimination were relatively moderate to high (22 - 88%). Intra-subject variability was not evaluated.

Distribution

Etelcalcetide is not actively distributed into red blood cells. Etelcalcetide binds moderately to plasma proteins (about 55%) and binding was concentration independent. Plasma binding in plasma from healthy volunteers and CKD patients was comparable. Drug-drug interactions due to protein displacement are not expected with etelcalcetide.

Based upon animal data, etelcalcetide may transfer over the placenta and may be excreted into milk.

The Vd in patients after single i.v. dosing was about 200 - 300 l. PopPK analysis indicate that in a typical patient, the steady-state volume of distribution was approximately 795.9 l, largely exceeding total body water. The mean Vss estimated in healthy subjects was also large (143.7 l). This may be attributed to the fast yet dynamic conjugation of etelcalcetide with albumin and possibly other plasma proteins. Given that this is a slow but dynamic process, conjugates (mainly albumin-conjugates) can be viewed as a reservoir for etelcalcetide, thus contributing to the moderately high estimate of volume of distribution.

Metabolism

In vitro data show that biotransformation of etelcalcetide appears to be the result of redox and/or chemical conversions rather than via metabolism by conventional metabolizing enzymes such as cytochrome P450 enzymes.

The inactive biotransformation products consist of mixed disulphides that arise from a reversible disulphide exchange of the L-cysteine moiety of etelcalcetide with other etelcalcetide molecules or endogenous thiols. The major product was a high molecular weight serum albumin adduct (SAPC). Other biotransformation products, formed upon disulphide exchange with low molecular weight thiols in blood such as glutathione and cystein-glycine, were also observed.

Haemodialysis was the predominant elimination pathway (approximately 60% of the estimated administered dose). The dialysate ^{14}C elimination rate half-life (mean, 40.2 days) was similar to the plasma terminal ^{14}C half-life (mean, 35.9 days). In patients on haemodialysis, minor amounts of the dose were excreted in urine (estimated mean, 3.2% of administered dose) and in faeces (estimated mean, 4.5% of administered dose).

After dialysis, etelcalcetide plasma levels partly rebounded, due to back conversion of etelcalcetide from the human serum albumin peptide conjugate (SAPC).

In healthy Japanese subjects, the amount excreted in urine over 48 h was 28.4% at the 5 mg dose level, which is in line with the fact that the major part of etelcalcetide is in the form of the human serum albumin peptide conjugate, which cannot be excreted in urine.

Elimination

The plasma elimination half-life and clearance of etelcalcetide after single dose in healthy volunteers is about 18 – 20 h and 5.4 – 8.1 l/h, respectively, and in patients on haemodialysis with secondary hyperparathyroidism about 128 – 183 h and 1.2 – 1.9 h, respectively.

The PK differs greatly between healthy subjects and patients receiving haemodialysis, because etelcalcetide is cleared by normal renal function, while the predominant clearance pathway for patients is haemodialysis.

The presence of binding anti-etelcalcetide antibodies had no apparent impact on plasma etelcalcetide concentrations.

A starting dose of 5 mg etelcalcetide is selected as at this dose, reductions in PTH in the patient population was observed. A dosing frequency of t.i.w. at the end of haemodialysis sessions was selected because haemodialysis effectively removes plasma etelcalcetide in patients. As mentioned before, plasma etelcalcetide concentrations are essentially at steady state after t.i.w. dosing for 4 weeks which supports the every 4 week dose titration schedule in the phase 3 studies.

Special patient groups

Based upon pre-dose concentrations and population pharmacokinetic analysis a small, but clinically non significant effect of gender and body weight was observed. Furthermore no effect of age and race was observed on the pharmacokinetics of etelcalcetide.

The etelcalcetide pharmacokinetics differs greatly between healthy subjects and patients receiving haemodialysis because etelcalcetide is cleared by normal renal function, while the predominant clearance pathway for patients is haemodialysis. However, the indicated patient group is CKD patients on dialysis, meaning that the recommended dose is based upon the data from this patient group.

No studies have been carried out in subjects with impaired hepatic function. Based on the metabolism and excretion pathways, it is not expected that a decreased hepatic function would affect the pharmacokinetics of etelcalcetide.

Interactions

In vitro data indicated that etelcalcetide is not metabolised by cytochrome P450 enzymes. In vitro data showed that etelcalcetide is not a substrate, inducer or inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In addition, etelcalcetide is not a substrate or inhibitor of Pgp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, PEPT1, or PEPT2. In addition, etelcalcetide did not inhibit BSEP. The renal transporters MATE1 and MATE2-K were not evaluated which is agreed considering the patients group where kidney function is largely absent.

No in vivo interaction studies are carried out. Based upon the available in vitro data, no interactions are expected on CYP and transporters level.

2.4.3. Pharmacodynamics

Mechanism of action

Secondary HPT is a disorder characterized by parathyroid gland hyperplasia and increased concentrations of circulating PTH. The disease is seen most commonly as a consequence of CKD. The principal regulator of PTH secretion is the calcium sensing receptor (CaSR) in parathyroid tissue. Calcimimetics target the CaSR in parathyroid tissue (Brown and Hebert, 1996; Brown et al, 1993), and provide a means of regulating PTH.

Etelcalcetide is an allosteric activator of the CaSR, binding directly to the extracellular domain and activating the receptor at a site which is distinct from the calcium activating site.

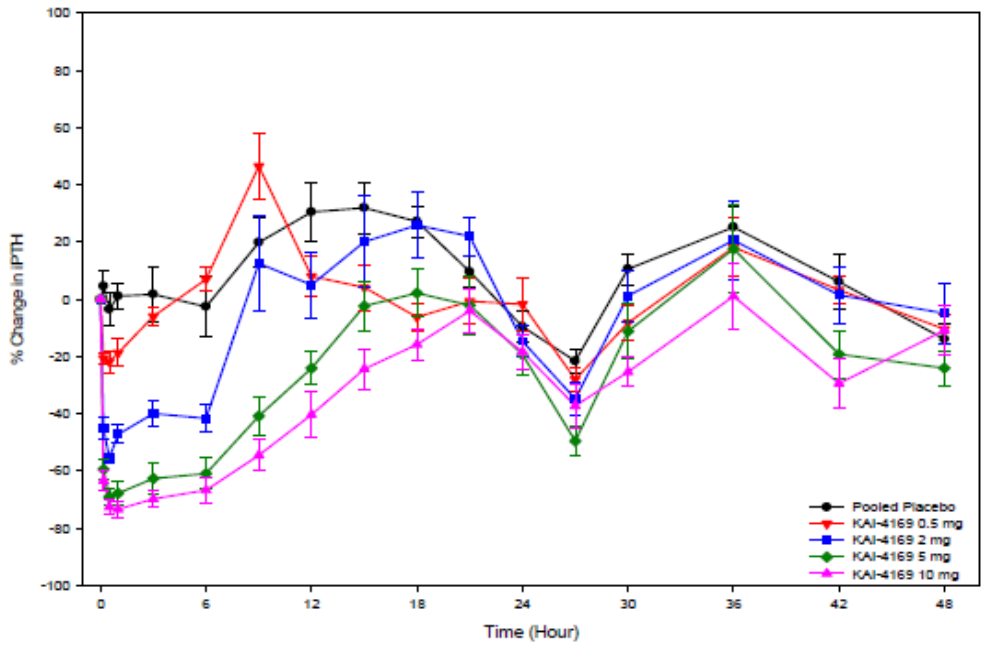
Primary and Secondary pharmacology

Four studies were primarily clinical pharmacology studies: one single dose study in healthy volunteers, one single dose study in non-Japanese patients, and two other studies performed in healthy Japanese subjects and in Japanese patients with secondary HPT receiving haemodialysis. The latter two are not considered sufficiently relevant for the current application and are therefore not separately discussed.

The **healthy volunteers single dose study** (20130107 (KAI-4169-001)) included 4 cohorts: 0.5, 2, 5 and 10 mg etelcalcetide administered by i.v. bolus injection. Each cohort included 8 subjects (randomized 6:2 to etelcalcetide or placebo). A total of 32 healthy men were enrolled and dosed.

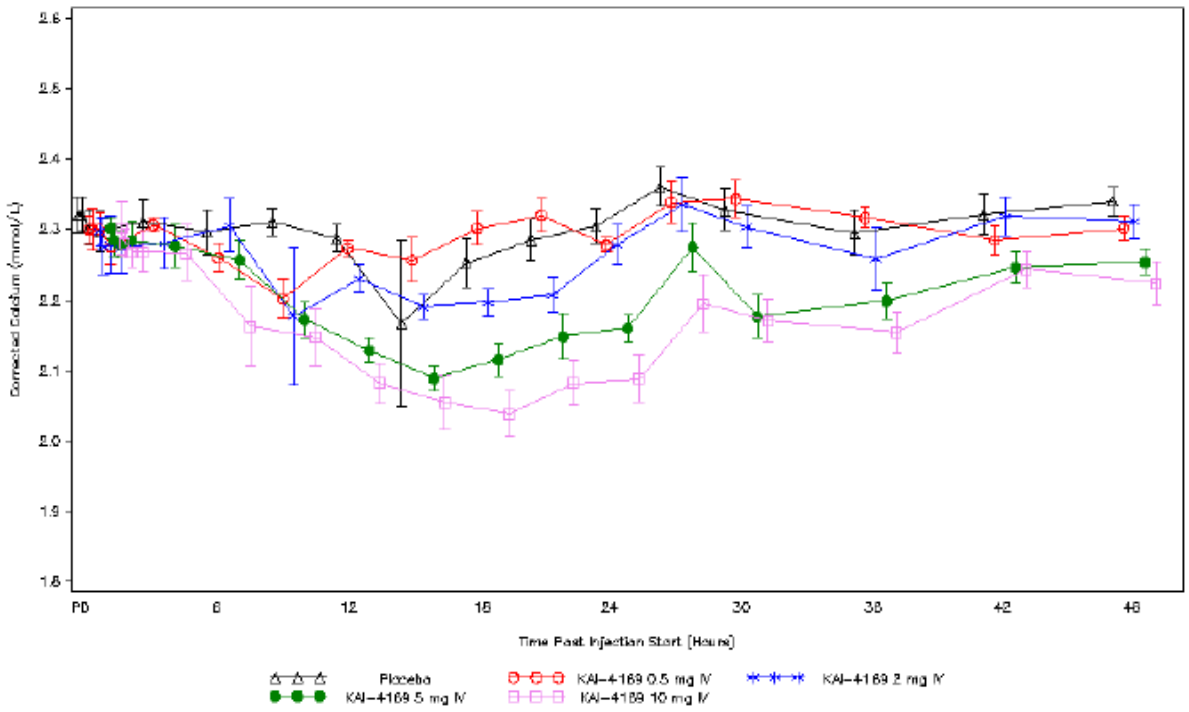
After a single i.v. dose of etelcalcetide, PTH nadir was seen after about 30 minutes. The maximum serum PTH reduction from baseline in the placebo, 0.5, 2, 5, and 10 mg dose groups was 3.5%, 21.7%, 55.4%, 69.0%, and 72.6%, respectively. The mean percent change from baseline in serum PTH over time is shown in figure 1 below. The maximum PTH suppression was transient and serum PTH levels gradually returned to baseline within 10 to 24 hours in healthy volunteers. The second dip in PTH levels in the healthy volunteers between 24-30 hours seen in placebo and treated subjects is likely due to the known circadian rhythm of serum PTH.

Figure 1 Mean (± SEM) Percent Change From Baseline in Serum PTH Over Time in Healthy Volunteers



Serum calcium concentrations decreased slowly after dose administration and reached the maximum decrease at 15 to 18 hours postdose in healthy volunteers. Mean serum calcium over time is shown in the figure below. Reduction of calcium is an expected consequence of PTH lowering. Serum calcium concentrations in the 2 mg i.v. dose group returned to baseline by approximately 24 hours whereas those of the 5- and 10 mg i.v. dose groups returned to baseline within approximately 48 hours in healthy volunteers.

Figure 2 Mean (± SEM) Serum Calcium Over Time



In the **single dose patient study** (20130139) a 2-period crossover design was used for cohorts 1 to 3 (i.v. doses of 5, 10, and 20 mg) with a 7 to 14 day period between etelcalcetide or placebo administration. Four subjects were enrolled in each cohort and were randomized 1:1 to etelcalcetide or placebo. The protocol was subsequently amended to remove the crossover design for cohorts 4 and 5, and 8 subjects were enrolled in cohorts 4 and 5 with 1:1 randomization. A total of 28 subjects (20 men and 8 women) were enrolled and dosed.

Parathyroid hormone decreased maximally by approximately 30 minutes and in a dose-dependent manner after single doses of etelcalcetide in CKD patients receiving haemodialysis. The duration of maximal PTH reduction and time to return to baseline appeared to be dose-related. At 65 hours postdose, serum PTH was suppressed -48.5%,-49.3%, and -62.6%, in the 20, 40, and 60 mg dose groups, respectively (see figure 3 below).

Serum calcium concentrations decreased to reach maximum suppression between 8 and 24 hours after etelcalcetide i.v. doses of 5 to 60 mg and remained suppressed over the 65 hours evaluated. The magnitude of serum calcium reduction from baseline ranged from 12% to 14% and appeared comparable for the 10, 20, 40, and 60 mg i.v. dose groups. Overall, the magnitude of serum calcium reduction in the 5 mg group was less apparent compared to other dose groups. No changes in mean serum calcium were observed in the placebo group (Figure below).

Figure 3 Mean (± SEM) Percent Change From Baseline in Serum PTH Versus Time Study 20130139 (Formerly KAI-4169-002): CKD Patients With Secondary HPT Receiving Haemodialysis

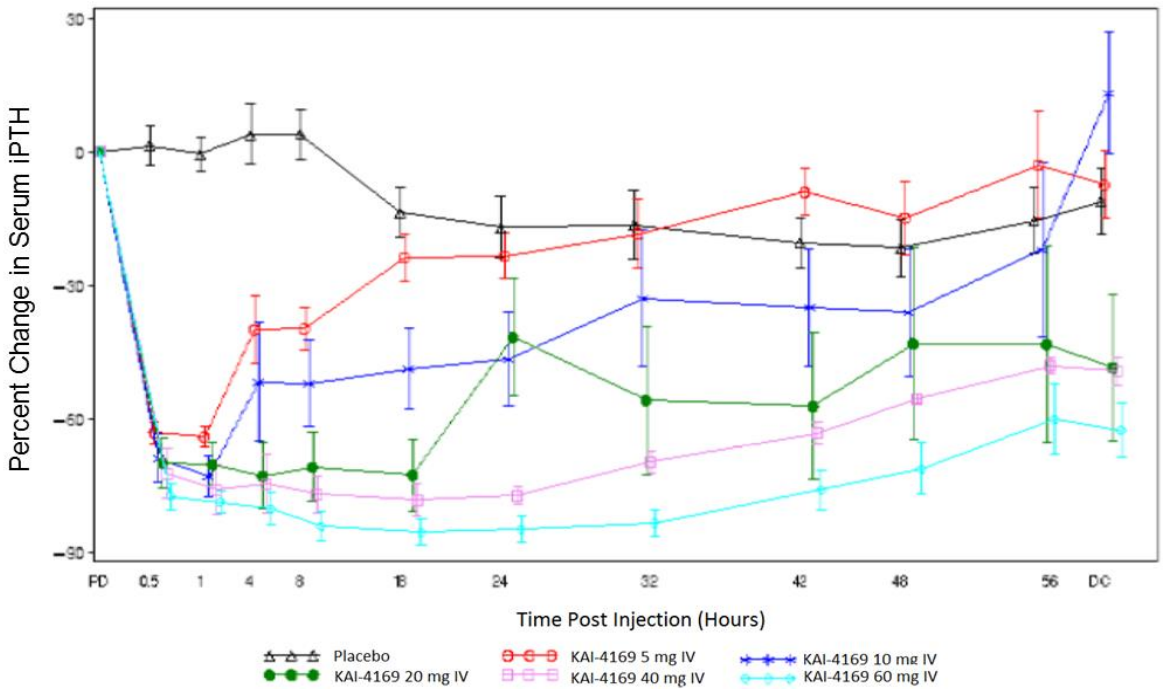
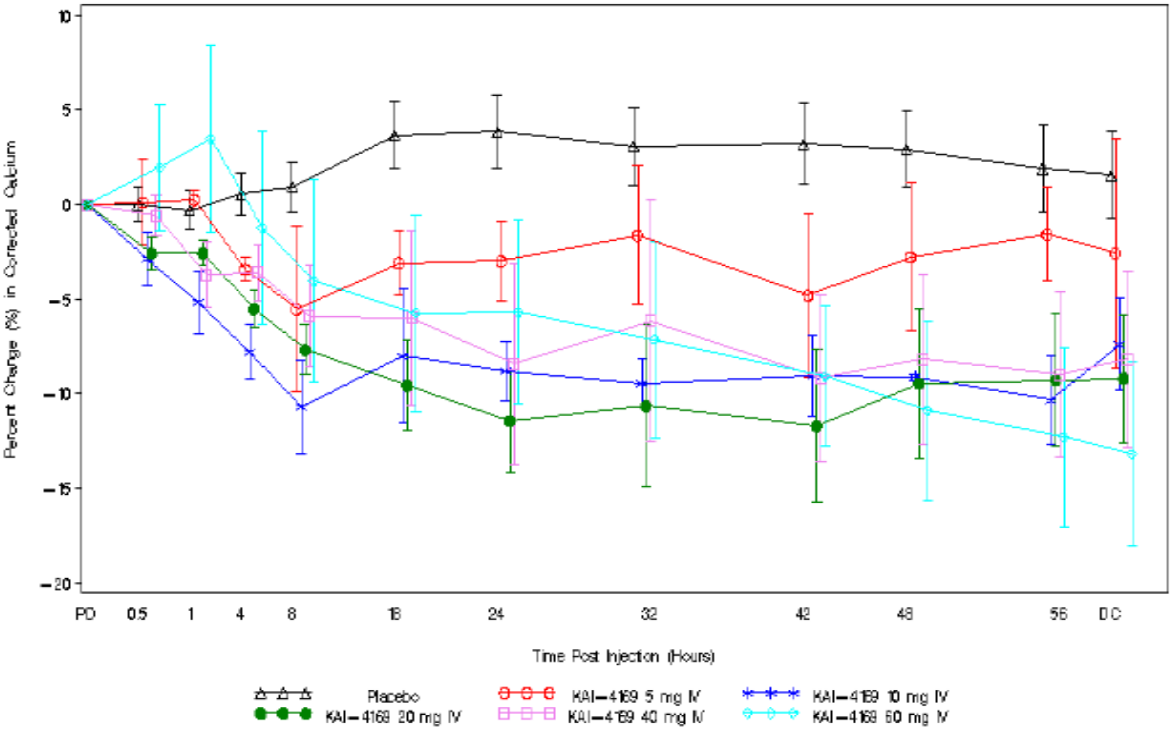


Figure 4 Mean (± SEM) Percent Change in Calcium Versus Time Study 20130139 (Formerly KAI-4169-002)



Population model

Data from one phase 1 and two phase 2 studies were used for the population model development (index dataset). In the absence of etelcalcetide, time courses of calcium and PTH were described using indirect response models. Selected covariates were tested as potential predictors of variability in model parameters. The covariates considered included age, body weight, sex, race, time on dialysis, baseline phosphorus and vitamin D. The influence of these covariates on the PD parameters was tested. Baseline PTH and calcium were not tested as covariates because PTH and calcium are part of the model structure. Any potential effect of baseline PTH and calcium on PD parameters would have been captured during model fit. A step-wise covariate analysis was carried out using univariate forward selection ($p < 0.05$) followed by backward elimination ($p < 0.01$).

The interaction between etelcalcetide, PTH and calcium was adequately described by a semi-mechanistic PK/PD model which incorporated the role of PTH in calcium regulation, the feedback loop of calcium on PTH production via the CaSR, and the activity of etelcalcetide plasma levels in increasing the sensitivity of the CaSR to calcium. After only a short delay, the administration of etelcalcetide is predicted to rapidly decrease PTH levels, followed by a slower decrease in calcium. No significant covariates were identified as predictors of PD variability. The PTH and calcium changes at the end of week 3 (day 21) and week 4 (day 28) are comparable; so sampling at week 3 and titrating at week 4 is appropriate.

2.4.4. Discussion on clinical pharmacology

The clinical program is considered appropriate for the objectives that are considered, to characterize the initial safety, tolerability, PK, PD, and exposure-response properties of etelcalcetide in healthy volunteers and CKD patients with secondary HPT receiving haemodialysis. From a pharmacological perspective, the two single dose studies, one in healthy volunteers, and one in patients are considered of most relevance. The studies in Japanese patients are of less relevance for the EU setting and are therefore not further discussed.

Both studies demonstrated a dose dependent effect in PTH reduction for single dose treatment of etelcalcetide doses between 2.5 and 60 mg. Also a lagged effect on calcium reduction can be observed.

A further model supports the proof of concept. A comparison between titration starting with 5 mg or fixed dosing of 10 mg indicates that titration with starting dose of 5 mg is a reasonable approach with comparable efficacy achieved in comparison to a fixed 10 mg dose but maybe less safety issues (lower chance of hypocalcaemia).

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology has been sufficiently established.

2.5. Clinical efficacy

2.5.1. Dose response studies

A multiple dose randomized, double-blind, placebo-controlled patient study in 87 patients (study 20120330) showed that treatment for up to 4 weeks with etelcalcetide 10 mg and 5 mg resulted in mean reductions from baseline in PTH during the efficacy assessment –period of 49.4% and 33.0%, respectively. The mean change from baseline in serum calcium (mean approximately 9.6 mg/dL) at endpoint was -13.0% in the 10 mg etelcalcetide dose group and -6.0% in the 5 mg etelcalcetide dose group.

A single-arm, open-label, 12-week, dose-titration study (study 20120331) in 37 subjects with secondary HPT receiving haemodialysis (baseline PTH was 853.4 (644.25) pg/mL (mean (sd)) starting at a 5 mg dose of etelcalcetide and titrated every 4 weeks based on the preceding serum iPTH (target an iPTH concentration ≥ 150 pg/mL and ≤ 300 pg/mL) and corrected Ca (cCa) levels to a maximum dose of 20 mg. The overall mean (95% CI) percent change in PTH concentration was -53.6% (-60.8%, -46.4%). Overall, 20 subjects (56%) exhibited a mean iPTH value ≤ 300 pg/mL during the efficacy period. The overall mean (95% CI) percent change from baseline in serum calcium during the efficacy period was -15.1% (-17.0%, -13.1%). The mean dose level at the end of treatment was 11.1 mg in subjects overall, 8.8 mg in subjects with baseline iPTH ≤ 700 pg/mL, and 14.5 mg in subjects with baseline iPTH > 700 pg/mL. At week 5, 26 subjects (74.3%) were receiving 10 mg of etelcalcetide. At week 9, the majority of subjects were receiving 10 mg (9 subjects [27.3%]), 15 mg (7 subjects [21.2%]), or 20 mg (8 subjects [24.2%])). At week 12, the majority of subjects were still receiving 10 mg (7 subjects [24.1%]), 15 mg (7 subjects [24.1%]), or 20 mg (5 subjects [17.2%]).

2.5.2. Main studies

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). Etelcalcetide is also sometimes referred to as AMG 416 throughout the text.

Table 2.1 Summary of efficacy for trial 20120229 (also known as KAI-4169-006)

Title: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 (etelcalcetide) in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Haemodialysis.	
Study identifier	EudraCT number: 2012-002805-23; Study 20120229

Design	A Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Subjects were randomized to either AMG 416 or placebo in a 1:1 ratio, stratified by mean screening PTH (< 600 pg/mL, between 600 and 1000 pg/mL, or > 1000 pg/mL), recent cinacalcet use within 8 weeks prior to randomization (yes or no), and region (North America or non-North America). All subjects, regardless of treatment assignment, received standard of care with calcium supplements, active vitamin D sterols, and phosphate binders, as prescribed by the individual Investigator.		
	Duration of main phase:		26 weeks
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		Open label for additional 52 weeks
Hypothesis	Superiority		
Treatments groups	Placebo group		Treatment: Subjects received placebo at a starting dose of 5 mg three times a week (TIW). The dose of investigational product may have been increased every 4 weeks (ie, weeks 5, 9, 13, and 17) to a maximum dose of 15 mg Duration: 26 weeks treatment period Number of randomized patients = 254
	AMG 416 group		Treatment: Subjects received AMG 416 at a starting dose of 5 mg three times a week (TIW). The dose of investigational product may have been increased every 4 weeks (ie, weeks 5, 9, 13, and 17) to a maximum dose of 15 mg to achieve target PTH levels ≤ 300 pg/mL, but no lower than 100 pg/mL on 2 consecutive samples at least 1 week apart, while maintaining appropriate cCa concentrations Duration: 26 weeks treatment period Number of randomized patients = 254
Endpoints and definitions	Primary endpoint		Proportion of subjects with > 30% reduction from baseline in mean predialysis PTH during the efficacy assessment period (EAP), defined as Weeks 20 to 27, inclusive
	Secondary endpoint		Proportion of subjects with mean predialysis PTH ≤ 300 pg/mL during the EAP
	Secondary endpoint		Percent change from baseline in predialysis PTH during the EAP
	Secondary endpoint		Percent change from baseline in predialysis cCa during the EAP
	Secondary endpoint		Percent change from baseline in predialysis cCa x P during the EAP
	Secondary endpoint		Percent change from baseline in predialysis phosphorus during the EAP
Database lock	Study Period: 12 March 2013 (date of first enrolment) to 12 June 2014 (date last subject completed follow-up)		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Intent to treat (Full analysis set) EAP = Week 20 to 27

Descriptive statistics and estimate variability	Treatment group	Placebo	AMG 416
	Number of subjects	N=254	N=254
	Subjects with >30% reduction in mean PTH during the EAP (n (%))[a]	21 (8.3)	188 (74.0)
	Subjects with ≤300 pg/mL in mean PTH during the EAP (n (%))[a]	13 (5.1)	126 (49.6)
	Number of subjects Percent change from baseline to EAP in Predialysis PTH (n) (Mean (SE), %)	219 13.00 (2.81)	229 -55.11 (1.94)
	Number of subjects Percent change from baseline to EAP in Predialysis cCa (n)	219	229
	(Mean (SE), %)	1.18 (0.29)	-7.29 (0.53)
	Number of subjects Percent change from baseline to EAP in Predialysis cCa x P (n)	213	227
	(Mean (SE), %)	-0.19 (1.44)	-14.34 (2.06)

	Number of subjects Percent change from baseline to EAP in Predialysis in Phosphorus (n)	214	227
	(Mean (SE), %)	-1.31 (1.42)	-7.71 (2.16)
Effect estimate per comparison	Subjects with >30% reduction in mean PTH during the EAP (primary)	Comparison groups	AMG 416 vs Placebo
		CMH-stratified odds ratio	32.46
		95 % CI	(18.71, 56.31)
		P-value[b]	p < 0.001
	Subjects with ≤300 pg/mL in mean PTH during the EAP	Comparison groups	AMG 416 vs Placebo
		CMH-stratified odds ratio	22.08
		95 % CI	(11.47, 42.48)
		P-value[b]	< 0.001
	Percent change from baseline to EAP in Predialysis PTH Treatment difference (AMG 416 – placebo) – adjusted analysis[d]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-71.11 (3.39)
		95 % CI, %	(-77.77, -64.46)
		P-value[d]	< 0.001
	Percent change from baseline to EAP in Predialysis cCa Treatment difference (AMG 416 – placebo) – adjusted analysis[d]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-8.38 (0.58)
		95 % CI, %	(-9.52, -7.23)
		P-value[d]	< 0.001
	Percent change from baseline to EAP in Predialysis cCa x P Treatment difference (AMG 416 – placebo) – adjusted analysis[d]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-14.99 (2.41)
		95 % CI, %	(-19.73, -10.25)
		P-value[d]	< 0.001
	Percent change from baseline to EAP in Predialysis Phosphorus	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-7.45 (2.47)
		95 % CI, %	(-12.31, -2.59)

	Treatment difference (AMG 416 – placebo)– adjusted analysis[d]	P-value[d]	0.003
Notes	To control the family-wise type I error rate for the evaluation of the efficacy endpoints, the secondary efficacy endpoints were to be tested for statistical significance only if the primary efficacy endpoint was statistically significant at the 2-sided significance level of 0.05. If this occurred, the secondary efficacy endpoints were to be tested sequentially in the following order: PTH ≤ 300 pg/mL, percent change from baseline to EAP in iPTH, cCa, cCa x P, and phosphorus.		

[a] Subjects were considered as not achieving the endpoint if they did not have data during the EAP (ie, nonresponder imputation)
CMH = Cochran-Mantel-Haenszel; n = number of subjects with observed data
[b] CMH test
[c] Estimated difference in mean percent change from baseline during the EAP for corresponding lab parameter between the treatment groups (AMG 416-placebo).
[d] Mixed-effects model including treatment, stratification factors, visit, and treatment by visit interaction as covariates

Table 2.2 Summary of efficacy for trial 20120230 (also known as KAI-4169-007)

Title: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of AMG 416 (etelcalcetide) in the Treatment of Secondary Hyperparathyroidism in Subjects With Chronic Kidney Disease on Haemodialysis.		
Study identifier	EudraCT number: 2012-002806-31; Study 20120230	
Design	A Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Subjects were randomized to either AMG 416 or placebo in a 1:1 ratio, stratified by mean screening PTH (< 600 pg/mL, between 600 and 1000 pg/mL, or > 1000 pg/mL), recent cinacalcet use within 8 weeks prior to randomization (yes or no), and region (North America or non-North America). All subjects, regardless of treatment assignment, received standard of care with calcium supplements, active vitamin D sterols, and phosphate binders, as prescribed by the individual Investigator.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks not applicable Open label for additional 52 weeks
Hypothesis	Superiority	
Treatments groups	Placebo group	Treatment: Subjects received placebo at a starting dose of 5 mg three times a week (TIW). The dose of investigational product may have been increased every 4 weeks (ie, weeks 5, 9, 13, and 17) to a maximum dose of 15 mg Duration: 26 weeks treatment period Number of randomized patients = 260

	AMG 416 group		Treatment: Subjects received AMG 416 at a starting dose of 5 mg three times a week (TIW). The dose of investigational product may have been increased every 4 weeks (ie, weeks 5, 9, 13, and 17) to a maximum dose of 15 mg to achieve target PTH levels ≤ 300 pg/mL, but no lower than 100 pg/mL on 2 consecutive samples at least 1 week apart, while maintaining appropriate cCa concentrations Duration: 26 weeks treatment period Number of randomized patients = 255
Endpoints and definitions	Primary endpoint		Proportion of subjects with > 30% reduction from baseline in mean predialysis PTH during the efficacy assessment period (EAP), defined as Weeks 20 to 27, inclusive
	Secondary endpoint		Proportion of subjects with mean predialysis PTH ≤ 300 pg/mL during the EAP
	Secondary endpoint		Percent change from baseline in predialysis PTH during the EAP
	Secondary endpoint		Percent change from baseline in predialysis cCa during the EAP
	Secondary endpoint		Percent change from baseline in predialysis cCa x P during the EAP
	Secondary endpoint		Percent change from baseline in predialysis phosphorus during the EAP
Database lock	Study Period: 12 March 2013 (date of first enrolment) to 12 May 2014 (date last subject completed follow-up)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Full analysis set) EAP = week 20 to 27		
Descriptive statistics and estimate variability	Treatment group	Placebo	AMG 416
	Number of subjects	N=260	N=255
	Subjects with >30% reduction in mean PTH during the EAP (n (%))[a]	25 (9.6)	192 (75.3)
	Subjects with ≤300 pg/mL in mean PTH during the EAP (n (%))[a]	12 (4.6)	136 (53.3)
	Number of subjects Percent change from baseline to EAP in Predialysis PTH (n) (Mean (SE), %)	237 13.72 (2.50)	227 -57.39 (1.91)

	Number of subjects Percent change from baseline to EAP in Predialysis cCa (n)	237	227
	(Mean (SE), %)	0.58 (0.29)	-6.69 (0.55)
	Number of subjects Percent change from baseline to EAP in Predialysis cCa x P (n)	234	223
	(Mean (SE), %)	-1.06 (1.42)	-15.84 (1.57)
	Number of subjects Percent change from baseline to EAP in Predialysis in Phosphorus (n)	234	223
	(Mean (SE), %)	-1.60 (1.42)	-9.63 (1.61)
Effect estimate per comparison	Subjects with >30% reduction in mean PTH during the EAP	Comparison groups	AMG 416 vs Placebo
		CMH-stratified odds ratio	30.80
		95 % CI	(18.18, 52.17)
		P-value[b]	p < 0.001
	Subjects with ≤300 pg/mL in mean PTH during the EAP	Comparison groups	AMG 416 vs Placebo
		CMH-stratified odds ratio	33.92
		95 % CI	(16.35, 70.37)
		P-value[b]	< 0.001
	Percent change from baseline to EAP in Predialysis PTH Treatment difference (AMG 416 – placebo) – adjusted analysis[d]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-71.34 (3.15)
		95 % CI, %	(-77.53, -65.14)
		P-value[d]	< 0.001
	Percent change from baseline to EAP in Predialysis cCa Treatment difference (AMG 416 – placebo) – adjusted analysis[c]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-7.20 (0.60)
		95 % CI, %	(-8.38, -6.03)
		P-value[d]	< 0.001
	Percent change	Comparison groups	AMG 416 vs Placebo

	from baseline to EAP in Predialysis cCa x P Treatment difference (AMG 416 – placebo) – adjusted analysis[d]	Estimate[c](SE), %	-14.58 (2.07)
		95 % CI, %	(-18.65, -10.51)
		P-value[d]	< 0.001
	Percent change from baseline to EAP in Predialysis Phosphorus Treatment difference (AMG 416 – placebo)– adjusted analysis[d]	Comparison groups	AMG 416 vs Placebo
		Estimate[c](SE), %	-8.04 (2.09)
		(95 % CI), %	(-12.15, -3.92)
		P-value[d]	< 0.001
Notes	To control the family-wise type I error rate for the evaluation of the efficacy endpoints, the secondary efficacy endpoints were to be tested for statistical significance only if the primary efficacy endpoint was statistically significant at the 2-sided significance level of 0.05. If this occurred, the secondary efficacy endpoints were to be tested sequentially in the following order: PTH ≤ 300 pg/mL, percent change from baseline to EAP in iPTH, cCa, cCa x P, and phosphorus.		

[a] Subjects were considered as not achieving the endpoint if they did not have data during the EAP (ie, nonresponder imputation)
CMH = Cochran-Mantel-Haenszel; n = number of subjects with observed data
[b] CMH test
[c] Estimated difference in mean percent change from baseline during the EAP for corresponding lab parameter between the treatment groups (AMG 416-placebo).
[d] Mixed-effects model included treatment, stratification factors, visit, and treatment by visit interaction as covariates

Table 2.3 Summary of efficacy for trial 20120360

Title: 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(etelcalcetide) in Haemodialysis Subjects With Secondary Hyperparathyroidism		
Study identifier	EudraCT number: 2013-000192-33	
Design	A phase 3, multicenter, randomized, active-controlled, double-blind, double-dummy, dose-titration study, with a 26-week treatment period to compare the therapeutic efficacy of AMG 416 and cinacalcet for lowering serum PTH levels among subjects with CKD on haemodialysis with SHPT. Subjects were randomized 1:1 to receive AMG 416 or cinacalcet stratified by serum PTH level (< 900 pg/mL, ≥ 900 pg/mL) and region (North America and non-North America). All subjects, regardless of treatment assignment, may receive standard of care as prescribed by the individual Investigator, with calcium supplements, phosphate-binding agents, and nutritional vitamin D supplements.	
	Duration of main phase:	26 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority, superiority	

Treatments groups	Cinacalcet group		Treatment: Subjects who were randomized to treatment with cinacalcet received daily oral doses of cinacalcet tablets and i.v. doses of placebo three times a week (TIW) at the end of each TIW dialysis session for 26 weeks. Oral doses of investigational product were to be taken at approximately the same time of day. The starting dose of cinacalcet was 30 mg daily and was titrated up to 180 mg daily as specified in the protocol. The treatment strategy was to achieve predialysis PTH ≤ 300 pg/mL but no lower than 100 pg/mL, while maintaining cCa ≥ 8.3 mg/dL. Duration: 26 weeks treatment period Number of randomized patients = 343
	AMG 416 group		Treatment: Subjects who were randomized to treatment with AMG 416 received i.v. doses of AMG 416 TIW at the end of each TIW dialysis session and daily oral doses of placebo tablets for 26 weeks. The starting dose of AMG 416 was 5 mg and was titrated between 2.5 and 15 mg as specified in the protocol in order to achieve the treatment target. Duration: 26 weeks treatment period Number of randomized patients = 340
Endpoints and definitions	Primary endpoint		Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the efficacy assessment period (EAP), defined as Weeks 20 to 27, inclusive (non-inferiority)
	Key Secondary endpoint		Achievement of a > 50% reduction from baseline in mean predialysis PTH during the EAP (superiority)
	Key Secondary endpoint		Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP (superiority)
	Key Secondary endpoint		Mean number of days of vomiting or nausea per week in the first 8 weeks (superiority)
Database lock	Study Period: 13 August 2013 (date of first enrolment) to 08 January 2015 (last subject completed follow-up)		

Results and Analysis

Analysis description	**Primary Analysis- Non-inferiority**		
Analysis population and time point description	Intent to treat (Full analysis set) EAP = week 20 to 27		
Descriptive statistics and estimate variability	Treatment group	Cinacalcet	AMG 416
	Number of subjects	N= 343	N=340

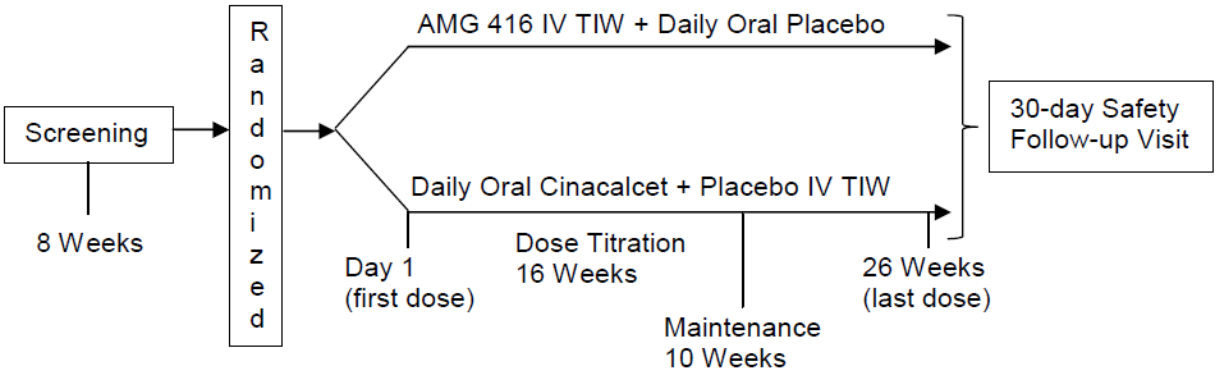
	Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP (non-inferiority) (n (%))	198 out of 310 (63.9)[a]	232 out of 298 (77.9)[a]
Effect estimate per comparison	Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP (non-inferiority)	Comparison groups	Cinacalcet vs AMG 416
		Stratified treatment difference[b] - %	-10.48
		95 % CI - %[c]	(-17.45, -3.51)
		P-value	N.A.
Notes	The pre-specified non-inferiority margin for the primary endpoint was 12%. AMG 416 was considered non-inferior to cinacalcet if the upper bound of the two-sided 95% confidence interval of the treatment difference (cinacalcet – AMG 416) was smaller than 12%.		
Analysis description	**Primary Analysis- Superiority**		
Analysis population and time point description	Intent to treat (Full analysis set)		
Descriptive statistics and estimate variability	Treatment group	Cinacalcet	AMG 416
	Number of subjects	N= 343	N=340
	Achievement of a > 50% reduction from baseline in mean predialysis PTH during the EAP (superiority) (n (%))	138 (40.2)[d]	178 (52.4)[d]
	Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP (superiority) (n (%))	198 (57.7)[d]	232 (68.2)[d]
	Mean number of days of vomiting or nausea per week in the first 8 weeks (superiority) (Adjusted mean (SE) [f], days)	0.3 (0.03)	0.4 (0.04)
Effect estimate per	Achievement of a	Comparison groups	AMG 416 vs Cinacalcet

comparison	> 50% reduction from baseline in mean predialysis PTH during the EAP (superiority)	CMH-stratified odds ratio (AMG 416:Cinacalcet)	1.65
		95 % CI	(1.21,2.23)
		P-value [e]	0.001
	Proportion of subjects with > 30% reduction from baseline in mean predialysis serum PTH level during the EAP (superiority)	Comparison groups	AMG 416 vs Cinacalcet
		CMH-stratified odds ratio (AMG 416:Cinacalcet)	1.59
		95 % CI	(1.16, 2.17)
		P-value [e]	0.004
	Mean number of days of vomiting or nausea per week in the first 8 weeks (superiority)	Comparison groups	AMG 416 vs Cinacalcet
		Treatment rate ratio [f]	1.2
		95 % CI [f]	(0.89, 1.49)
		P-value [f]	0.27
Notes	To control the family-wise type I error rate for the evaluation of the efficacy endpoints, the secondary efficacy endpoints were to be tested for statistical significance only if the primary efficacy endpoint met the non-inferiority criterion. If this occurred, the three key secondary endpoints were to be tested for superiority sequentially at the 5% significance level.		

CMH = Cochran-Mantel-Haenszel;
[a] Proportions presented were observed (before data imputation); the primary analysis used the multiple imputation approach described in footnote [b].
[b] Mantel-Haenszel estimator of the difference in proportions between treatment groups stratified by the randomization stratification factors. All randomized subjects were included in the primary analysis. Imputation under the non-inferiority 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.
[c] Estimated by the Mantel-Haenszel approach as described in footnote [b].
[d] Subjects were considered as not achieving the endpoint if they did not have data during the EAP (ie, nonresponder imputation)
[e] CMH test
[f] Generalized linear mixed model including screening value of number of days of nausea and vomiting, treatment, stratification factors, study weeks and treatment by study weeks as covariates.

Methods (phase 3 studies)

Figure 5 General study design (active controlled study shown below, for the placebo-controlled studies the two arms were etelcalcetide and placebo i.v. TIW)



The effects of etelcalcetide **withdrawal** on PTH, calcium, phosphorus, and cCa x P were evaluated in the treatment completer analysis set of the 6-month placebo-controlled combined dataset by the 30-day follow-up.

Randomization was **stratified** by mean screening PTH (< 600 pg/mL, ≥ 600 to ≤1000 pg/mL, and > 1000 pg/mL), prior cinacalcet use (within 8 weeks before randomization), and region (North America or non-North America) in the placebo controlled studies and by PTH concentration (< 900 or ≥ 900 pg/mL) and region (North America or non-North America) in the active controlled study.

Central laboratories were used to analyze chemistry, coagulation panel, haematology, pregnancy, PTH, 25-hydroxyvitamin D, BSAP, CTX, and FGF-23 samples. Serum samples were analyzed for anti-etelcalcetide antibodies by Amgen. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

When serum albumin was < 4.0 g/dL, the calcium level was corrected according to the following formula; otherwise cCa was equal to total serum calcium: cCa (mg/dL) = total serum calcium (mg/dL) + (4 – albumin [g/dL]) x 0.8. Values for cCa x P were calculated as the product of cCa (mg/dL) and phosphorus (mg/dL); cCa and P were from the same sample. Analyses for PTH used the Advia Centaur assay method. This is a method to assay intact PTH.

Eligible subjects were adults ≥ 18 years of age receiving haemodialysis (TIW) for ≥ 3 months. Subjects had stable dialysate calcium concentration (≥ 2.25 mEq/L in the placebo controlled studies and ≥ 2.5 mEq/L in the active controlled study) and had screening predialysis PTH of > 400 pg/mL in the placebo controlled studies and > 500 pg/mL in the active-controlled study, and cCa ≥ 8.3 mg/dL. Subjects who were receiving vitamin D sterols, phosphate binders, or calcium supplements must have been on stable doses.

Subjects were excluded if they had received cinacalcet within 4 weeks of screening in the placebo controlled studies and within 3 months of screening in the active controlled study, or had a parathyroidectomy within 3 months of dosing or were anticipated to undergo a parathyroidectomy or kidney transplant during the treatment period. Subjects with a history of certain cardiovascular disease or cardiac abnormality or a history of seizure or who were receiving treatment for seizure disorder were excluded.

The **starting dose** of etelcalcetide in these three phase 3 studies was 5 mg administered i.v. TIW at the end of the haemodialysis session. The dose was increased at study weeks 5, 9, 13, and 17, according to the algorithm in the table below, to achieve predialysis serum PTH ≤ 300 pg/mL. The maximum etelcalcetide dose allowed was 15 mg i.v. TIW. In Study 20120360, the starting dose of cinacalcet was 30 mg once daily, and cinacalcet dose adjustments are summarized in the table below.

Table 2.4 etelcalcetide and Cinacalcet Dose Increase Guidelines Based on PTH

Predialysis PTH (pg/mL) Measurement	etelcalcetide Dose Adjustment	Cinacalcet Dose Adjustment
PTH > 450	Increase by 5 mg	Increase dose by 30 mg
300 < PTH ≤ 450	Increase by 2.5 mg	Increase dose by 30 mg
PTH ≤ 300	Maintain dose	Maintain dose

Table 2.5 Concomitant Therapy Guidelines for Studies 20120229, 20120230, and 20120360

Therapy	Screening	Treatment Period
Calcium supplements	No more than 50% maximum dose change within 2 weeks before screening and stable through randomization	Dose adjustment at investigator's discretion
Phosphate binders	No more than 50% maximum dose change within 2 weeks before screening and stable through randomization	Dose increase allowed if 2 consecutive predialysis P values > 5.5 mg/dL Dose reduction allowed if 2 consecutive predialysis P values < 3.0 mg/dL
Vitamin D sterols	No more than 50% maximum dose change within 4 weeks before screening and stable through randomization	Dose reduction allowed if 2 consecutive central laboratory cCa > 10.6 mg/dL Dose reduction or discontinuation allowed if cCa > 11.0 mg/dL or subject develops symptomatic hypercalcaemia
Nutritional Vitamin D	As prescribed by investigator with no restrictions	As prescribed by investigator with no restrictions

Approximately 86% of etelcalcetide treated patients **completed the studies**, while approximately 77% in the placebo or comparator arm completed the study.

Study Participants

The **study population** in the placebo controlled study 20120229 consisted of 57.3% men and 42.7% women with a mean (standard deviation [SD]) age of 57.7 (14.6) years and a range of 21 to 93 years; 34.6% of subjects were ≥ 65 years old. Most subjects were white (68.5%), followed by black (27.8%) and Asian (1.6%). Baseline values for PTH, calcium, phosphorus, and cCa × P were similar between treatment groups.

Subjects were stratified according to screening PTH (33.7% screening PTH < 600 pg/mL, 45.1% screening PTH between 600 and 1000 pg/mL, and 21.3% screening PTH > 1000 pg/mL), cinacalcet use within 8 weeks before randomization (13.2% yes, 86.8% no), and by region (51.4% North America, 48.6% non-North America).

The **study population** in the placebo controlled study 20120230 consisted of 63.5% men and 36.5% women with a mean (SD) age of 58.7 (14.3) years and a range of 22 to 91 years; 35.1% of subjects were ≥ 65 years old. Most subjects were white (64.5%), followed by black (28.0%) and Asian (3.7%). Baseline values for PTH, calcium, phosphorus, and cCa x P were similar between treatment groups. Subjects were stratified according to screening PTH (32.6% screening PTH < 600 pg/mL, 46.4% screening PTH between 600 and 1000 pg/mL, and 21.0% screening PTH > 1000 pg/mL), by cinacalcet use within 8 weeks before randomization (12.0% yes, 88.0% no), and by region (57.5% North America, 42.5% non-North America).

The **study population** in the active controlled study (20120360) consisted of 56.2% men and 43.8% women with a mean (SD) age of 54.7 (14.1) years and a range of 18 to 87 years; 26.1% of subjects were ≥ 65 years old. Most subjects were white (78.8%), followed by black (15.5%) and Asian (2.3%). Demographics were well balanced between treatment groups. Baseline values for PTH, calcium, phosphorus, and cCa x P were similar between treatment groups. Subjects were stratified according to screening PTH (49.8% PTH < 900 pg/mL; 50.2% PTH ≥ 900 pg/mL) and by region (30.5% North America; 69.5% non-North America).

Clinical studies in special populations

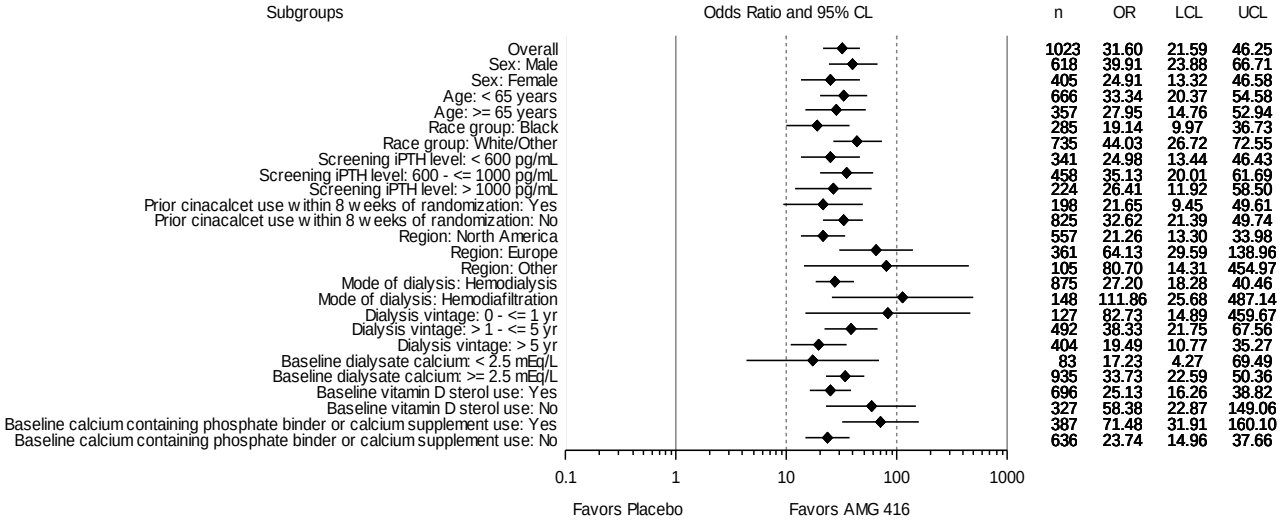
The current investigated population in the clinical studies are patients with chronic kidney disease on dialysis and with secondary hyperparathyroidism. No clinical studies were performed in other special populations.

Analysis performed across trials (pooled analyses AND meta-analysis)

Subgroup analyses in the 6-month placebo-controlled combined dataset

The primary and secondary endpoints for the integrated analysis of the 6-month placebo-controlled combined dataset and the controlled clinical study were analyzed by demographics, disease severity, and concomitant therapy subgroups. Subgroup analyses for the >30% reduction in PTH are shown below.

Figure 6 Treatment Difference in Proportion of Subjects With > 30% Reduction From Baseline in PTH During the Efficacy Assessment Period by Subgroup (6-month Placebo-controlled Combined Dataset – Full Analysis Set)



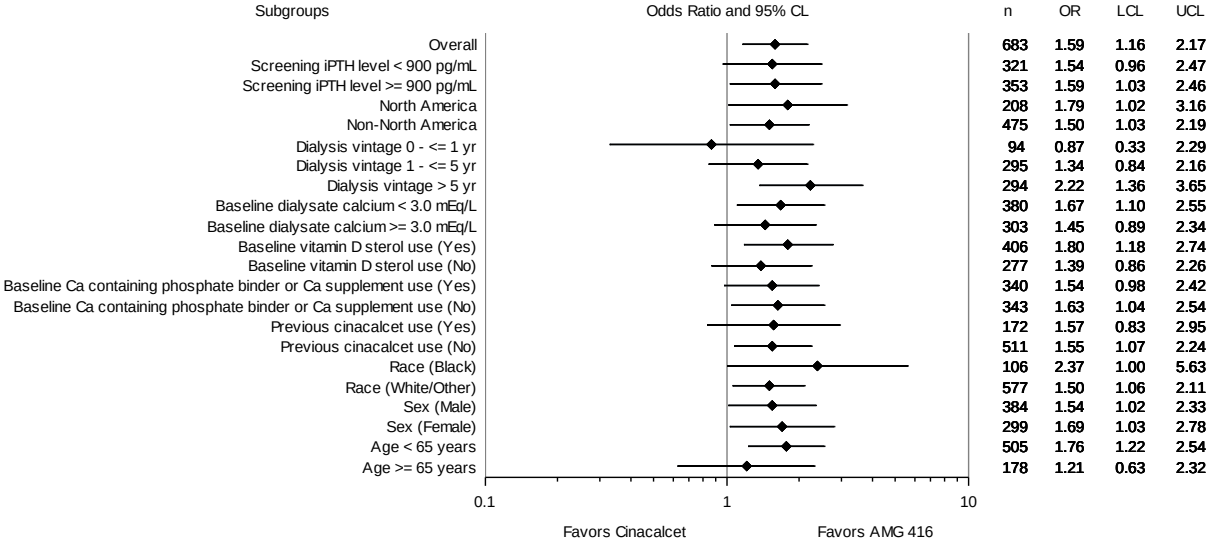
This pool includes data from the two placebo-controlled studies 20120229 and 20120230.

Full analysis set: all randomized subjects in the pool.

Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/ise/figures/f-lb-txdif-ipth.sas

Output: fise-04-036-lb-txdif-ipth-pc.rtf (Date Generated: 05JUN2015:17:26:30) Source Data: adam.adlb

Figure 7 Treatment Difference in Proportion of Subjects with > 30% Reduction from Baseline in PTH During the Efficacy Assessment Period by Subgroup (Study 20120360 – Full Analysis Set)



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

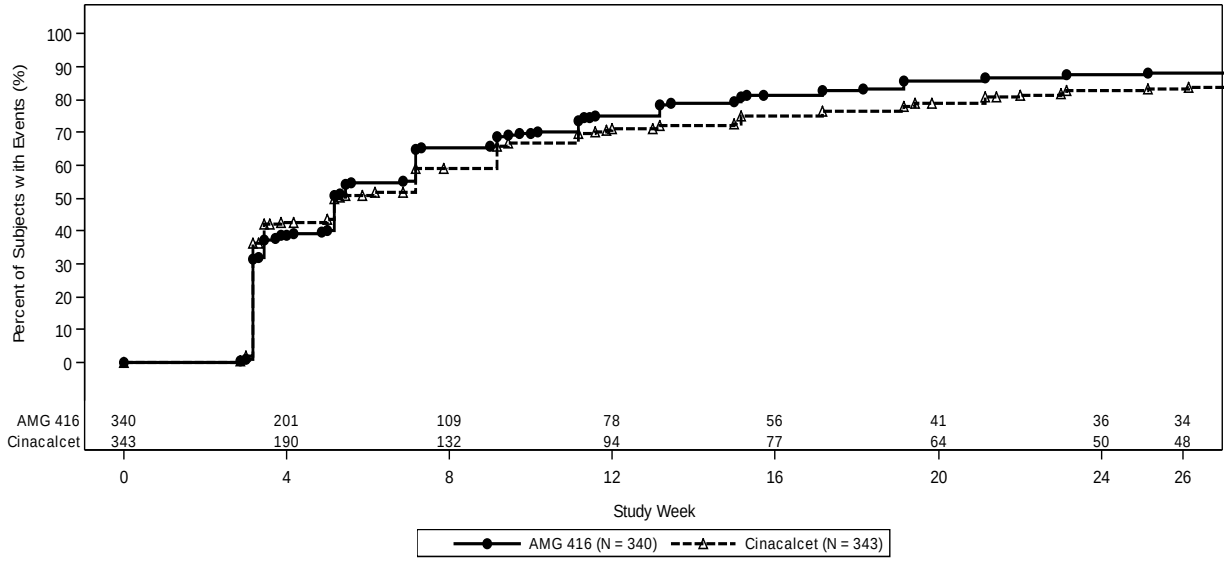
Program: /userdata/stat/amg416/sHPT/20120360/analysis/final/figures/f-lb-ipth.sas
Output: f14-04-002-lb-prop-ipth-sub.rtf (Date Generated: 02MAR2015: 9:48:15) Source Data: adam.adlb

A possible treatment modifying effect of dialysis vintage was investigated based on a post-hoc analysis, considering the vintage as a continuous variable and the percentage change PTH as a continuous variable. From the figures provided no obvious relationship between treatment effect and dialysis vintage could be observed.

Additional analyses in the active controlled study

- PTH reduction of >30% over time

Figure 8 Kaplan-Meier Estimates of Time to First Occurrence of PTH > 30% Reduction From Baseline (Study 20120360)



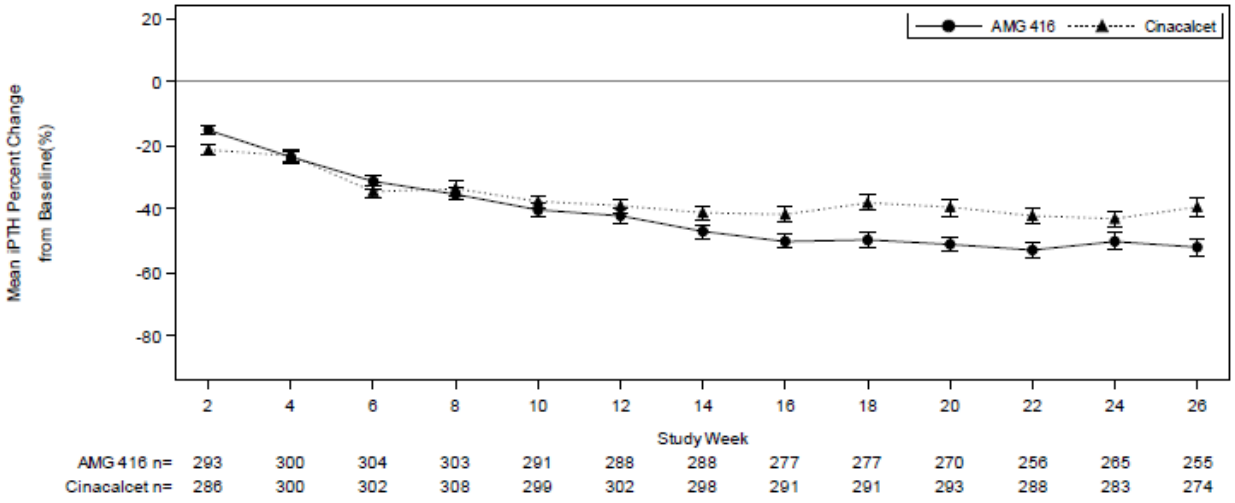
Rolling averages of 3 iPTH values instead of single time point values were used
Full analysis set: all randomized subjects

Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/ise/figures/f-eff-tte.sas
Output: fise-04-059-eff-tte-ipth-h2h.rtf (Date Generated: 19MAY2015:13:50:18) Source Data: adam.adtte

- Change in PTH

The mean percentage change over time of PTH is presented below.

Figure 9 Mean (Standard Error) Percent Change From Baseline in Parathyroid Hormone Over Time by Treatment Group (Safety Analysis Set With On-treatment Approach)



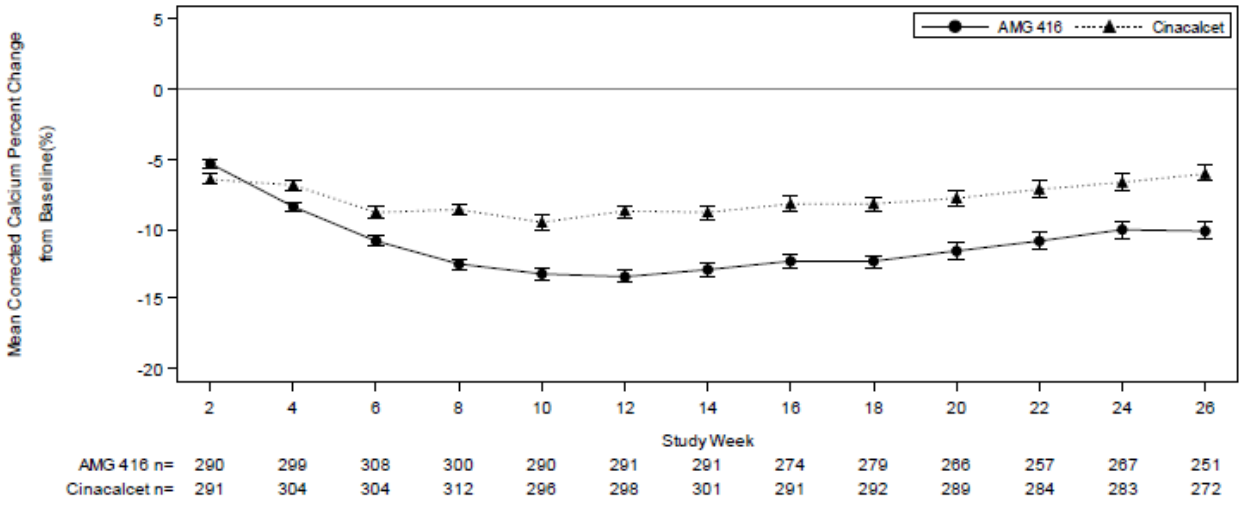
- Change in calcium

Subjects in the etelcalcetide group had a greater mean [standard error] percent change from baseline in calcium during the EAP compared with those in the cinacalcet group (-9.83% [0.49%] versus -6.28% [0.44%], respectively).

Table 2.6 Percent Change From Baseline in Corrected Calcium During the Efficacy Assessment Period (Mixed-effects Model Repeated Measures) (Full Analysis Set)

	Cinacalcet (N = 343)	AMG 416 (N = 340)	Treatment Difference
Percent change from baseline in cCa during the EAP			
n	310	298	
Mean (SE) - %	-6.28 (0.44)	-9.83 (0.49)	
Adjusted analysis[a]			
Estimate (SE) - %			-3.48 (0.65)
95% CI - %			-4.76, -2.21
p-value			< 0.001

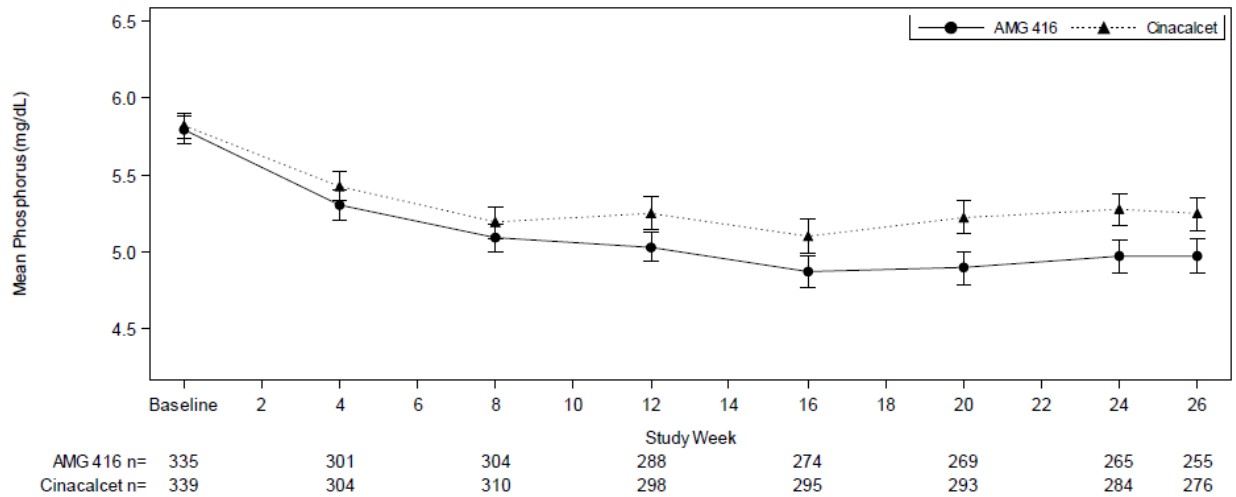
Figure 10 Mean (Standard Error) Percent Change From Baseline in Corrected Calcium Over Time by Treatment Group (Safety Analysis Set With On-treatment Approach)



- Serum phosphorus change

A similar proportion of subjects achieved a mean predialysis serum phosphorus concentration ≤ 4.5 mg/dL during the EAP in the etelcalcetide (32.1%) and cinacalcet (29.2%) groups.

Figure 11 Mean (Standard Error) Phosphorus Concentration Over Time by Treatment Group (Safety Analysis Set With On-treatment Approach)



- Exploratory analyses on bone markers

Greater reductions in BSAP, CTX, and FGF-23 (exploratory endpoints) from baseline were observed for the etelcalcetide group compared with changes observed for the cinacalcet group.

Table 2.7 Change in Serum BSAP, CTX, and FGF-23 Concentrations From Baseline to Week 27 (Full Analysis Set)

Change from baseline to week 27	Cinacalcet (N = 343)	AMG 416 (N = 340)
BSAP - µg/L		
n	280	270
Mean (SE)	-0.27 (2.16)	-10.76 (2.59)
Median	-3.11	-7.13
Q1, Q3	-11.79, 6.24	-15.58, 0.50
CTX – ng/L		
n	268	259
Mean (SE)	-425.30 (78.05)	-1048.22 (72.91)
Median	-490.00	-980.00
Q1, Q3	-1190.00, 390.00	-1750.00, -220.00
FGF-23 – pg/mL		
n	293	274
Mean (SE)	-1671.3 (850.7)	-6443.7 (1172.5)
Median	-607.6	-1798.8
Q1, Q3	-4271.5, 380.4	-8834.9, -86.4

Supportive studies

In addition to the three phase 3 studies, long term data have been provided.

Table 2.8 Description of Long-term Efficacy Datasets

Dataset	Parent Study or Studies / Duration of Exposure	OLE Study / Duration of Exposure	Number of Subjects	Total Duration of Exposure
Pivotal parent study through open-label extension combined dataset (phase 3)	20120229 and 20120230 / up to 26 weeks	20120231 / up to 52 weeks[a]	509	Up to 78 weeks
Phase 2 parent study through open-label extension combined dataset	20120331 / up to 12 weeks	20120334 / up to 106 weeks[b]	37	Up to 118 weeks

OLE = open-label extension

[a] The data from Study 20120231 included in the integrated dataset is based on an interim analysis, and not all subjects had completed the study at the time of the analysis.

[b] The planned study duration for 20120334 was approximately 40 weeks for extension period 1 and an additional 2 years for extension period 2, but the study was terminated early.

Phase 2 long term data

Figure 12 Mean (SE) Parathyroid Hormone (pg/mL) Over Time (Full Analysis Set With On-treatment Approach)

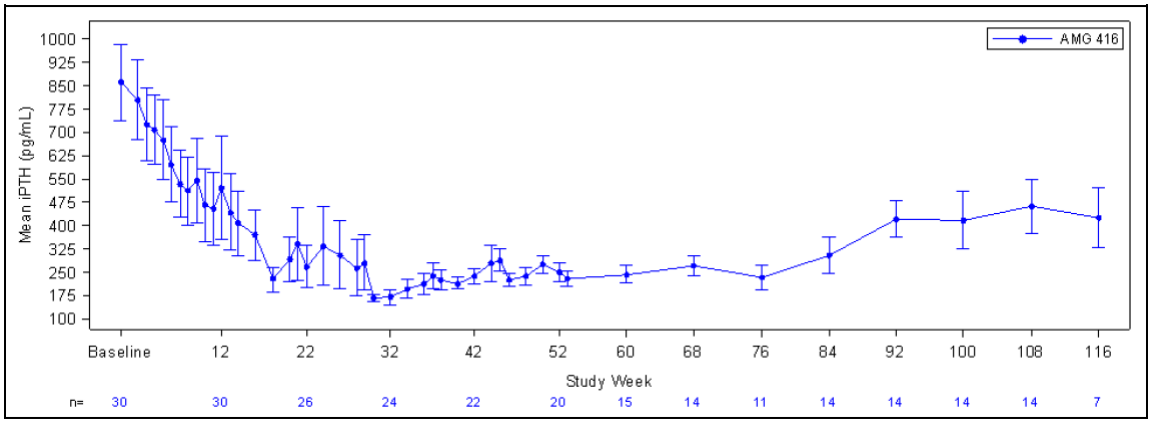
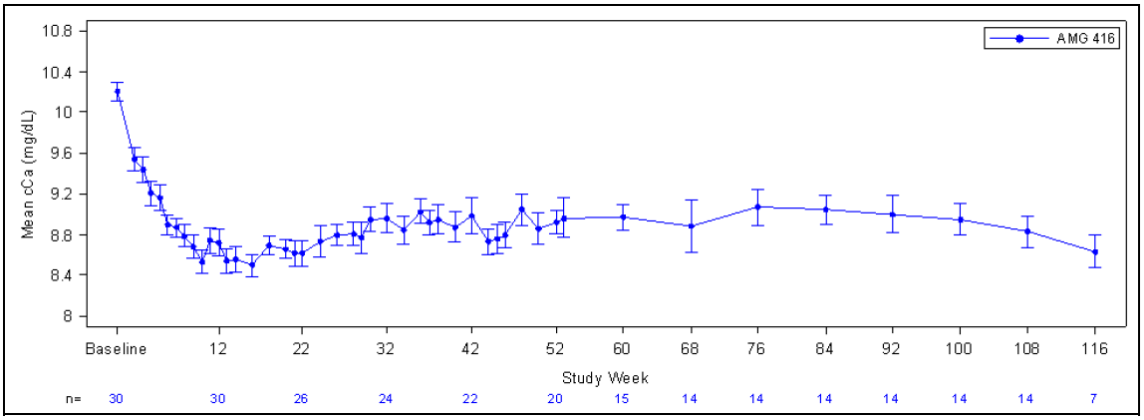


Figure 13 Mean (SE) Corrected Calcium (mg/dL) Over Time (Full Analysis Set With On-treatment Approach)



Phase 3 long term data

Figure 14 Mean (SE) Parathyroid Hormone Percent Change From Baseline Over Time (Pivotal Parent AMG 416 (etelcalcetide) Through Open-label Extension Combined Dataset – Full Analysis Set)

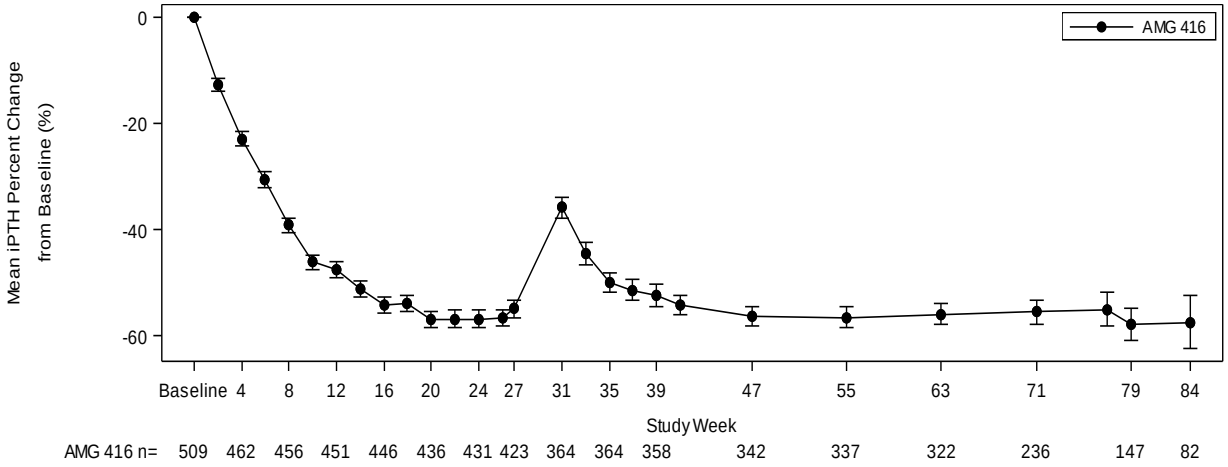


Figure 15 Mean (SE) Corrected Calcium Percent Change From Baseline Over Time (Pivotal Parent AMG 416 (etelcalcetide) Through Open-label Extension Combined Dataset – Full Analysis Set)

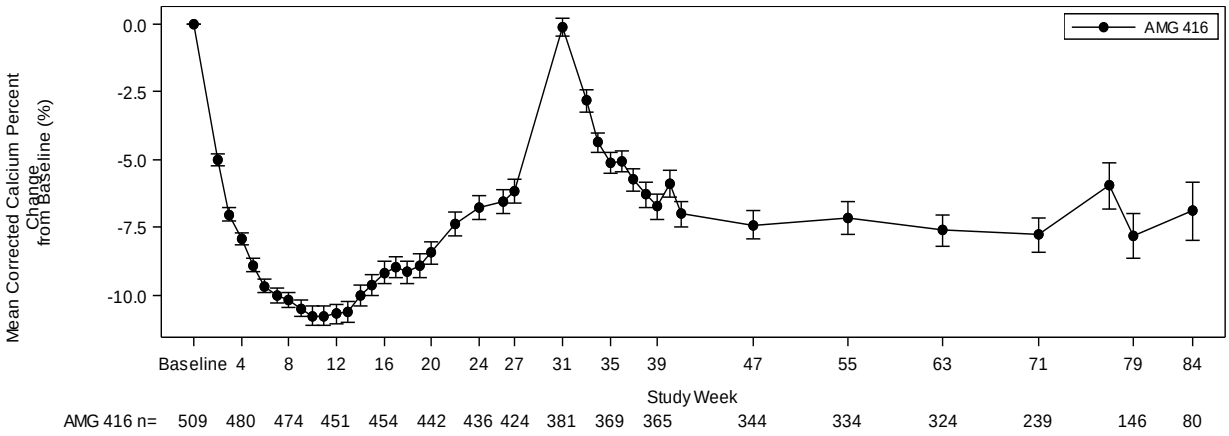
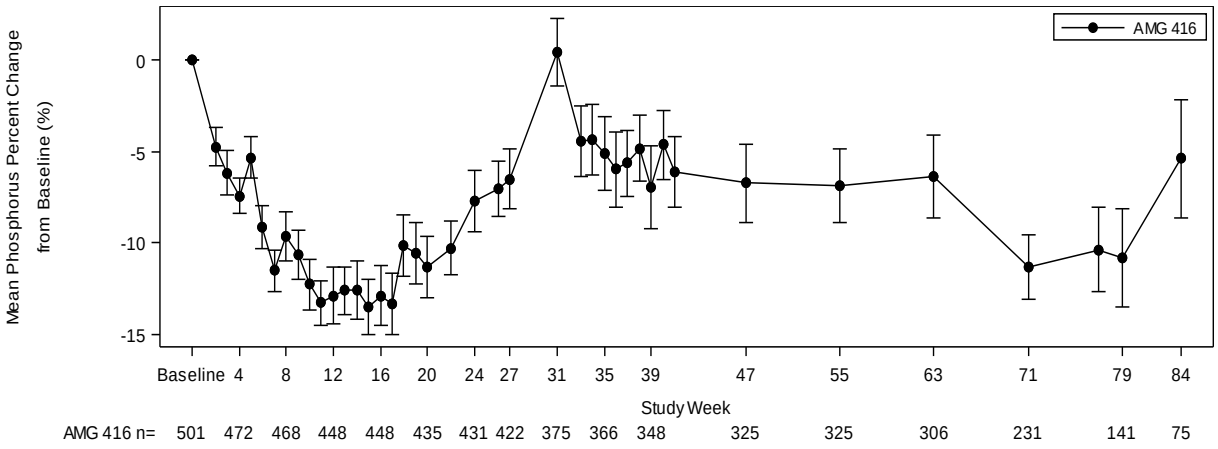


Figure 16 Mean (SE) Phosphorus Percent Change From Baseline Over Time (Pivotal Parent AMG 416 (etelcalcetide) Through Open-label Extension Combined Dataset – Full Analysis Set)



Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	**350/1773**	**170/1773**	**27/1773**

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

General

Evaluation and confirmation of the effect by means of two placebo controlled trials and one study that compared etelcalcetide to cinacalcet is considered appropriate to have a sufficient understanding of the efficacy and safety of etelcalcetide in the indication that is claimed. In addition, additional long-term safety and efficacy data have been presented by two open-label extension studies.

These were multicentre studies with recruitment in several countries across the globe which enables extrapolation of the data. Several countries in Europe have been included as well, important to be able to conclude on the results for the EU population.

The inclusion criteria are considered appropriate to represent a dialysis population with secondary hyperparathyroidism (SHPT). In the comparator study more stringent levels of initial PTH levels were defined than for the placebo-controlled trials as this study included an endpoint that evaluated a > 50% reduction in PTH. The argumentation is acceptable that a lower PTH eligibility criterion may have resulted in on-treatment PTH values that were below the lower limit of the target range. In addition, hypocalcaemia should have been absent.

The exclusion criteria are acceptable. Patients should not have recently used cinacalcet, intended for a similar target population, or surgical interference in the target organ of parathyroid gland and kidney. From a safety perspective, exclusion of vulnerable patient groups (history of certain cardiac disorders in the past 6 months such as myocardial infarction, CHF III or IV, ventricular arrhythmia) is accepted. However, as a CKD patient population on haemodialysis is known to be at risk for cardiovascular comorbidity, the external validity of these studies may be somewhat compromised.

Clear guidance was applied for concomitant therapy during screening for calcium supplementation, vitamin D sterols, and phosphate binders, while for nutritional vitamin D no restriction applied. This is considered needed and acceptable. During study, for the most important concomitant therapy options, phosphate binders and vitamin D sterols, strict rules were applied, which is considered acceptable and needed as these interfere with the main outcome of the study.

The flexible treatment algorithm used in the phase 3 studies is in line with previous smaller studies and based on achievement of PTH levels and the intent not to compromise the cCa levels. This is considered appropriate. Such treatment algorithm warrants regular monitoring of PTH, cCa and phosphorus. For the comparator study a similar dosing algorithm was also applied to achieve predialysis serum PTH levels ≤ 300 pg/mL with flexible adjustments based on too low levels of PTH, calcium or adverse events including suspension of treatment. This is considered appropriate.

The primary and secondary objectives are largely based on evaluation of improved control of laboratory markers in secondary HPT. This is acceptable and reflects current clinical practice. The primary biochemical endpoint of proportion of subjects achieving a reduction of PTH levels from baseline by >30% can be considered a relevant and clinical meaningful endpoint as patients on dialyses suffer from extensive elevated levels of PTH. This endpoint has also been used as a secondary endpoint in the EU marketing authorisation application for cinacalcet. The proportion achieving lower levels than 300 pg/ml is an acceptable secondary endpoint and is of importance in considering the primary endpoint results as it provides more information on the absolute relevant reduction in PTH. This endpoint was used in the cinacalcet marketing authorisation application as a primary endpoint. Furthermore, monitoring of cCa reductions and cCa x P, and P alterations have been associated with calcimimetics and provide further understanding of the effect of etelcalcetide secondary to lowering of PTH. In addition, exploratory objectives investigating effects of etelcalcetide on (high turnover) bone markers are considered important with respect to evaluation of more clinically relevant outcomes. More relevant clinical outcomes such as fracture incidences or need for parathyroidectomy, and other symptoms and signs associated with secondary HPT are not investigated. Feasibility of such studies may be questioned due to the need of large clinical studies during a more extensive period of time. For instance, fracture incidence in dialysis patients has been estimated to be 7.45 per 1000 person years for males and 13.63 per 1000 person years for females based on USRDS data (Alem, KI, 2000). Also, any significant effect could also not be demonstrated in the “Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events” (EVOLVE) study with cinacalcet.

The randomisation procedure is considered appropriate. Blinding procedures are also considered appropriate, as well as the applied visit schedules.

Measurements of laboratory values by central laboratories is considered important for blinding of measurements for patient and investigator, and for standardisation of methods used for quantification of measurements, consequently reducing variability. In particular, iPTH measurements are prone for variability. Although other methods exist, intact PTH measurements are currently (still) the most used method in clinical practice to measure PTH, and it is therefore acceptable. The method used for correction of serum calcium measurements for low levels of serum albumin can also be considered to reflect practical principles and is therefore acceptable.

Specific comparator study considerations

Non-inferiority investigation on the primary endpoint of proportion of patients with >30% reduction of PTH is accepted. Subsequent secondary superiority investigation is acceptable, as it suggested that etelcalcetide may have stronger and/or faster effects than cinacalcet possibly due to it's binding properties to the calcium receptor. In this respect, the same approach was used for the evaluation of proportion of patients with > 50% reduction of PTH, which is acceptable as well.

The assessment of PTH has been performed at a single time point prior to dialysis and at least 12h post dosing of cinacalcet. This is considered appropriate, as a model simulation the PTH levels over time demonstrated a similar effect as the single time point chosen.

The third superiority secondary endpoint (safety endpoint) of mean number of days of vomiting or nausea per week in the first 8 weeks could be of relevance from a safety perspective depending on the magnitude. A Nausea/Vomiting Symptom Assessment was used as a patient outcome. Such a patient outcome questionnaire can be acceptable and is commonly used for such type of assessment although this specific questionnaire is not generally known (for instance, in oncology associated trials a Functional Living Index of Emesis (FLIE) is an accepted questionnaire; see also Guideline on non-clinical and clinical development of medicinal products for the treatment of nausea and vomiting associated with cancer therapy).

Efficacy data and additional analyses

Dose justification

Dose justification is based on a 4 week placebo controlled phase 2 study comparing multiple dosing effects on PTH (and calcium) levels for the 5 and 10 mg dose and a single open-label dose titration study.

These studies provide some knowledge on the dose response after multiple dosing according to the dosing algorithm applied, showing that the 10 mg is more effective than the 5 mg dose during 4 weeks of titration. Also, the 10 mg is the most used dose, and 8 patients (24%) needed the highest 20 mg to achieve a long term reduction in PTH and serum calcium levels within the acceptance range. Comparisons of effect of the 5 mg dose in the phase 3 studies and the open-label phase 2 study have been made, demonstrating comparable effect sizes after 3 weeks of treatment. These data are considered being reassuring in terms of consistency of effect, although only data for the short 3-4 weeks term have been presented. The 15 mg dose has been chosen as the maximum dose as the 20 mg dose displayed a higher need for dose interruptions due to AEs.

Placebo controlled studies

There were no major differences in the disposition between study drug and placebo and between both studies, although the discontinuation rate was high within the placebo group (approximately 21-24%). Yet, reassuring is that discontinuations in the treatment group were less than for placebo, and mainly attributable

to less patients with rising PTH as a specified discontinuation rule. Proportion of patients who were lost to follow up were slightly larger in the etelcalcetide treatment groups, however, still limited to 30 patients in total for etelcalcetide. Randomisation was successful as no substantial differences could be noticed between treatment groups. Furthermore, both studies showed large similarity for the patients included with no major differences. This allows for presentation of integrated results of both studies. Included patients represent a dialyses population with increased levels of PTH (approximately around 800 pg/ml) and for whom around 40% were treated already for more than 5 years with haemodialysis. Elderly patients were well represented with around 35% of patient older than 65 years, although only approximately 14% of patients older than 75 years were included. Patients were equally distributed for the region stratification factor of North America vs non-North America. Patients extensively used other medication of interest with about 70% using vitamin D sterols, and around 83% using phosphate binders, and about 37% using calcium containing phosphate binders or calcium supplements.

In both placebo controlled trials in patients with a mean PTH level at baseline of approximately 840 pg/mL, a clear significant difference in the proportion of patients reaching more than 30% reduction in PTH could be observed for the treatment with etelcalcetide versus placebo treatment at 26 weeks (380 subjects [74.7%] vs. 46 subjects [8.9%], respectively, $p<0.001$). This effect already started 2 weeks after start of therapy and was maintained throughout the treatment period. Also significantly more subjects reached PTH levels ≤ 300 pg/mL while on etelcalcetide during this period (262 subjects [51.5%] vs 25 subjects [4.9%], respectively, $p<0.001$).

The data indicate that after each titration step more patients reached the event of the >30% reduction in PTH. A considerable proportion of patients needed to be titrated to the highest 15 mg dose to reach this endpoint (18-23%). During the procedure the applicant provided further information on individual dose titrations in both placebo- and active controlled studies. Most patients (>80%) experienced only one period of temporary dose suspension while a low number of patients needed permanent discontinuation. Incidence of too low calcium levels and hypocalcaemia appeared to decrease with increasing duration as was seen for the number of dose suspensions. Overall, temporary suspensions (with or without dose reduction) appear manageable for etelcalcetide. The need for regular PTH monitoring has been addressed in the SmPC, as well as the dose adaptations needed in response to PTH levels < 100 pg/ml and how re-initiation doses need to be determined.

The data further showed a secondary significant reduction in cCa with etelcalcetide treatment in comparison to placebo (-7.0% vs 0.87%, respectively, with baseline levels around 9.65 mg/dL) with a maximum effect reached after 10 to 12 weeks of therapy after which the difference in cCa reduction slightly narrowed between treatment and placebo. Similarly, this could be observed for the cCa x P percentage change over time, and was also significantly different. Also, a relative reduction in phosphorus was demonstrated (-8.7% vs -1.5%, respectively, with baseline levels around 5.8 mg/dL). The largest effects were seen between week 6 and 20, although variability was larger than for the other laboratory values.

Numerical reductions could also be observed for exploratory endpoints of bone markers in bone specific alkaline phosphatase (BSAP) and Type I collagen C-telopeptide (CTX) at weeks 12 and 27 in the etelcalcetide group relative to the placebo group, which may indicate a positive effect on bone turnover. Similarly for fibroblast growth factor-23, involved in regulation of phosphate concentration, a numerically decrease could be observed for both studies with etelcalcetide compared to placebo.

After treatment withdrawal, calcium, cCa x P, and phosphorus nearly returned to baseline values which support the observed pharmacological effect and the need for continuous etelcalcetide treatment. However, PTH values remained at a 40% reduction compared to baseline. It could be argued that the withdrawal

follow-up of 30 days might have been too short for several individuals due to several possible reasons, e.g. persistent drug effect of etelcalcetide, vitamin D sterol and calcium supplement use during the washout period, changes in calcium-sensing receptor (CaSR) expression and increased sensitivity to serum calcium after etelcalcetide treatment, changes in bone remodelling during etelcalcetide treatment, and/or secondary hyperparathyroidism (HPT) disease heterogeneity.

Subgroup analyses showed that a robust positive effect on the primary endpoint of > 30% reduction from baseline in PTH and on the secondary endpoint of proportion of subjects with PTH ≤ 300 pg/mL. No substantial differences for the stratification factors of baseline PTH category, and prior cinacalcet use were noticed. Although some differences appear for some subgroups, this may be due to chance finding or have been reasonably explained (e.g. subgroup of baseline vitamin D sterole use; more efficacy in patients without baseline vitamin D sterol use).

Active controlled study

There were no major differences in the disposition between etelcalcetide and cinacalcet. The percentage of patients who discontinued is acceptable with no major differences between both treatment arms. Almost all patients were given at least one dose of treatment. The number of patients who were lost to follow up were slightly larger in the etelcalcetide arm, however, still limited to 12 patients for etelcalcetide. Reassuring is the lower number of discontinuations due to adverse events. Treatment arms were properly balanced as no substantial differences can be noticed. Included patients represent a dialyses population with increased levels of PTH (approximately around 1100 pg/ml), which is slightly higher than the placebo controlled studies due to different inclusion criteria. In addition, around 43% of patients were treated already for more than 5 years with dialyses. Acceptable numbers of elderly patients were included with around 26% of patient older than 65 years of age, although only approximately 8% of patients older than 75 years of age were included. Patients extensively used other medication of interest with about 60% using vitamin D sterols, and around 49% using phosphate binders, and about 50% using calcium containing phosphate binders or calcium supplements.

Non-inferiority has been demonstrated with 77.9% of subjects in the etelcalcetide group versus 63.9% of subjects in the cinacalcet group meeting the endpoint of > 30% reduction from baseline in mean predialysis serum PTH: difference of -10.48% (-17.45%, -3.51%) with the upper bound of the 2-sided 95% CI being lower than the prespecified margin for noninferiority <12%.

In addition, analyses were performed to identify whether etelcalcetide was superior to cinacalcet with regard to the reduction of mean predialysis serum PTH levels during the study. Results show that with the titration algorithm chosen in the study, the proportion of patients achieving > 30% reduction from baseline in mean predialysis serum PTH, as well as the proportion of patients achieving > 50% reduction, was higher with etelcalcetide than with cinacalcet when compared at the chosen efficacy assessment time period of weeks 20 to 27 of the study. PTH levels over time demonstrated a slightly higher reduction for etelcalcetide versus cinacalcet starting at approximately 12 weeks of treatment until 26 weeks of treatment, supporting above analyses. The data also indicate that after each titration step more patients on etelcalcetide reached the event of the > 30% reduction in PTH compared to cinacalcet. These results should be considered in the context of the relative faster titration scheme used for etelcalcetide (5 mg general starting dose up to 15 mg maximum dose with allowed incremental steps of 2.5-5 mg at 4-weekly intervals) compared to cinacalcet (30 mg starting dose up to 180 maximum dose with allowed incremental steps of 30 mg or 60 mg [ie, from 120 mg to 180 mg] at 4-weekly intervals).

Etelcalcetide was not superior to cinacalcet with regard to the number of days vomiting and nausea per week during observation of the first 8 weeks. Further, vomiting and nausea investigated separately supported this absence of superiority.

Since the number of days vomiting and nausea per week during observation of the first 8 weeks did not reach the superiority level of pre-specified significance level of 0.05, and even showed a slightly numerical inferior effect, no conclusions based on statistics could be drawn for subsequent endpoints. Nevertheless, treatment with etelcalcetide resulted in numerically lower levels of calcium over time, starting to show an immediate difference after start of treatment. Similar observations apply to the phosphorus concentration over time.

Numerically greater reductions could be observed for bone markers of bone specific alkaline phosphatase (BSAP) and Type I collagen C-telopeptide (CTX) at week 27 in the etelcalcetide group in comparison to the cinacalcet group, although great variability is noticed. With the uncertainty noticed, this may indicate a positive effect on bone turnover. Similarly for fibroblast growth factor-23, involved in regulation of phosphate concentration, a numerical decrease could be observed.

The slightly faster treatment algorithm for etelcalcetide could have led to slightly higher proportion of temporary dose interruptions with etelcalcetide (23%) compared to cinacalcet (19%). Also, a slightly higher proportion of patients were treated with dose increase of vitamin D sterols and/or calcium-containing phosphate binder or calcium supplement during these dose suspensions, though this did not substantially affect the PTH efficacy. A slightly higher proportion of etelcalcetide patients needed downtitrations (6.3% vs 1.2% for cinacalcet at week 5; 16.6% vs 11.4% at week 17 but, the treatment effect at every titration week was better for etelcalcetide than for cinacalcet, thus downtitration appear not to affect the better effect on PTH over time for etelcalcetide. Also slightly more patients had a PTH < 100 pg/ml when compared to cinacalcet.

Long term effect

Patients from the placebo controlled studies have been enrolled in an open-label phase 3 extension study (384 patients received etelcalcetide during both parent and extension studies; at least 75 at week 84). Patients from the open-label phase 2 study titration study have been enrolled in an open-label extension phase 2 study (30 patients received etelcalcetide in both parent and extension studies; 7 at week 116). During the phase 2 extension study, the reduction in PTH and serum calcium was maintained, although slight increases in these levels could be observed. In particular, during extended treatment beyond 52 weeks this could be observed albeit patient numbers became more limited. The phase 3 extension study demonstrates that the PTH reduction can be maintained during 78 weeks of treatment, although a clear line between a titration and a maintenance phase in etelcalcetide treatment appears to be lacking. Dose adaptions have been necessary at various time points during prolonged treatment, driven by PD response.

PTH levels increased again during the withdrawal phase although baseline levels were not reached. Similar results were observed for the other markers calcium and phosphorus, although the difference is that these returned to baseline levels. Furthermore, they did not decrease to a similar extent as observed during the placebo-controlled phase.

2.5.4. Conclusions on clinical efficacy

The phase 3 studies demonstrated that etelcalcetide significantly reduced PTH levels in comparison to existing background therapy. This was further supported by significant reductions in the secondary

parameters cCa and phosphorus. Also, numerical reductions were seen in the exploratory endpoints for bone markers including bone specific alkaline phosphatase (BSAP), Type I collagen C-telopeptide (CTX), and FGF-23. Reductions in PTH, cCa and phosphorus could be maintained during long term extension up till 78-112 weeks of treatment. Etelcalcetide demonstrated larger reductions in PTH levels than cinacalcet with the titration algorithm and time points chosen in the study; frequency of nausea and vomiting were not significantly different between both treatments. The effect on PTH was supported by numerical reductions in cCa and phosphorus. Also, some numerical lowering of specific bone markers could be observed.

2.6. Clinical safety

Safety data from the 6-month placebo-controlled combined dataset which includes all data collected in the 2 double-blind pivotal studies (20120229, 20120230) are presented. Separately, data from the 6-month active-controlled study (20120360) have been included. Further, long term safety data from the phase 3 open-label extension phase have been included. Etelcalcetide is also sometimes referred to as AMG 416 throughout the text.

Patient exposure

For the entire clinical development program **1704 subjects** received at least 1 dose of etelcalcetide (Table 2.9). A total of 499 subjects were exposed for at least 1 year.

Table 2.9 Total subject exposure to etelcalcetide in clinical trials[a] by duration – Safety Analysis Set.

Secondary HPT	≥ 1 dose n	> 12 weeks n	> 24 weeks n	> 36 weeks n	> 52 weeks n	> 64 weeks n	>78 weeks n	> 96 weeks n	Total n (subj-yrs)
Randomized Double-Blind Studies[b]	924	766	696	0	0	0	0	0	924 (380.2)
Phase 1 studies[c]	43	0	0	0	0	0	0	0	43 (0.1)
Phase 2/3 studies	881	766	696	0	0	0	0	0	881 (380.1)
All Studies	1704	1388	1199	900	499	287	56	14	1704 (1253.2)
Phase 1 studies[c]	49	0	0	0	0	0	0	0	49 (0.1)
Phase 2/3 studies	1655	1388	1199	900	499	287	56	14	1655 (1253.1)

[a] All studies include: Phase 1 studies (20130107, 20130139 and 20130147) and phase 2/3 studies (20120229, 20120230, 20120360, 20120330, 20120331, 20120334, 20120359, 20120231, and 20130213).
[b] Randomized double-blind studies include: Phase 1 studies (20130107, 20130139) and phase 2/3 studies (20120229, 20120230, 20120360, and 20120330).
[c] Phase 1 Study 20130107 is a healthy volunteer study
HPT = hyperparathyroidism; n=number of subjects exposed to AMG 416; subj-yrs= total subject-years of exposure.
Data from completed studies and ongoing studies as of Jan 15th 2015 are included. A study is considered as completed if the clinical study database is locked.
Safety analysis set includes subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/eurmp/tables/t-exp-ct-dur.sas
Output: t1-02-exp-ct-dur-week.rtf (Date generated: 21JUL2015:06:00) Source data: adam.adsl

In phase 2 and phase 3 clinical studies, a total of **1655 subjects** received at least 1 dose of etelcalcetide, 1199 (72.4%) received etelcalcetide for > 24 weeks, and 499 (30.2%) received etelcalcetide for > 52 weeks. The mean (SD) **duration of exposure** was 39.5 (24.5) weeks. The **most frequent dose** (ie, the dose level at which the subject spent the most time) was 5 mg for 40.0% of subjects (Table 2.10). The extent of exposure to etelcalcetide was in accordance with guidance from Health Authorities and International Conference on Harmonisation guidelines (ICH E1). No limitations of the safety database in relation to the proposed target population could be identified.

Table 2.10 Summary of exposure to etelcalcetide (all phase 2 and phase 3 clinical studies, safety analysis set).

	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)
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)
Duration of exposure (weeks)					
n	1655	503	1289	37	841
Mean	39.5	23.6	32.9	69.7	45.5
SD	24.5	5.9	17.4	56.7	23.8
Median	38.6	25.9	37.6	51.7	42.1
Q1, Q3	20.9, 55.7	25.7, 25.9	15.7, 49.3	18.7, 141.0	25.9, 67.1
Min, Max	0, 156	0, 27	0, 76	0, 156	0, 90
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)

Baseline demographics were generally well balanced between treatment groups.

Concomitant medication use was mostly comparable between the study groups. However, a noticeable difference between study groups is observed for calcium supplements at baseline. The applicant explored the issue but could not identify sources to explain the numerical differences in the rates of calcium supplements at baseline. It is considered a chance finding. The imbalance is unlikely to substantially affect primary analyses and the impact on the benefit-risk balance is considered minor.

Adverse events

Adverse events were analysed and reported using integrated safety data from the etelcalcetide trials In the 6 month placebo controlled pool, 461 subjects (91.7%) in the etelcalcetide group and 410 subjects (79.9%) in the placebo group had **treatment emergent adverse events** (Table 2.11).

The subject incidence of serious adverse events (25.8% etelcalcetide; 29.0% placebo), adverse events leading to discontinuation (1.8% etelcalcetide; 2.5% placebo), and fatal adverse events (2.2% etelcalcetide; 2.9% placebo) was not higher in the etelcalcetide group compared with the placebo group.

In the active-controlled study, 92.9% of etelcalcetide subjects and 90.0% of cinacalcet subjects had **treatment emergent adverse events**.

The subject incidence of serious adverse events (25.1% etelcalcetide; 27.3% cinacalcet), adverse events leading to discontinuation of investigational product (5.6% etelcalcetide; 4.7% cinacalcet), and fatal adverse events (2.7% etelcalcetide; 1.8% cinacalcet) was in general comparable between treatment groups.

Table 2.11 Subject incidence of treatment emergent adverse events 6 month placebo/active controlled dataset (Safety Analysis Set).

	Study 20120229		Study 20120230		Total placebo-controlled studies		Study 20120260 Active-controlled	
	Placebo N=254	AMG 416 N=251	Placebo N=259	AMG 416 N=252	Placebo N=513	AMG 416 N=503	Cinacalcet N=341	AMG 416 N=338
All TEAE n (%)	200 (78.7)	230 (91.6)	210 (81.1)	231 (91.7)	410 (79.9)	461 (91.7)	307 (90.0)	314 (92.9)
Mild	*67 (26.4)*	*62 (24.7)*	*74 (28.6)*	*75 (29.8)*	*141 (27.5)*	*137 (27.2)*	*85 (24.9)*	*112 (33.1)*
Moderate	*70 (27.6)*	*103 (41.0)*	*85 (32.8)*	*100 (39.7)*	*155 (30.2)*	*203 (40.4)*	*154 (45.2)*	*133 (39.3)*
Severe	*56 (22.0)*	*55 (21.9)*	*42 (16.2)*	*50 (19.8)*	*98 (19.1)*	*105 (20.9)*	*55 (16.1)*	*52 (15.4)*
Life threatening	*7 (2.8)*	*10 (4.0)*	*9 (3.5)*	*6 (2.4)*	*16 (3.1)*	*16 (3.2)*	*13 (3.8)*	*17 (5.0)*
Serious TEAEs	78 (30.7)	68 (27.1)	71 (27.4)	62 (24.6)	149 (29.0)	130 (25.8)	93 (27.3)	85 (25.1)
Discontinuation due to TEAEs	7 (2.8)	5 (2.0)	6 (2.3)	4 (1.6)	13 (2.5)	9 (1.8)	16 (4.7)	19 (5.6)
Fatal TEAEs	7 (2.8)[a]	7 (2.8)[b]	8 (3.1)	4 (1.6)c	15 (2.9)	11 (2.2)	6 (1.8)	9 (2.7)

[a] In the placebo group, Subject 22966089005 died after the follow-up period and therefore is not included in the list of subjects with treatment emergent fatal adverse events. Subject 22948005001 died after completing the study but within the follow-up period; this subject is included as having a fatal treatment emergent adverse event but is not included in Table 9-1 as a discontinuation due to death.
[b] Subject 22966017001 and Subject 22966049003 died after the follow-up period and therefore are not included in the list of subjects with treatment emergent fatal adverse events.
[c] Subject 23066026008 died > 30 days after the last dose of study treatment and therefore is not included in the list of subjects with treatment emergent fatal adverse events.
Source: Modified from Table 14-6.1 and Table 14-6.11 (study 20120229), Modified from Table 14-6.1 and Table 14-6.9 (Study 20120260). Modified from Table 14-6.1 and Table 14-6.11.(Study 20120230)

The most **common adverse event** within the placebo-controlled studies was **asymptomatic blood calcium decreased** (63.8% etelcalcetide; 10.1% placebo) (Table 2.12). This includes asymptomatic reductions in calcium below 7.5 mg/dl or asymptomatic reductions in serum corrected calcium between 7.5 and < 8.3 mg/dl that required medical management or that the investigator deemed clinically significant.

Other common adverse events that occurred with a **greater frequency** in the etelcalcetide group compared to placebo (≥ 5% in the etelcalcetide group with ≥ 1% difference from placebo) were **blood calcium decreased** (63.8% etelcalcetide; 10.1% placebo), muscle spasms (11.5% etelcalcetide; 6.6% placebo), diarrhea (10.7% etelcalcetide; 8.6% placebo), nausea (10.7% etelcalcetide; 6.2% placebo), vomiting (8.9% etelcalcetide; 5.1% placebo), headache (7.6% etelcalcetide; 6.0% placebo), and **hypocalcaemia** (7.0% etelcalcetide; 0.2% placebo). Symptomatic reductions in serum corrected calcium < 8.3 mg/dL were reported as adverse events of "hypocalcaemia", and the associated signs and symptoms were also captured.

A **similar pattern** was observed for the active-controlled study and consistent with the placebo controlled studies. For the most frequently reported adverse events, **asymptomatic blood calcium decreased** (68.9% etelcalcetide; 59.8% cinacalcet) was higher, while nausea (18.3% etelcalcetide; 22.6% cinacalcet), vomiting (13.3% etelcalcetide; 13.8% cinacalcet), and diarrhoea (6.2% etelcalcetide; 10.3% cinacalcet) were numerically lower for etelcalcetide than for cinacalcet. Also **hypocalcaemia** (5.0% etelcalcetide; 2.3% cinacalcet) was higher.

The Kaplan Meier estimate of median time to the first hypocalcaemia event was 9.6 weeks in the etelcalcetide arm in placebo-controlled studies and 9.7 weeks in the etelcalcetide arm in the active-controlled study.

Table 2.12 Subject incidence of treatment emergent adverse events occurring in ≥5% of subjects in any arm (6-month Placebo/Active-controlled dataset – Safety Analysis Set).

	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)

Overall, 73.4% of subjects (300.1 per 100 subject-years) in the phase 3 long-term open-label extension combined dataset had at least 1 treatment emergent adverse event. The most common adverse event **blood calcium decreased** (31.0%; 60.9 per 100 subject-years), being highest in subjects who received placebo in the parent studies (55.9%; 120.2 per 100 subject-years), which was expected as these subjects had not previously received etelcalcetide. **Other common adverse events** by preferred term (≥ 7%) were diarrhea (7.8%; 11.6 per 100 subject-years), nausea (7.0%; 10.3 per 100 subject-years), and vomiting (7.0%; 10.3 per 100 subject-years).

For the 6 month placebo controlled pool, during the study, a higher percentage of subjects in the etelcalcetide group compared with the placebo group received **vitamin D sterols** (78.3% etelcalcetide; 69.6% placebo) and **calcium-containing phosphate binder or calcium supplement** (70.4% etelcalcetide; 49.3% placebo). Overall, 84.7% of subjects in the etelcalcetide group and 86.5% of subjects in the placebo group received phosphate binders during the study. The majority of subjects in both groups had no change in **dialysate calcium** during the study (74.2% etelcalcetide; 95.7% placebo). A higher proportion of etelcalcetide subjects had only increases in dialysate calcium from baseline during the study (24.9% etelcalcetide; 2.7% placebo).

Adverse events of special interest

In the 6-month placebo/active controlled pool, most events in the **hypocalcaemia** were mild or moderate in severity (Table 2.13). One (0.3%) subject each in the etelcalcetide and cinacalcet treatment arms in the active-controlled study and no subjects in the placebo-controlled studies had a serious adverse event of blood calcium decreased. No subject had a serious adverse event of hypocalaemia. A total of 5 (1.0%) subjects in the etelcalcetide arm had events of hypocalcaemia that led to discontinuation of investigational product.

Table 2.13 Overview of treatment-emergent events of interest. Hypocalcaemia. 6-month placebo / active-controlled pool (Safety Analysis Set).

	Total placebo-controlled studies		20120360	
	Placebo (N = 513) ev n (%)	AMG 416 (N = 503) ev n (%)	Cinacalcet (N = 341) ev n (%)	AMG 416 (N = 338) ev n (%)
Severity				
Mild	44, 38 (7.4)	394, 213 (42.3)	244, 124 (36.4)	304, 177 (52.4)
Moderate	17, 14 (2.7)	179, 141 (28.0)	108, 84 (24.6)	87, 70 (20.7)
Severe	1, 1 (0.2)	2, 2 (0.4)	6, 5 (1.5)	7, 5 (1.5)
Life threatening	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Unknown	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Fatal	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Leading to discontinuation of investigational product	0, 0 (0.0)	5, 5 (1.0)	2, 2 (0.6)	0, 0 (0.0)
Serious adverse events	0, 0 (0.0)	0, 0 (0.0)	1, 1 (0.3)	1, 1 (0.3)
Blood calcium decreased	0, 0 (0.0)	0, 0 (0.0)	1, 1 (0.3)	1, 1 (0.3)

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Total placebo-controlled studies: Studies 20120229 and 20120230.
Safety analysis set: all subjects in the pool who received at least one dose of IP.
Coded using MedDRA version 17.1
ev: number of events.
n: number of subjects. Severity is summarized at preferred term level for each subject, ie, n is subject-preferred term count for severity. If a subject had a preferred term with multiple severities, the worst severity is considered for the preferred term for the subject.

Secondary to low calcium, rates of events **potentially associated with increased neuromuscular irritability** were also higher versus placebo and mainly consisted of paresthesia (4.8% etelcalcetide; 0.6% placebo), hypoesthesia (1.8% etelcalcetide; 0.8% placebo), and myalgia (1.6% etelcalcetide; 0.2% placebo). In the active controlled study, these events were reported at comparable or somewhat higher frequencies for etelcalcetide compared to cinacalcet (paresthesia: 2.1% etelcalcetide vs 1.8% cinacalcet; hypoesthesia (1.2% etelcalcetide vs 0.9% cinacalcet; myalgia: 1.5% etelcalcetide vs 0.6% cinacalcet).

The rates of adverse events **potentially associated with the effect of decreased calcium on cardiac repolarization** (syncope, convulsion, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular tachyarrhythmia) were similar between etelcalcetide and placebo or cinacalcet (Table 2.14).

The percentage of subjects with adverse events of **convulsions** (SMQ) was low and similar between treatment groups in the placebo-controlled studies (0.8% etelcalcetide; 1.0% placebo) and active-controlled study (0.9% etelcalcetide; 0.6% cinacalcet). No events were fatal. One subject in the etelcalcetide arm in the placebo-controlled study had convulsion concurrent with both blood calcium decreased and hypocalcaemia. etelcalcetide was temporarily withheld and corrected calcium returned to normal and the subject continued in the study.

The subject incidence of **ventricular tachyarrhythmias (SMQ)** (0.4% etelcalcetide; 0.8% placebo and (0% etelcalcetide; 0% cinacalcet) was low and similar in both etelcalcetide versus placebo or cinacalcet. Two (0.4%) subjects in the etelcalcetide group and no subjects in the placebo group had ventricular tachycardia (Table 2.14). Both subjects continued drug without similar events. The events were not considered related to etelcalcetide. No subjects in the etelcalcetide group and 1 (0.2%) subject in the placebo group had ventricular tachyarrhythmia and ventricular fibrillation. There were no cases of Torsade de pointes.

Within the phase 3 open-label extension combined dataset, the crude subject incidence and exposure-adjusted incidence rates of adverse events of ventricular tachyarrhythmias (0.6%, 0.9 per 100 subject-years) were low. One subject (0.1%, 0.1 per 100 subject-years) had Torsade de pointes. The subject remained on etelcalcetide (dose not changed). The investigator assessed the event of Torsade de pointes as not related to etelcalcetide.

Table 2.14 Subject incidence of treatment emergent adverse events potentially associated with drug effect on cardiac repolarization (6-month placebo/active controlled combined dataset – Safety Analysis Set).

	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 (%)
Syncope	5 (1.0)	4 (0.8)	2 (0.6)	4 (1.2)
Convulsion	4 (0.8)	4 (0.8)	2 (0.6)	1 (0.3)
Sudden death	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.3)
Ventricular tachycardia	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Ventricular fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachyarrhythmia	1 (0.2)	0 (0.0)	0 (0.0)	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 6.5

Although incidence was low, slightly higher incidence of **Torsade de pointes/QT prolongation** (1.2% etelcalcetide vs 0.6% placebo; 0.3% etelcalcetide vs 0% cinacalcet) were found. Within the phase 3 open-label extension combined dataset, the crude subject incidence and exposure-adjusted incidence rates of Torsade de pointes/QT prolongation (0.4%, 0.5 per 100 subject-years) were low. Within the placebo-controlled studies, 12-lead ECGs (triplicate; central independently assessed) and blood samples for the assessment of etelcalcetide and serum cCA concentrations were collected predialysis and 10 to 30 minutes after haemodialysis on day 1 and weeks 5, 13, and 26, or at early termination (predialysis only). A **higher percentage** of subjects in the etelcalcetide treatment group compared with placebo had **shifts in QTcF, postbaseline QTcF**, or **maximum increase from baseline** of > 30 to 60 msec or > 60 msec (see Table 2.15).

The most common (≥ 1%) adverse event potentially associated with a drug effect on cardiac repolarization in the phase 3 open-label extension combined dataset terms was **syncope** (1.7%, 2.4 per 100 subject-years). The exposure-adjusted incidence rate of **sudden death** was 0.3 per 100 subject-years, which was lower than the exposure-adjusted incidence rate reported in the placebo arm of EVOLVE (0.7 per 100 subject-years).

Table 2.15 Predialysis corrected QTcF interval maximum postbaseline and maximum increase from baseline categories (6-month placebo-controlled combined data set – Safety Analysis Set).

	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 (%)
Baseline – n (%)						
≤ 450	210 (82.7)	179 (71.3)	199 (76.8)	198 (78.6)	409 (79.7)	377 (75.0)
> 450 to 480	25 (9.8)	46 (18.3)	31 (12.0)	36 (14.3)	56 (10.9)	82 (16.3)
> 480 to 500	6 (2.4)	6 (2.4)	14 (5.4)	7 (2.8)	20 (3.9)	13 (2.6)
> 500	4 (1.6)	2 (0.8)	2 (0.8)	0 (0.0)	6 (1.2)	2 (0.4)
Missing	9 (3.5)	18 (7.2)	13 (5.0)	11 (4.4)	22 (4.3)	29 (5.8)
Maximum post-baseline – n (%)						
≤ 450	176 (69.3)	123 (49.0)	173 (66.8)	133 (52.8)	349 (68.0)	256 (50.9)
> 450 to 480	49 (19.3)	72 (28.7)	47 (18.1)	71 (28.2)	96 (18.7)	143 (28.4)
> 480 to 500	13 (5.1)	14 (5.6)	15 (5.8)	22 (8.7)	28 (5.5)	36 (7.2)
> 500	4 (1.6)	14 (5.6)	6 (2.3)	10 (4.0)	10 (1.9)	24 (4.8)
Missing	12 (4.7)	28 (11.2)	18 (6.9)	16 (6.3)	30 (5.8)	44 (8.7)
Maximum increase from baseline – n (%)						
≤ 30	221 (87.0)	167 (66.5)	223 (86.1)	178 (70.6)	444 (86.5)	345 (68.6)
> 30 to 60	16 (6.3)	46 (18.3)	13 (5.0)	53 (21.0)	29 (5.7)	99 (19.7)
> 60	0 (0.0)	4 (1.6)	0 (0.0)	2 (0.8)	0 (0.0)	6 (1.2)
Missing	17 (6.7)	34 (13.5)	23 (8.9)	19 (7.5)	40 (7.8)	53 (10.5)

This combined dataset includes data from the two placebo-controlled studies 20120229 and 20120230.
Safety analysis set: all subjects in the combined dataset 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.
The observations with the following diagnosis or findings were excluded from analyses: artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block.
Source: ISS Table 7.44

An Event Adjudication Committee **adjudicated specific adverse events** (death, cardiovascular events [myocardial infarction, stroke, and congestive heart failure requiring hospitalization], and seizures) in a blinded manner. The subject incidence of adjudicated TEAEs is shown in Table 2.16. The subject incidence of adjudicated confirmed **congestive heart failure requiring hospitalisation** and **myocardial infarction** was higher for etelcalcetide treatment group both in the placebo-controlled studies and active controlled study.

Table 2.16 Summary of subject incidence of adjudicated treatment-emergent adverse events 6-month placebo-controlled pool (Safety Analysis Set).

	20120229		20120230		Total placebo-controlled studies	
Events	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 (%)
Death	7 (2.8)	7 (2.8)	8 (3.1)	4 (1.6)	15 (2.9)	11 (2.2)
Confirmed myocardial infarction	2 (0.8)	3 (1.2)	3 (1.2)	5 (2.0)	5 (1.0)	8 (1.6)
Confirmed stroke	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)	2 (0.4)
Confirmed congestive heart failure requiring hospitalization	2 (0.8)	7 (2.8)	4 (1.5)	4 (1.6)	6 (1.2)	11 (2.2)
Confirmed seizure	2 (0.8)	2 (0.8)	3 (1.2)	3 (1.2)	5 (1.0)	5 (1.0)
Personal history of seizure	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.2)

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This pool includes data from the two placebo-controlled studies 20120229 and 20120230.
Safety analysis set: all subjects in the pool who received at least one dose of IP.

About 3% of subjects in the etelcalcetide arm had **cardiac failure** (3.2% etelcalcetide versus 2.5% placebo, 3.0% etelcalcetide versus 0.6% cinacalcet). Although some numerical differences were noted in the subject

incidence of adverse events in the cardiac failure in the etelcalcetide arm compared to placebo and cinacalcet, the rate was consistent with the 6-month background rate of 3.3% in the placebo arm of the EVOLVE study, a large cardiovascular outcomes study conducted in subjects with CKD on dialysis.

In the placebo-controlled studies, severe, life-threatening, or fatal events of cardiac failure were similar (Table 2.17). Three (0.9%) subjects had fatal adverse events of cardiac failure with etelcalcetide in the active controlled study: 2 (0.6%) subjects had cardiac failure acute, and 1 (0.3%) subject had cardiac failure. None of the fatal adverse events were associated with low serum corrected calcium. All cases involved subjects with numerous co-morbid conditions that likely contributed to the events of cardiac failure, and the investigator assessed all 3 events as not related to study drug. No pattern of temporal associations of cardiac heart failure cases with etelcalcetide exposure was observed in placebo-controlled studies or the active-controlled study.

Table 2.17 Overview of treatment emergent events of interest. Cardiac failure. 6-months placebo/active-controlled pool (Safety Analysis Set).

	Total placebo-controlled studies		20120360	
	Placebo (N = 513) ev n (%)	AMG 416 (N = 503) ev n (%)	Cinacalcet (N = 341) ev n (%)	AMG 416 (N = 338) ev n (%)
Severity				
Mild	2, 2 (0.4)	2, 2 (0.4)	0, 0 (0.0)	1, 1 (0.3)
Moderate	4, 4 (0.8)	9, 8 (1.6)	1, 1 (0.3)	4, 4 (1.2)
Severe	10, 8 (1.6)	8, 7 (1.4)	1, 1 (0.3)	1, 1 (0.3)
Life threatening	1, 1 (0.2)	2, 2 (0.4)	0, 0 (0.0)	4, 4 (1.2)
Unknown	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Fatal	2, 2 (0.4)	1, 1 (0.2)	0, 0 (0.0)	3, 3 (0.9)
Leading to discontinuation of investigational product	1, 1 (0.2)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Serious adverse events	12, 8 (1.6)	16, 12 (2.4)	1, 1 (0.3)	5, 5 (1.5)
Acute pulmonary oedema	1, 1 (0.2)	3, 2 (0.4)	0, 0 (0.0)	1, 1 (0.3)
Cardiac failure	1, 1 (0.2)	2, 2 (0.4)	0, 0 (0.0)	1, 1 (0.3)
Cardiac failure acute	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	2, 2 (0.6)
Cardiac failure chronic	0, 0 (0.0)	1, 1 (0.2)	0, 0 (0.0)	0, 0 (0.0)
Cardiac failure congestive	5, 5 (1.0)	6, 5 (1.0)	1, 1 (0.3)	0, 0 (0.0)
Cardiogenic shock	0, 0 (0.0)	1, 1 (0.2)	0, 0 (0.0)	0, 0 (0.0)
Pulmonary oedema	5, 3 (0.6)	3, 3 (0.6)	0, 0 (0.0)	1, 1 (0.3)

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Total placebo-controlled studies: Studies 20120229 and 20120230.
Safety analysis set: all subjects in the pool who received at least one dose of IP.
Coded using MedDRA version 17.1
ev: number of events.
n: number of subjects. Severity is summarized at preferred term level for each subject, ie, n is subject-preferred term count for severity.
If a subject had a preferred term with multiple severities, the worst severity is considered for the preferred term for the subject.

A higher proportion of etelcalcetide had events in the **hypophosphatemia**; 1.4% etelcalcetide versus 0.4% placebo in the placebo–controlled studies and 1.5% etelcalcetide versus 0.9% cinacalcet in the active controlled study. Most events of hypophosphatemia were mild (7 events) or moderate (5 events), with no severe events reported. None of the events in the etelcalcetide arms were serious or resulted in discontinuation of the investigational product. One (0.3%) subject in the cinacalcet arm had a hypophosphatemia event that was serious and led to discontinuation of investigational product.

About 20% of patients in the etelcalcetide arm experienced **infusion reaction**s; 19.7% etelcalcetide versus 17.7% placebo and 20.1% etelcalcetide versus 15.5% cinacalcet in the placebo and active controlled studies, respectively. The subject incidence was primarily driven by events that constituted nondescript constitutional symptoms such as hypertension, hypotension, and pyrexia, which are commonly observed in the CKD patient

population. Hypertension (6.2% etelcalcetide; 5.7% placebo), hypotension (6.0% etelcalcetide; 5.1% placebo), and pyrexia (4.0% etelcalcetide; 3.9% placebo) were balanced between the etelcalcetide and placebo groups. Most infusion reactions were mild or moderate in severity. In the placebo-active combined dataset, 1 subject in each treatment arm had an event that led to discontinuation and 1 subject, except for the cinacalcet arm, had a fatal event.

The subject incidences of **hypersensitivity** were similar in the etelcalcetide and comparator arm (4.4% etelcalcetide versus 3.7% placebo, and 5.6% etelcalcetide versus 5.0% cinacalcet) in the placebo-controlled and active controlled study, respectively. Two (0.4%) subjects in the etelcalcetide arm of the placebo-controlled studies had serious adverse events (palpable purpura and shock). These were not considered related to study drug. Three subjects in the etelcalcetide group of the active-controlled study discontinued study drug due to adverse events. One event of bronchospasm, and 2 subjects experienced dermatitis, which were non-serious and considered related to etelcalcetide. The one non-serious event of bronchospasm led to discontinuation. The rates of individual adverse events suggestive of hypersensitivity (e.g., rash, rash pruritic, urticaria, eyelid edema, and periorbital edema) were infrequent and balanced between etelcalcetide and placebo groups. No serious events indicative of anaphylactic-type reactions were reported in the etelcalcetide arms in either the placebo-controlled studies or the active-controlled study. Possible hypersensitivity and infusion reaction adverse events were **analyzed by anti-drug antibody status** in the placebo-controlled studies. Of the 13 subjects who had positive binding antibody post-baseline with a negative or no result at baseline, 1 (7.7%) subject had a potential hypersensitivity or infusion reaction-related adverse event (pyrexia); this event was unlikely to be related to the development of post-baseline binding antibodies to etelcalcetide. Although drug-induced hypersensitivity remains a potential risk with etelcalcetide, the potential hypersensitivity and infusion reaction adverse events identified using pre-specified search criteria were not attributed to etelcalcetide, and there was no evidence of an association of hypersensitivity or infusion reaction adverse events with anti-drug antibody status.

The subject incidence of events in the **fractures** was lower for etelcalcetide in the placebo-controlled studies (1.6% etelcalcetide; 2.9% placebo) and similar in the etelcalcetide and cinacalcet arms in the active-controlled study (2.1% etelcalcetide; 2.6% cinacalcet). In the placebo-controlled studies, approximately half of all events were severe. In the active-controlled study, most events in the etelcalcetide arm were mild or moderate, and approximately half of events in the cinacalcet arm were severe. A total of 27 subjects (2.1%; 3.0 per 100 subject-years) in the phase 3 long-term open-label extension combined dataset had events in the fractures. Fifteen subjects (1.2%) had severe events. No events were fatal or led to discontinuation of the investigational product.

Table 2.18 Overview of type of fractures in the placebo controlled studies and the active controlled study

	Total placebo-controlled studies		20120360	
Events of Interest Preferred Term	Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)	Cinacalcet (N = 341) n (%)	AMG 416 (N = 338) n (%)
Fractures (EOI)	15 (2.9)	8 (1.6)	9 (2.6)	7 (2.1)
Femur fracture	3 (0.6)	2 (0.4)	3 (0.9)	0 (0.0)
Tibia fracture	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)
Hip fracture	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Lower limb fracture	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Rib fracture	3 (0.6)	1 (0.2)	1 (0.3)	1 (0.3)
Scapula fracture	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Spinal fracture	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Ankle fracture	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Avulsion fracture	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Clavicle fracture	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Facial bones fracture	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Foot fracture	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.3)
Fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Fracture nonunion	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hand fracture	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Pathological fracture	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Pelvic fracture	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)
Radius fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

No subjects in either treatment group had **adynamic bone** adverse events.

In the placebo-controlled studies, **dialysis vascular access thrombosis** events (6.0% etelcalcetide; 5.8% placebo) were similar. In the active-controlled study, a lower proportion of etelcalcetide subjects had these events (3.0% etelcalcetide; 4.7% cinacalcet). Most events were mild or moderate in severity. No events were fatal or led to discontinuation of investigational product.

In the placebo-controlled studies, **adverse drug reactions (ADRs)** for etelcalcetide were determined as those that occurred in ≥ 5% of etelcalcetide subjects and with a ≥ 1% greater frequency than placebo subjects. In the absence of the placebo arm, the difference in the event frequency in the etelcalcetide arm compared to the event frequency in the control group was not taken into consideration in the active-controlled study. Events in that occurred at a rate < 5% were also medically reviewed and included as adverse drug reactions based on biological plausibility, pharmacology, and medical importance as well as the difference in the events' frequency from placebo. Events that were considered adverse drug reactions are presented in Table 2.19. The majority of ADRs in both the placebo- and active controlled studies were mild to moderate in severity and no apparent differences were seen between treatment groups for both the placebo and active controlled studies.

Safety information from all other clinical studies and long-term open-label extension studies was also evaluated, and no additional adverse events were identified as adverse drug reactions.

Table 2.19 Subject incidence of adverse drug reactions (Placebo / Active controlled Dataset – Safety Analysis Set).

	Total Phase 3 Placebo-controlled Studies (20120229 and 20120230)		Study 2012360	
System Organ Class Preferred Term	Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)	Cinacalcet (N=341) n (%)	AMG 416 (N=338) n (%)
Gastrointestinal disorders				
Diarrhoea	44 (8.6)	54 (10.7)		
Nausea	32 (6.2)	54 (10.7)	77 (22.6)	62 (18.3)
Vomiting	26 (5.1)	45 (8.9)	47 (13.8)	45 (13.3)
Investigations				
Blood calcium decreased	52 (10.1)	321 (63.8)	204 (59.8)	233 (68.9)
Metabolism and nutrition disorders				
Hypocalcaemia	1 (0.2)	35 (7.0)	8 (2.3)	17 (5.0)
Hyperkalaemia[a]	16 (3.1)	22 (4.4)	18 (5.3)	13 (3.8)
Hypophosphataemia	1 (0.2)	7 (1.4)		
Musculoskeletal and connective tissue disorders				
Muscle spasms	34 (6.6)	58 (11.5)	20 (5.9)	22 (6.5)
Myalgia	1 (0.2)	8 (1.6)		
Nervous system disorders				
Headache	31 (6.0)	38 (7.6)		
Paraesthesia[b]	6 (1.2)	31 (6.2)	9 (2.6)	11 (3.3)
Vascular Disorders				
Hypotension			10 (2.9)	23 (6.8)

Safety Analysis Set: all subjects who received at least one dose of IP

Serious adverse events and deaths

In the placebo-controlled studies, 130 subjects (25.8%) in the etelcalcetide group and 149 subjects (29.0%) in the placebo group had a **serious adverse event**. In the active-controlled study, 85 subjects (25.1%) in the etelcalcetide group and 93 subjects (27.3%) in the cinacalcet group had serious adverse events.

The most frequently reported serious adverse events in the placebo controlled studies (≥ 1% of subjects in the etelcalcetide arm) were hyperkalaemia (2.0% etelcalcetide; 0.4% placebo), pneumonia (2.0% etelcalcetide; 2.7% placebo), angina pectoris (1.4% etelcalcetide; 0.6% placebo), fluid overload (1.2% etelcalcetide; 1.4% placebo), atrial fibrillation (1.0% etelcalcetide; 1.0% placebo) and cardiac failure congestive (1.0% etelcalcetide; 1.0% placebo) (Table 2.20). Hyperkalaemia and angina pectoris were more frequently reported for etelcalcetide. The only serious adverse event that occurred in ≥ 1% of subjects in the etelcalcetide arm of the active controlled study was gangrene (4 subjects [1.2%] etelcalcetide; 0 subjects [0%] cinacalcet). No subject had a serious adverse event of hypocalcaemia.

Table 2.20 Subject incidence of serious treatment emergent adverse events occurring in ≥1% of subjects in any pooled treatment arm (6-month placebo/active-controlled combined dataset – Safety Analysis Set.

	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

None of the **hyperkalaemia** events in either group in the placebo controlled studies were assessed by the investigator as related to study medication. All subjects in the etelcalcetide arm had major risk factors for hyperkalaemia at the time of the event, such as missed dialysis sessions, noncompliance with a low-potassium diet, and low serum bicarbonate. All subjects in the etelcalcetide arm recovered and continued with the study without re-occurrence of hyperkalaemia with the exception of 1 subject who reported a second episode of hyperkalaemia 1.5 month after restarting treatment. The investigator assessed both events as not related to etelcalcetide because of co-morbid conditions as well as the presence of alternative causalities.

Only a numerical imbalance for **angina pectoris** was reported in study 20120229 (2.4% etelcalcetide; 0.4% placebo) and not for study 20120230 (0.4% etelcalcetide; 0.8% placebo). All cases of angina pectoris had numerous confounding factors at baseline for ischemic heart disease, such as diabetes mellitus, coronary artery disease, and myocardial infarction. None of these events were assessed as related to etelcalcetide by the investigator. None of the events resulted in any dose modifications of etelcalcetide. In addition, a review of baseline medical history in Study 20120229 revealed significantly higher rates of pre-existing co-morbid conditions in the etelcalcetide arm compared to placebo. The higher rates of pre-existing co-morbid conditions related to major domains of cardiovascular risks in the etelcalcetide arm compared to placebo in the 20120229 study is a likely explanation of the observed imbalance in the rates of on-treatment events of angina pectoris in this study. No significant imbalances in pre-existing conditions related to ischemic disease were noted in the 20120230 study.

A total of 376 subjects (29.2%; 51.2 per 100 subject-years) in the phase 3 long-term open-label extension combined dataset had serious adverse events. The most frequently reported (> 1%) serious adverse events were hyperkalaemia (2.2%; 3.1 per 100 subject-years), pneumonia (1.6%; 2.2 per 100 subject-years), cardiac failure congestive (1.5%; 2.1 per 100 subject-years), syncope (1.2%; 1.6 per 100 subject-years), cellulitis (1.1%; 1.5 per 100 subject-years), fluid overload (1.1%; 1.5 per 100 subject-years),and sepsis (1.1%; 1.5 per 100 subject-years).

A total of 11 subjects (2.2%) in the etelcalcetide group and 15 subjects (2.9%) in the placebo group had treatment emergent **fatal adverse events**. The causes of death in both the etelcalcetide and placebo arms were consistent with the population's baseline comorbid conditions and similar to causes of death in the general population of patients with CKD on dialysis. With the exception of 1 case, none of the events with fatal outcomes were assessed as related to investigational product.

Four additional subjects (3 etelcalcetide and 1 placebo) had fatal events that occurred after the follow-up period of 30 days after the last dose of study treatment. The causes of death were reported as chronic renal failure, sudden cardiac death, and gastrointestinal haemorrhage for patients that received prior on etelcalcetide, one, cardiac valve disease was reported in the placebo group.

A total of 9 subjects (2.7%) in the etelcalcetide group and 6 subjects (1.8%) in the cinacalcet group had treatment emergent **fatal adverse events** in the active controlled study. Acute cardiac failure was reported in 2 subjects (0.6%) in etelcalcetide and 0 subjects in cinacalcet. Two additional subjects had fatal events that occurred after the safety follow-up period of 30 days. One subject in the etelcalcetide group had a fatal event of chronic renal failure, and 1 subject in the cinacalcet group had a fatal event of acute myocardial infarction after the follow-up period. None of the fatal adverse events were considered to be related to the investigational product.

Table 2.21 Subject Incidence of Fatal Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency (6-month Placebo/Active-controlled Combined Dataset - Safety Analysis Set)

	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 fatal treatment emergent adverse events	15 (2.9)	11 (2.2)	6 (1.8)	9 (2.7)
Biliary cancer metastatic	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac arrest	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)
Cardiac failure congestive	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Gangrene	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Graft haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Postoperative respiratory failure	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Road traffic accident	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Sepsis	2 (0.4)	1 (0.2)	1 (0.3)	1 (0.3)
Sudden death	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.3)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Arteriovenous graft site haemorrhage	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Bacterial sepsis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Brain death	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure acute	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Endocarditis bacterial	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic stroke	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxic-ischaemic encephalopathy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pneumonia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Poor peripheral circulation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure chronic	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ventricular fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

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 fatal adverse events. The most common fatal adverse events were 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 haemorrhage (2 subjects (0.2%); 0.2 per 100 subject-years), and septic shock (2 subjects (0.2%); 0.2 per 100 subject-years). Compared with the phase 3 open-label extension combined dataset, the exposure-adjusted incidence rate of cardiac arrest (1.3

per 100 subject-years cinacalcet; 1.3 per 100 subject-years placebo) and sudden death (0.5 per 100 subject-years cinacalcet; 0.7 per 100 subject-years placebo) in the EVOLVE study was similar.

Laboratory findings

Reductions in PTH were evaluated as efficacy endpoints in the placebo and active controlled studies. These are discussed within the efficacy section.

In the combined placebo-controlled studies, a higher **proportion of patients** in the Parsabiv group compared with patients in the placebo group developed at least one **serum corrected calcium value < 7.0 mg/dL** (7.6% etelcalcetide; 3.1% placebo), < 7.5 mg/dL (27.1% etelcalcetide; 5.5% placebo), and < 8.3 mg/dL (78.6% etelcalcetide; 19.4% placebo) (Table 2.22).

In the placebo controlled studies more **shifts** from grade 0 to grade 3 **of decreased corrected calcium** (corrected calcium between 6-<7 mg/dL; 6.0% etelcalcetide; 1.9% placebo) were found for etelcalcetide; however, shifts to grade 4 decreased corrected calcium were similar (corrected calcium < 6.0 mg/dL; 1.4% etelcalcetide; 1.0% placebo). In the active controlled study, proportion of shifts from grade 0 to grade 3 decreased corrected calcium was slightly lower for etelcalcetide (5.9% etelcalcetide; 7.0% cinacalcet), while slightly higher for grade 4 decreased corrected calcium (2.1% etelcalcetide; 1.2% cinacalcet).

A similar proportion of etelcalcetide and cinacalcet subjects had **≥ 1 postbaseline corrected calcium** concentration < 7.0 mg/dL (8.6% etelcalcetide; 9.5% cinacalcet) and < 7.5 mg/dL (26.5% etelcalcetide; 26.7% cinacalcet). A higher proportion of etelcalcetide subjects had ≥ 1 postbaseline corrected calcium concentration < 8.3 mg/dL (82.7% etelcalcetide; 72.7% cinacalcet) (Table 2.22).

Table 2.22 Exposure adjusted and crude subject incidence rate of post-baseline low serum corrected calcium values 6- Month Placebo/Active-Controlled Pool (Safety Analysis Set).

	Total placebo-controlled studies		20120360	
	Placebo (N = 513) n/Y s c	AMG 416 (N = 503) n/Y s c	Cinacalcet (N = 341) n/Y s c	AMG 416 (N = 338) n/Y s c
Subjects with ≥ 1 post-baseline cCa value - N1	511	499	337	336
cCa < 7.0 mg/dL	16/264.0, 6.1, 3.1	38/254.4, 14.9, 7.6	32/172.4, 18.6, 9.5	29/166.3, 17.4, 8.6
cCa < 7.5 mg/dL	28/259.2, 10.8, 5.5	135/221.0, 61.1, 27.1	90/152.7, 58.9, 26.7	89/145.7, 61.1, 26.5
cCa < 8.3 mg/dL	99/232.3, 42.6, 19.4	392/101.2, 387.4, 78.6	245/81.6, 300.3, 72.7	278/65.1, 427.2, 82.7

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Total placebo-controlled studies: Studies 20120229 and 20120230.
N = The number of subjects in safety analysis set.
n = Subject incidence
Y = Total Subject-year Exposure for patients with ≥ 1 post-baseline cCa value and is calculated as date of the first event of low calcium or date of the last cCa value if the subject experienced no low calcium event - date of Day 1 + 1, summed over all subjects(N1) (yrs).
s = Exposure-adjusted subject incidence rate per 100 subject year = 100* n/Y.
c = Crude subject incidence rate = 100*n/N1.

A total of 133 subjects in the placebo-controlled studies and 79 subjects in the active controlled study had a least 1 incident of **corrected calcium < 7.5 mg/dL that led to the etelcalcetide dose being withheld**. The median Kaplan Meier estimate of **time to recovery** was 2.1 weeks and 2.9 weeks in the placebo-controlled studies and active-controlled study, respectively. Of the 113 subjects in the placebo-controlled studies who had at least 1 incident of corrected calcium < 7.5 mg/dL that led to the etelcalcetide dose being withheld, 104 (92.0%) subjects had corrected calcium recovery to ≥ 8.3 mg/dL, and the median Kaplan Meier estimate of time to recovery was 2.1 weeks. A total of 87.5% had corrected calcium value recovery at 4 weeks, and 99.0% recovered at 7 weeks. Of the 79 subjects in the active controlled study who had at least 1 incident of corrected calcium < 7.5 mg/dL that led to the etelcalcetide dose being withheld, 76 (96.2%) subjects had corrected calcium recovery to ≥ 8.3 mg/dL, and the Kaplan Meier estimate of median time to

recovery was 2.9 weeks. Calcium corrected value recovered in almost all patients within 8 weeks. These results demonstrate that temporarily discontinuing etelcalcetide and protocol-specified treatment (adjustments in dialysate calcium, vitamin D sterols, or calcium supplements) were effective in allowing calcium values to recover.

Starting from the beginning of the open-label extension study, by 6 months, corrected calcium was < 7.0 mg/dL for 43 subjects (3.4%; 9.3 per 100 subject-years), < 7.5 mg/dL for 158 subjects (12.4%; 36.2 per 100 subject-years), and < 8.3 mg/dL for 710 subjects (55.9%; 251.0 per 100 subject-years). By 12 months, corrected calcium was < 7.0 mg/dL for 53 subjects (4.2%; 7.3 per 100 subject-years), < 7.5 mg/dL for 191 subjects (15.0%; 28.8 per 100 subject-years), and < 8.3 mg/dL for 784 subjects (61.7%; 211.1 per 100 subject-years. By 18 months, corrected calcium was < 7.0 mg/dL for 54 subjects (4.3%; 7.1 per 100 subject-years), < 7.5 mg/dL for 193 subjects (15.2%; 28.1 per 100 subject-years), and < 8.3 mg/dL for 792 subjects (62.4%; 210.1 per 100 subject-years). These results indicate that the incidence of decreases in calcium is relatively stable over time (Table 2.23).

Table 2.23 Exposure adjusted and crude subject incidence rate of post-baseline low serum corrected calcium value phase 3 long term OLE pool (Safety Analysis Set).

	Placebo in Parent Studies	Cinacalcet in Parent Study	AMG 416 in controlled Parent Studies	AMG 416 in single arm parent study	Total
	AMG 416 (N = 383) n/Y s c	AMG 416 (N = 206) n/Y s c	AMG 416 (N = 577) n/Y s c	AMG 416 (N = 123) n/Y s c	AMG 416 (N = 1289) n/Y s c
Up to 6 months					
Subjects with ≥ 1 post-baseline cCa value - N1	383	195	569	123	1270
cCa < 7.0 mg/dL	19/159.5, 11.9, 5.0	2/46.8, 4.3, 1.0	18/204.6, 8.8, 3.2	4/50.8, 7.9, 3.3	43/461.7, 9.3, 3.4
cCa < 7.5 mg/dL	79/144.0, 54.8, 20.6	8/46.4, 17.3, 4.1	61/196.1, 31.1, 10.7	10/49.4, 20.3, 8.1	158/435.9, 36.2, 12.4
cCa < 8.3 mg/dL	292/71.4, 408.9, 76.2	82/36.3, 226.0, 42.1	277/139.6, 198.5, 48.7	59/35.6, 165.9, 48.0	710/282.8, 251.0, 55.9
Up to 12 months					
Subjects with ≥ 1 post-baseline cCa value - N1	383	195	569	123	1270

	Placebo in Parent Studies	Cinacalcet in Parent Study	AMG 416 in controlled Parent Studies	AMG 416 in single arm parent study	Total
	AMG 416 (N = 383) n/Y s c	AMG 416 (N = 206) n/Y s c	AMG 416 (N = 577) n/Y s c	AMG 416 (N = 123) n/Y s c	AMG 416 (N = 1289) n/Y s c
cCa < 7.0 mg/dL	25/269.8, 9.3, 6.5	2/48.1, 4.2, 1.0	22/318.9, 6.9, 3.9	4/91.2, 4.4, 3.3	53/728.0, 7.3, 4.2
cCa < 7.5 mg/dL	99/231.5, 42.8, 25.8	8/47.7, 16.8, 4.1	69/297.9, 23.2, 12.1	15/86.7, 17.3, 12.2	191/663.7, 28.8, 15.0
cCa < 8.3 mg/dL	313/93.0, 336.5, 81.7	82/36.8, 222.9, 42.1	311/187.5, 165.9, 54.7	78/54.1, 144.1, 63.4	784/371.4, 211.1, 61.7
Up to 18 months					
Subjects with ≥ 1 post-baseline cCa value - N1	383	195	569	123	1270
cCa < 7.0 mg/dL	25/282.3, 8.9, 6.5	2/48.1, 4.2, 1.0	22/331.3, 6.6, 3.9	5/94.4, 5.3, 4.1	54/756.1, 7.1, 4.3
cCa < 7.5 mg/dL	99/241.1, 41.1, 25.8	8/47.7, 16.8, 4.1	69/308.9, 22.3, 12.1	17/89.4, 19.0, 13.8	193/687.0, 28.1, 15.2
cCa < 8.3 mg/dL	317/94.2, 336.7, 82.8	82/36.8, 222.9, 42.1	315/191.0, 164.9, 55.4	78/55.1, 141.7, 63.4	792/377.0, 210.1, 62.4

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Placebo in parent studies: 20120229 and 20120230. Cinacalcet in parent study: 20120360.
AMG 416 in controlled parent studies: 20120229, 20120230 and 20120360. AMG 416 in single-arm parent study: 20120359.
This pool only includes data from Phase 3 OLE studies 20120231 and 20130213.
N = The number of subjects in safety analysis set.
n = Subject incidence
Y = Total Subject-year Exposure for patients with ≥ 1 post-baseline cCa value and is calculated as date of the first event of low calcium or date of the last cCa value if the subject experienced no low calcium event - date of Day 1 + 1, summed over all subjects(N1) (yrs).
s = Exposure-adjusted subject incidence rate per 100 subject year = 100* n/Y.
c = Crude subject incidence rate = 100*n/N1.

Subjects in the etelcalcetide treatment group had a higher subject incidence of **shifts** from grade 0 to grade 3 **decreased phosphorus** (1-<2.0 mg/dL) -in the placebo-controlled studies (10.5% etelcalcetide; 4.1% placebo). A similar proportion of subjects in the etelcalcetide and cinacalcet treatment groups had

shifts from grade 0 to grade 3 decreased phosphorus (5.9% etelcalcetide; 4.1% cinacalcet). No shifts to grade 4 were observed in the placebo-controlled studies or the active-controlled study.

Within the parent etelcalcetide through open-label extension combined dataset, a total of 95 subjects (11.3%) had shifts from grade 0 to grade 3 decreased phosphorus.

A higher proportion of subjects in the etelcalcetide arm had at least 1 **potassium concentration** > 5.5 mmol/L compared with the placebo arm (31.0% etelcalcetide; 27.0% placebo). No imbalance was observed between groups in the proportions of subjects with more severe threshold categories of potassium concentrations: > 6 mmol/L (10.4% etelcalcetide; 9.3% placebo) or > 7 mmol/L (1.0% etelcalcetide; 1.8% placebo). Adverse events of hyperkalaemia and blood potassium have been described above.

A similar proportion of subjects had shifts from grade 0 to grade 3 **decreased potassium** in both the placebo-controlled studies (0.6% etelcalcetide; 0.4% placebo) and active-controlled study (0.3% etelcalcetide; 0% cinacalcet). In the placebo-controlled studies, a higher proportion of subjects in the etelcalcetide arm had shifts from grade 0 to grade 3 increased potassium (4.6% etelcalcetide; 1.6% placebo); however, similar proportions of subjects had shifts from grade 0 to grade 4 increased potassium (0.4% etelcalcetide; 0.6% placebo). No subjects in the active-controlled study had shifts from grade 0 to grade 3 or 4 increased potassium.

Within the parent etelcalcetide through open-label extension combined dataset, a total of 43 subjects (5.1%) had shifts from grade 0 to grade 3 increased potassium, and 7 subjects (0.8%) had shifts from grade 0 to grade 4 increased potassium.

In the evaluation of **liver parameters**. less than 1% of subjects in any treatment group in the placebo/active-controlled combined dataset had shifts from grade 0 to grade 3 increased ALT, grade 0 to grade 4 increased AST, and grade 0 to grade 3 increased bilirubin. No subjects had shifts from grade 0 to grade 4 increased ALT or bilirubin or grade 0 to grade 3 increased AST. No subjects had laboratory values that met the criteria for potential Hy's law cases. The proportions of subjects with elevations in ALT, AST, and bilirubin were similar in the placebo and etelcalcetide arms.

In the long term study data, two subjects (0.2%) had ALT or AST > 3 × ULN and total bilirubin ≥ 2 × ULN at any visit, and both subjects received placebo in the parent studies. A medical review of these cases suggested underlying comorbidities that contributed to the abnormal liver tests; therefore, these subjects did not meet Hy's law criteria.

No clinically significant trends were noted in other serum chemistry or haematology parameters

Safety in special populations

In the 6-Month placebo controlled pool, subjects in the etelcalcetide group with a **screening PTH concentration** of 600 pg/mL to ≤ 1000 pg/mL had the highest subject incidence of treatment emergent adverse events (94.1%) compared with subjects with a screening PTH concentration < 600 pg/mL (88.8%) or > 1000 pg/mL (91.1%). Etelcalcetide subjects with a screening PTH > 1000 pg/mL had a lower subject incidence of serious adverse events (21.4%) compared with subjects with screening PTH of 600 to ≤ 1000 pg/mL (26.2%) or < 600 pg/mL (28.2%). Although placebo subjects had a similar subject incidence of treatment emergent adverse events regardless of screening PTH, subjects with screening PTH > 1000 pg/mL had a higher subject incidence of treatment emergent serious adverse events (35.1%) compared with subjects with screening PTH < 600 pg/mL (27.8%) and 600 pg/mL to ≤ 1000 pg/mL (27.0%).

Etelcalcetide subjects with screening PTH of 600 pg/mL to ≤ 1000 pg/mL had a higher subject incidence of blood calcium decreased (67.4%) and hypocalcaemia (9.0%) compared with subjects with screening PTH < 600 pg/mL (55.3% blood calcium decreased and 4.1% hypocalcaemia). Etelcalcetide subjects with screening PTH > 1000 pg/mL had the highest subject incidence of blood calcium decreased (69.6%) and a subject incidence of hypocalcaemia of 7.1%. Placebo subjects with screening PTH of 600 pg/mL to ≤ 1000 pg/mL had a higher subject incidence of blood calcium decreased (11.2%) compared with subjects with screening PTH < 600 pg/mL (9.5%) and > 1000 pg/mL (9.0%). The subject incidence of hypocalcaemia was similar regardless of screening PTH.

For the 6-month placebo-controlled combined dataset, subgroup analyses of adverse events were performed for **region**: north America, Europe, and other. The other region included Australia, Israel, and the Russian Federation. In the etelcalcetide group, subjects in Europe (94.2%) and other (94.7%) regions had a higher subject incidence of treatment emergent adverse events compared with subjects in North America (89.5%). Subjects in Europe (19.9%) and other (21.1%) regions had a lower subject incidence of serious adverse events compared with subjects in North America (30.5%).

Etelcalcetide subjects in other regions had the highest subject incidence of blood calcium decreased (82.5%) and hypocalcaemia (17.5%), followed by subjects in Europe (66.7% blood calcium decreased and 7.0% hypocalcaemia) and subjects in North America (58.2% blood calcium decreased and 4.7% hypocalcaemia). A similar pattern was observed in placebo subjects.

A similar subject incidence of **men and women** had treatment emergent adverse events in both the etelcalcetide (90.3% male versus 93.8% female) and placebo treatment groups (80.6% male versus 78.9% female). A higher proportion of women in both groups had treatment emergent serious adverse events compared with men (30.3% women vs 23.1% men etelcalcetide; 34.4% women vs 25.3% men placebo). However, the incidence of serious adverse events was comparable or numerically lower in the etelcalcetide arm than the placebo arm for both men and women.

A higher proportion of men than women in the etelcalcetide group had blood calcium decreased (66.2% vs 60.0%) and hypocalcaemia (8.1% vs 5.1%), while the subject incidence of both events was similar in men and women in the placebo group.

In the etelcalcetide treatment group, a similar proportion of subjects aged **< 65 years and ≥ 65 years** had treatment emergent adverse events (Table 2.24). The subject incidences of treatment emergent adverse events, serious adverse events, adverse events leading to discontinuation, and fatal adverse events were higher in subjects ≥ 65 years compared with subjects < 65 years in the placebo group, and the subject incidences of treatment emergent adverse events, serious adverse events, and fatal adverse events were highest in **subjects ≥ 75 years**. The subject incidence of treatment emergent fatal adverse events was higher in the placebo group compared to the etelcalcetide group in subjects ≥ 65 years (2.8% etelcalcetide; 5.1% placebo) and ≥ 75 years (1.4% etelcalcetide; 7.8% placebo).

A higher proportion of subjects aged < 65 years in both groups had blood calcium decreased (67.8% etelcalcetide; 11.3% placebo) and hypocalcaemia (8.6% etelcalcetide; 0.3% placebo) compared with subjects aged ≥ 65 years (blood calcium decreased 56.5% etelcalcetide, 7.9% placebo; hypocalcaemia 4.0% etelcalcetide, 0% placebo).

Table 2.24 Summary of subject incidence of treatment emergent adverse events by subgroup of age (6-month placebo-controlled combined dataset – Safety Analysis Set).

MedDRA Terms	Age <65 number (%)		Age ≥ 65 number (%)		Age ≥75 number (%)	
Number subjects in subgroup	Placebo N=336	AMG 416 N=326	Placebo N=177	AMG 416 N=177	Placebo N=64	AMG 416 N=72
Total AEs	261 (77.7)	300 (92.0)	149 (84.2)	161 (91.0)	58 (90.6)	68 (94.4)
Serious AEs – Total	86 (25.6)	74 (22.7)	63 (35.6)	56 (31.6)	26 (40.6)	17 (23.6)
- Fatal	6 (1.8)	6 (1.8)	9 (5.1)	5 (2.8)	5 (7.8)	1 (1.4)
AE leading to discontinuation investigational product	6 (1.8)	7 (2.1)	7 (4.0)	2 (1.1)	2 (3.1)	0 (0.0)

A further specification of adverse events of interest for the elderly population by age groups (<65 yrs, 65-74 yrs, 75-84 yrs and 85 yrs and above) did not reveal any safety signal. Of note, the age group above 85 years of age is small (n=10 in both treatment groups), precluding any conclusions for this age group.

Safety related to drug-drug interactions and other interactions

The biotransformation products of etelcalcetide are mixed disulfides that arise from a reversible disulfide exchange reaction of the L-cysteine moiety of etelcalcetide with other etelcalcetide molecules or endogenous thiols, such as albumin or glutathione. This thiol exchange is the primary route of biotransformation. Nonclinical studies demonstrated that etelcalcetide was not subject to metabolism by hepatic cytochrome P450 enzymes, was not an inhibitor or inducer of the hepatic cytochrome P450 enzymes, and was not a substrate or inhibitor of common drug transporters, suggesting that there is a low risk of pharmacokinetic drug-drug interactions. Therefore, clinical drug interaction studies have not been conducted.

Data from cell-based assays suggest a simple additive effect on the CaSR when cinacalcet and etelcalcetide are administered together. An in vitro study with HEK293T cell lines stably transfected with the human CaSR (R20130030) determined that co-administration of etelcalcetide and cinacalcet HCl resulted in simple additive effect rather than super-additivity. Therefore, co-administration may pose an increased risk of hypocalcaemia. In a single-arm study designed to evaluate whether treatment with 5 mg etelcalcetide given 3 times a week could be safely initiated 7 days after cinacalcet therapy is discontinued, a low subject incidence of corrected calcium < 7.5 mg/dL (0.7%) during the 4-week treatment period was observed with no events of symptomatic hypocalcaemia (Study 20120359). Corrected calcium concentrations should be ≥ 8.3 mg/dL before cinacalcet can be initiated after discontinuation of etelcalcetide.

No drug interaction studies have been conducted with other compounds that reduce calcium. Etelcalcetide should be administered with caution and calcium more closely monitored when patients are taking these therapeutics.

Discontinuation due to AES

Within the placebo-controlled studies, a total of 9 (1.8%) subjects in the etelcalcetide group and 13 (2.5%) subjects in the placebo group **discontinued due to an adverse event**. The most common adverse events leading to discontinuation was **blood calcium decreased** (n=5 1.0% etelcalcetide; 0.0% placebo). No other adverse event led to discontinuation in more than 1 subject in the etelcalcetide arm.

A total of 8 subjects (%) had adverse events leading to discontinuation that were considered to be **related to study treatment**: decreased blood calcium (n=5), nausea and vomiting (both events in the same subject), and hyperhidrosis and gastrointestinal malformation (gastrointestinal arteriovenous malformation; both events in the same subject), and chest discomfort and hemiparesis (both in the same subject).

Within the active-controlled study, a total of 19 (5.6%) subjects in the etelcalcetide group and 16 (4.7%) subjects in the cinacalcet group **discontinued due to an adverse event**. The most frequently reported (> 1 subject in the etelcalcetide arm) events that led to the discontinuation were vomiting (n=3 0.9% etelcalcetide; n=1 0.3% cinacalcet), nausea (n=2 0.6% etelcalcetide; n=1 0.9% cinacalcet), and dermatitis (n=2 0.6% etelcalcetide; 0% cinacalcet).

Twenty-two subjects (10 subjects etelcalcetide, 12 subjects cinacalcet) had adverse events leading to the discontinuation of investigational product that were considered to be **related to study treatment**. These were vomiting (3 subjects), nausea and dermatitis (2 subjects each), and bronchospasm, increased hepatic enzyme, muscular weakness, and decreased weight (1 subject each) for etelcalcetide. In the cinacalcet group, these were nausea (3 subjects), asymptomatic decreased blood calcium (2 subjects), and abdominal pain, cardiac arrest, convulsion, decreased appetite, diarrhoea, hypophosphatemia, optic neuritis, upper abdominal pain, and vomiting (1 subject each).

A total of 39 subjects (3.0%; 4.3 per 100 subject-years) in the phase 3 long-term open-label extension combined dataset had adverse events leading to discontinuation. The most common (≥ 2 subjects) adverse events leading to discontinuation were nausea (0.4%; 0.5 per 100 subject-years), cardiac arrest (0.3%; 0.4 per 100 subject-years), vomiting (0.3%; 0.4 per 100 subject-years), cellulitis (0.2%; 0.2 per 100 subject-years), and hypocalcaemia (0.2%; 0.2 per 100 subject-years).

2.6.1. Discussion on clinical safety

The safety profile of etelcalcetide was studied in a patient population representative of the intended target population on haemodialysis, except that vulnerable patient groups were excluded from the studies (history of certain cardiac disorders in the past 6 months such as myocardial infarction, CHF III or IV, ventricular arrhythmia). Within phase 2 and phase 3 clinical studies, a total of 1655 subjects received at least 1 dose of etelcalcetide of which 499 received etelcalcetide for over 1 year. This is mandatory given the chronic nature of treatment and in agreement with guideline recommendations. The most frequently used dose was 5 mg which is the recommended initial dose to be given by bolus injection 3 times per week. About 12% of patients received the maximal dose of 15 mg during most of the time. Therefore, the safety profile was assessed over the recommended dose range. A dose-response relationship of adverse events was not shown, but this should be interpreted cautiously as the dose is titrated over time. In addition, no distinct relationship between fast titration and AE incidences was shown.

The percentage of patients with any TEAE was high, which is to be expected in this population with extensive co-morbidity. Most events were of mild to moderate nature and discontinuations due to adverse events were limited (1.8% in placebo-controlled studies and 5.6% in the active controlled study). Long term open label safety data were mostly in line with the controlled safety data, however, frequency of some AEs seems to slightly decrease over time in the long-term follow-up studies, suggesting an increased vulnerability of patients starting treatment and an adaptation to the treatment in the long term. The AE pattern appears comparable between the titration and stable phase.

Overall, the safety profile was dominated by events related to etelcalcetides primary and secondary mechanisms of action of lowering PTH levels and calcium levels. Therefore, patients have to be closely monitored during the titration phase and during the remainder of the study and should not be treated when serum calcium levels were below the lower limit of the normal range (exclusion criteria in clinical studies). The most frequently reported adverse event was asymptomatic blood calcium decreased (63.8% etelcalcetide vs 10.1% placebo and 68.9% etelcalcetide vs 59.8% cinacalcet). A contraindication not to use etelcalcetide when the corrected calcium level is below the lower limit of the normal range can be in principle accepted, given the frequent observations of calcium decrease.

Furthermore, symptomatic events of hypocalcaemia were reported in 7.0% (placebo-controlled studies) and 5.0% (active controlled study) of patients and more often for etelcalcetide than for cinacalcet (2.3%). Although these events of decreased calcium levels were mild to moderate in severity, transient, and rarely resulted in permanent discontinuation of study drug (n=5 placebo-controlled studies), about one quarter to one third of patients on etelcalcetide *temporary* discontinued treatment due to low serum calcium levels. Additional information on treatment discontinuation did not reveal additional safety concerns. No dose-dependent increase in the rate and durations of dose withholds with etelcalcetide was observed.

In addition, potential adverse events associated with low calcium levels were further explored. Worsening heart failure has already been identified as a risk for cinacalcet. Higher incidences of AEs of cardiac failure (3.2% etelcalcetide; 2.5% placebo and 3.0% etelcalcetide versus 0.6% cinacalcet), independent adjudicated events of congestive heart failure requiring hospitalization (2.2% etelcalcetide versus 1.2% placebo) and MI (1.6% etelcalcetide versus 1.0% placebo) have been reported for etelcalcetide and are of potential concern. Whether a causal relationship exists is difficult to ascertain given that these cases were confounded by comorbidities commonly seen in haemodialysis patients, but they appear not to be related to hypocalcaemia. Moreover, the number of events is limited which does not allow to draw firm conclusions. As potentially vulnerable patient groups were excluded from the studies (history of certain cardiac disorders in the past 6 months such as myocardial infarction, CHF III or IV, ventricular arrhythmia), incidences might be higher in real practice, as a CKD patient population on haemodialysis is known to be at risk for cardiovascular comorbidity. However, the overall subject incidence of cardiac failure events appears similar to that observed in both placebo and cinacalcet groups during the first 6 months of the EVOLVE study. Yet, the applicant has proposed a warning statement on the risk of worsening heart failure in section 4.4 of SmPC and included it as a potential risk in the RMP, which is supported.

The risk for QT prolongation is also thought to be associated with reductions of serum calcium and has been identified in the cinacalcet dossier. Similarly, a higher incidence of QT prolongation has been observed with etelcalcetide in comparison to placebo (> 500 msec 4.8% etelcalcetide vs 1.9% placebo). No data are available in comparison to cinacalcet. In vitro evaluation on hERG channels and preclinical safety pharmacology data in dogs showed that the QTc prolongation was associated with calcium levels and not directly to the drug. Moreover, an analysis on the phase 3 data adjusting for the calcium effect did not identify any direct QT prolonging effect of etelcalcetide, which is reassuring. Events possibly associated with QT prolongation such as ventricular arrhythmias, syncope, convulsions, and sudden deaths were very limited and not different between treatment groups. No meaningful differences in QTcF prolongations across age groups were detected in response to etelcalcetide. However, an absence of adverse events potentially associated with QTc prolongation does not allow for any firm conclusions, as these events are generally sparse and thus the potential to find any difference is low. The applicant has now proposed warnings on the risk of ventricular arrhythmia, and QT prolongations in section 4.4 of SmPC and included these as identified risks (QT prolongations) or potential risks (ventricular arrhythmia) in the RMP. This is considered acceptable.

In addition, QT prolongation has been included as an ADR in section 4.8 of the SmPC because of the increased frequency with etelcalcetide.

Also, a warning on convulsions is included in section 4.4 and identified as a potential risk in the RMP which is considered appropriate.

Other events like muscle spasms, myalgia and paraesthesia which can occur as manifestations of hypocalcaemia were found to be higher than placebo and are included in section 4.8 of the SmPC, which is considered appropriate. Incidences were numerically slightly higher but in the same order of magnitude for etelcalcetide compared to cinacalcet.

Phosphate reduction is also related to the reduction of PTH and phosphate levels will be regularly monitored in the patient population. Hypophosphatemia was also higher for etelcalcetide than for cinacalcet, likely due to the stronger PTH decreasing effect (1.5% etelcalcetide versus 0.9% cinacalcet).

Besides effects associated with PTH reduction, gastrointestinal adverse events were also frequently reported. Adverse events considered potentially related to etelcalcetide were nausea (10.7-18.3%), vomiting (8.9 – 13.3%) and diarrhoea (10.7%, no ADR active controlled study). This type of events was also frequently reported for cinacalcet (nausea: 22.6%, vomiting 13.8%). Overall, the type of adverse events included in section 4.8 of the SmPC is supported.

Hyperkalaemia is frequently seen in patients with CKD and included as an ADR; frequencies were somewhat higher than placebo (4.4% etelcalcetide vs 3.1% placebo), but numerically lower than for cinacalcet (3.8% etelcalcetide vs 5.3% cinacalcet). Chronic oversuppression of PTH may result in adynamic bone disease. No cases of adynamic bone disease were identified which may be explained by the relatively short term follow-up and the lack of bone biopsies. A warning is included in section 4.4 including recommendations for treatment and fractures (a consequence of adynamic bone disease) is included as a potential risk in the RMP.

Fractures could be the result of increased bone turnover activity and defective mineralization due to increased levels of PTH. Currently, the fracture rate was lower in the etelcalcetide compared to placebo (1.6% etelcalcetide vs 2.9% placebo) and similar to cinacalcet (2.1% etelcalcetide vs 2.6% cinacalcet). From a safety perspective, these data are reassuring although the follow-up period is limited.

The interaction potential for pharmacokinetic drug-drug interactions for etelcalcetide is low due the lack of interaction with CYP450 enzymes. This may be a benefit over cinacalcet for which drug-drug interactions have been included in the SmPC. Of most relevance for etelcalcetide are the pharmacodynamics interactions with other drugs that could lower serum calcium levels and this is clearly stated in section 4.5 of the SmPC. A specific warning on concurrent administration with cinacalcet is justified based on the additive effect on CaSR signalling seen in cell-based assays. This has also been included as a potential risk in the RMP, which is endorsed.

The safety profile appears comparable for the subgroups studied including gender, age, race and geographic region. Paediatric patients are currently not included in the intended target population. Patients with hepatic impairment were excluded. This information is currently included in section 5.2 of the SmPC. The safety data do not indicate any worse effect on the liver, therefore specific warnings related to this are not required.

Antibodies to etelcalcetide were observed in about 11% of patients of which most already had pre-existing antibodies. No impact on the safety profile was seen for hypersensitivity and infusion reactions. Overall, these type of reactions were limited and not considered to be attributed to etelcalcetide.

Medication adherence is not an issue as etelcalcetide is an intravenous product given with the haemodialysis and will therefore be controlled by dialysis unit staff.

2.6.2. Conclusions on clinical safety

The safety profile of etelcalcetide is mainly characterised by events related to its primary mechanism of action as a calcimimetic and the majority of the reported events were of mild to moderate nature. The overall safety profile is approximately similar to cinacalcet. The most important risk of etelcalcetide is hypocalcaemia and associated events that can occur secondary to reductions in serum calcium (ie, QTc prolongation, ventricular arrhythmia, convulsions, and worsening heart failure). Hypocalcaemia and reduced calcium levels occurred slightly more with etelcalcetide than with cinacalcet, possibly also due to a more potent titration scheme for etelcalcetide. However, the dialysis population visits a dialysis unit three times a week with regular monitoring by specialized staff which could cover this. Specific guidance in the SmPC allows to prevent and manage the risks. Follow-up through routine pharmacovigilance activities seems sufficient.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypocalcemia Worsening heart failure QT prolongation secondary to hypocalcemia
Important potential risks	Ventricular arrhythmias Infusion and hypersensitivity reactions Convulsions Fractures Co-administration of etelcalcetide and cinacalcet HCl (including other drugs that reduce calcium)
Missing information	Use in pregnancy and lactation

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypocalcemia	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 4.7, Effects on ability to drive and use machines • Section 4.8, Undesirable effects • Section 4.9, Overdose • Section 5.1, Pharmacodynamic properties • Section 5.3, Preclinical safety data Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide o Warnings and precautions • Possible side effects	None
Worsening heart failure	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide o Warnings and precautions • Possible side effects	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks (continued)		
QT prolongation secondary to hypocalcemia	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide ○ Warnings and precautions • Possible side effects	None
Important Potential Risks		
Ventricular arrhythmias	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide ○ Warnings and precautions	None
Infusion and hypersensitivity reactions	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide	None

Convulsions	Proposed relevant text is provided in the following sections of the SmPC:
	• Section 4.4, Special warnings and precautions for use
	• Section 5.3, Preclinical safety data
	Proposed relevant text is provided in the following sections of the PIL:
	• What you need to know before you use etelcalcetide
	  ○ Warnings and precautions
	  ○ Driving and using machines
	• Possible side effects
		None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks (continued)		
Fractures	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Proposed relevant text is provided in the following sections of the PIL: • What etelcalcetide is and what it is used for • What you need to know before you use etelcalcetide ○ Warnings and precautions	None
Co-administration of etelcalcetide and cinacalcet HCl (including other drugs that reduce calcium)	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 5.1, Pharmacodynamic properties Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide ○ Other medicines and etelcalcetide	None
Missing Information		
Use in pregnancy and lactation	Proposed relevant text is provided in the following sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data Proposed relevant text is provided in the following sections of the PIL: • What you need to know before you use etelcalcetide ○ Pregnancy and breastfeeding	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Parsabiv (etelcalcetide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Secondary HPT is a disorder characterized by parathyroid gland hyperplasia and increased concentrations of circulating PTH. The disease is seen most commonly in the setting of chronic kidney disease (CKD). etelcalcetide is an allosteric activator of the CaSR, binding directly to the extracellular domain and activating the receptor at a site which is distinct from the calcium activating site. This is assumed to increase the sensitivity of the CaSR to calcium, thereby reducing the overexpression of PTH and its levels in circulation.

Benefits

Beneficial effects

The demonstration of efficacy of etelcalcetide for the treatment of secondary HPT in patients with chronic kidney disease (CKD) on haemodialysis is primarily based on 2 pivotal, double-blind, placebo-controlled 26-week studies, **20120229** and **20120230**. The studies, identical in design, enrolled 508 and 515 patients, respectively. Efficacy was evaluated during the efficacy assessment period (EAP; weeks 20 to 27). The primary endpoint of each study was the proportion of subjects with > 30% reduction from baseline in predialysis PTH during the EAP.

In addition, a phase 3, double-blind, double-dummy, 26-week study (**20120360**) compared etelcalcetide and cinacalcet in subjects with secondary HPT receiving haemodialysis; the study enrolled 683 patients. The primary endpoint was the same as for the placebo-controlled studies but was analysed for non-inferiority (primary) or superiority (secondary) of etelcalcetide compared to cinacalcet.

Etelcalcetide treatment (3 times a week i.v. infusion after dialysis according to a flexible titration schedule starting at 5 mg) in dialysis patients with secondary hyperparathyroidism (SHPT) for 26 weeks showed a significantly greater proportion of patients with a reduction of the PTH by > 30% after 20-27 weeks over placebo. This effect was seen in two placebo controlled phase 3 studies (380 subjects [74.7%] vs. 46 subjects [8.9%], respectively, p<0.001; mean baseline PTH level of approximately 840 pg/ml). Furthermore, etelcalcetide was non-inferior to cinacalcet using the same primary endpoint (proportion patients > 30% reduction PTH) showing a treatment difference of -10.48% (-17.45%, -3.51%) with the upper bound of the 2-sided 95% (-3.51%) being substantially lower than the prespecified lower margin to demonstrate noninferiority (12%). Subsequent secondary analyses of proportion of patients with PTH reduction by > 50% and > 30% demonstrated etelcalcetide to be statistically significantly superior to cinacalcet when compared in the context of the titration algorithm chosen in the study. In the placebo controlled studies, significantly more subjects reached ≤ 300 pg/mL in PTH of approximately 50% during the evaluation period of 26 weeks (262 subjects [51.5%]) vs 25 subjects [4.9%], respectively, p<0.001).

Additionally, significantly larger reductions in cCa were observed as well as reduction in phosphorus in the placebo controlled studies, with the cCa x P product also being reduced.

The effect was maintained during 78 weeks open-label phase 3 extension (384 patients received etelcalcetide during both parent and extension studies; at least 75 at week 84) and 116 weeks open-label phase 2 extension (30 patients received etelcalcetide in both parent and extension studies; 7 at week 116), although the difference in PTH levels diminished over time and patient numbers were very limited at the last time points.

Clear guidance was applied for concomitant therapy during screening for calcium supplementation, vitamin D sterols, and phosphate binders, while for nutritional vitamin D no restrictions were applied in the comparator phase 3 study. During the study, for the most important concomitant therapy options (phosphate binders and vitamin D sterols) strict rules applied, which is considered necessary as these may interfere with the study outcome.

Uncertainty in the knowledge about the beneficial effects

The data indicate that after each titration step more patients reached a >30% reduction in PTH, likely to be related to the relative faster titration scheme used for etelcalcetide (5 mg general starting dose up to 15 mg maximum dose with allowed incremental steps of 2.5-5 mg at 4-weekly intervals) compared to cinacalcet (30 mg starting dose up to 180 maximum dose with allowed incremental steps of 30 mg or 60 mg [ie, from 120 mg to 180 mg] at 4-weekly intervals). A considerable proportion of patients needed to be titrated to the

highest dose of 15 mg to reach this endpoint (18-23%). Also, the data indicate that, though this did not compromise the efficacy results, there was a slightly higher proportion of temporary dose interruptions with etelcalcetide (23%) compared to cinacalcet (19%), a slightly higher proportion of patients with dose increases of vitamin D sterols and/or calcium-containing phosphate binder or calcium supplement during dose suspensions. A slightly higher proportion of etelcalcetide patients needed down-titrations (6.3% vs 1.2% for cinacalcet at week 5; 16.6% vs 11.4% at week 17) but the treatment effect at every titration week was in favour of etelcalcetide when compared with cinacalcet. Therefore, down-titration appears not to affect the efficacy of etelcalcetide.

Regular PTH monitoring over time is considered mandatory as a continuous stable dose appears not to be reached in a relevant proportion of patients. Recommendations regarding dose adaptations in response to PTH levels < 100 pg/ml and re-initiation dose administrations have been included in the SmPC.

PTH values remained 40% reduced compared to baseline during the withdrawal phase of etelcalcetide after the placebo controlled phase 3 studies (week 27-31). A likely explanation could be that the withdrawal follow-up of 30 days could have been too short for several individuals due to several possible reasons, e.g. persistent drug effect of etelcalcetide, vitamin D sterol and calcium supplement use during the washout period, changes in calcium-sensing receptor (CaSR) expression and increased sensitivity to serum calcium after etelcalcetide treatment, changes in bone remodelling during etelcalcetide treatment, and/or secondary hyperparathyroidism (HPT) disease heterogeneity.

While also numerically lower levels of cCa and phosphorus were found with etelcalcetide in the comparator study, no statistical substantiation was possible because the third secondary endpoint (the number of days vomiting and nausea per week during the first 8 weeks) was not found to be superior for etelcalcetide in comparison to cinacalcet. Also, vomiting and nausea as investigated separately did not show superiority for etelcalcetide. In addition, the number of days vomiting and nausea per week over time was somewhat higher for etelcalcetide in comparison to cinacalcet for most of the time points investigated.

Numerically greater reductions could be observed for bone markers of bone specific alkaline phosphatase (BSAP) and Type I collagen C-telopeptide (CTX) at week 27 in the etelcalcetide group both in comparison to placebo and to cinacalcet, although substantial variability is noticed. With the uncertainty noticed, this may indicate a positive effect on bone turnover. Similarly, for fibroblast growth factor-23, involved in regulation of phosphate concentration, a numerical decrease could be observed.

A positive effect on the primary endpoint of >30% reduction from baseline in PTH and on the secondary endpoint of proportion of subjects with PTH ≤ 300 pg/mL could be observed for relevant subgroups in the combined placebo controlled studies and in the active-controlled study. Although some differences in treatment effect are suggested in some subgroups in the placebo controlled studies, these may be due to chance finding or could be reasonably explained, e.g. for baseline vitamin D sterol use; more efficacy in patients without baseline vitamin D sterol use). The small size of most of these subgroups and the high variability that was observed generally do not allow for conclusions to be drawn.

Although the PK profile and the consequential effect on PTH levels are different for etelcalcetide and cinacalcet, the assessment of the level of PTH just before dialysis is an appropriate timing to measure efficacy (lowest levels of etelcalcetide) and is considered not to favour etelcalcetide.

Risks

Unfavourable effects

Overall, the safety profile was dominated by events related to etelcalcetides primary and secondary mechanisms of action of lowering PTH levels and calcium levels. Despite that patients were to be closely monitored during the titration and remaining phase of the study and should not be treated when serum calcium levels were below the lower limit of the normal range, the most frequently reported adverse event was asymptomatic decreased blood calcium (63.8% etelcalcetide vs 10.1% placebo and 68.9% etelcalcetide vs 59.8% cinacalcet). Furthermore, symptomatic events of hypocalcaemia were reported in 7.0% (placebo-controlled studies) and 5.0% (active controlled study) of patients and more often for etelcalcetide than for cinacalcet (2.3%). These events of decreased calcium levels were mild to moderate in severity, transient (median recovery 2.1- to 2.9 weeks), and rarely resulted in permanent discontinuation of study drug (n=5 placebo-controlled studies). Phosphate reductions were also related to the reduction of PTH. Hypophosphatemia was also higher for etelcalcetide than for cinacalcet, likely due to the stronger PTH decreasing effect and titration scheme (1.5% etelcalcetide versus 0.9% cinacalcet).

A higher incidence of QT prolongation has been observed with etelcalcetide in comparison to placebo (> 500 msec 4.8% etelcalcetide vs 1.9% placebo). The risk for QT prolongation is thought to be associated with reductions of serum calcium and has been identified in the cinacalcet dossier as well. No data are available in comparison to cinacalcet as this was not investigated. In vitro evaluation on hERG channels and preclinical safety pharmacology data in dogs showed that the QTc prolongation was associated with calcium levels and not directly with the drug. Moreover, an analysis on the phase 3 data, adjusting for the calcium effect, did not identify any direct QT prolonging effect of etelcalcetide. Yet, QT prolongation has been included as an ADR in section 4.8 of the SmPC because of the increased frequency with etelcalcetide.

Besides effects associated with PTH reduction, gastrointestinal adverse events were also frequently reported. Adverse events considered potentially related to etelcalcetide were nausea (10.7-18.3%), vomiting (8.9 – 13.3%) and diarrhoea (10.7%, no ADR active controlled study). This type of events was also frequently reported for cinacalcet (nausea: 22.6%, vomiting 13.8%). It was suggested that the i.v. formulation as compared to the orally administered cinacalcet might mitigate these treatment-related AEs by bypassing the intestinal tract. However, no benefit of etelcalcetide was seen over cinacalcet as regards nausea and vomiting.

The frequency of premature discontinuations due to adverse events were limited in etelcalcetide-treated patients (1.8% in placebo-controlled studies and 5.6% in the active controlled study).

Hyperkalaemia is frequently seen in patients with CKD and included as an ADR; frequencies were somewhat higher than for placebo (4.4% etelcalcetide vs 3.1% placebo), but numerically lower than for cinacalcet (3.8% etelcalcetide vs 5.3% cinacalcet).

Uncertainty in the knowledge about the unfavourable effects

About 23-36% of patients on etelcalcetide *temporarily* discontinued treatment due to low serum calcium levels, whereas down-titrations were also needed in a large proportion of patients who temporarily discontinued, with a slightly higher frequency for etelcalcetide than for cinacalcet. This difference is also likely to be associated with the relative faster titration scheme of etelcalcetide. However, efficacy was still improved compared to cinacalcet. Additional information on treatment discontinuation did not reveal additional safety concerns.

In addition, potential adverse events associated with low calcium levels were further explored. Higher incidences of AEs of cardiac failure (3.2% etelcalcetide; 2.5% placebo and 3.0% etelcalcetide versus 0.6% cinacalcet) and independently adjudicated events of congestive heart failure requiring hospitalization (2.2% etelcalcetide versus 1.2% placebo) have been reported for etelcalcetide and are of potential concern, although the number of events is limited which does not allow to draw firm conclusions. Whether a causal relationship exists is difficult to ascertain given possible confounding by comorbidities commonly seen in haemodialysis patients, although they appear not to be related to the setting of hypocalcaemia. As vulnerable patient groups were excluded from the studies (history of certain cardiac disorders in the past 6 months such as myocardial infarction, CHF III or IV, ventricular arrhythmia), incidences might be higher in real practice, as a CKD patient population on haemodialysis is known to be at risk for cardiovascular comorbidity, and therefore the external validity of these studies may be somewhat compromised. However, the incidence of cardiac failure events appears similar to that observed in both placebo and cinacalcet groups during the first 6 months of the EVOLVE study. Yet, the applicant has included a warning statement on the risk of worsening heart failure in section 4.4 of SmPC and included it as a potential risk in the RMP, which is supported.

Events possibly associated with QT prolongation such as ventricular arrhythmias, syncope, convulsions, and sudden deaths were very limited and not different between treatment groups. However, an absence of adverse events potentially associated with QTc prolongation does not allow for any firm conclusions, as these events are generally sparse and thus the potential to find any difference is low. The applicant has now included warnings on the risk of ventricular arrhythmia, and QT prolongations in section 4.4 of SmPC and included these as identified risks (QT prolongations) or potential risks (ventricular arrhythmia) in the RMP. This is considered acceptable. A warning on convulsions is included in section 4.4 and identified as potential risks in the RMP which is considered appropriate.

The safety profile appears comparable for the subgroups studied including gender, age, race and geographic region.

The interaction potential for pharmacokinetic drug-drug interactions for etelcalcetide is low due the lack of interaction with CYP450 enzymes. This may be a benefit over cinacalcet for which drug-drug interactions have been included in the SmPC. Of most relevance for etelcalcetide are the pharmacodynamics interactions with other drugs that could lower serum calcium levels and this is clearly stated in section 4.5 of the SmPC. A specific warning on concurrent administration with cinacalcet is justified based on the additive effect on lowering PTH levels seen in preclinical studies with a potential increased risk of hypocalcaemia. This has also been included as a potential risk in the RMP, which is endorsed.

Fractures can also be the result of increased levels of PTH which results in increased bone turnover activity and defective mineralization. Currently, the fracture rate was lower in the etelcalcetide compared to placebo (1.6% etelcalcetide vs 2.9% placebo) and similar to cinacalcet (2.1% AMG 416 vs 2.6% cinacalcet). From a safety perspective, these data are reassuring although the follow-up period is limited.

Chronic oversuppression of PTH may result in adynamic bone disease. No cases of adynamic bone disease were identified which may be explained by the relatively short term follow-up and the lack of bone biopsies. A warning is included in section 4.4 including recommendations for treatment and adynamic bone disease is included as a potential risk in the RMP.

Effects Table

Effects Table for etelcalcetide for treatment of patients with chronic kidney disease on haemodialysis therapy and with secondary hyperparathyreoidism (SHPT) (data cut-off: November 2015). Data for the placebo-controlled studies are presented separately.

Effect	Short Description	Unit	Etel-calcetide	PLB	Cinacalcet	Uncertainties/ Strength of evidence	References
		Favourable Effects					
PTH reduction	Proportion of patients with >30% reduction in PTH (week 20-27)	%	74.0	8.3		Significant vs control (OR 32; 95%CI (19-56)	
			75.3	9.6		Significant vs control (OR 31; 95%CI (18-52)	
			68.2		57.7	Superior to cinacalcet (OR 1.59; 95%CI (1.16-2.17) p=0.004) after non-inferiority testing (treatment difference -10.5 95%CI (-17.5; -3.5) ; the applied titration scheme may have led to reach the primary endpoint more frequently (by study end) with etelcalcetide vs. cinacalcet	
		Unfavourable Effects					
Ca decrease	Asymptomatic decrease in Ca	%	63.8	10.1		23-36% of patients on AMG 416 *temporarily* discontinued treatment discontinuation due to blood calcium decreased (n=5 1.0% etelcalcetide; 0.0% placebo)	
			68.9		59.8		
Hypo-calcaemia	Symptomatic decrease in Ca	%	7.0	0.2			
			5.0		2.3		
Ca decrease -associated AEs	Paresthesia	%	4.8 2.1	0.6	1.8	Defined as neuromuscular irritability events	

Effect	Short Description	Unit	Etel-calcetide	PLB	Cinacalcet	Uncertainties/ Strength of evidence	References
	Hypoesthesia		1.8 1.2	0.8	 0.9		
	Myalgia		1.6 1.5	0.2	 0.6		
	QT prolongation/ Torsade de pointes	%	1.2	0.6		Defined as cardiac repolarization-associated events	
			0.3		0		
	Syncope		0.8	1.0			
			1.2		0.6		
	Convulsions		0.8	1.0			
			0.9		0.6		
	Ventricular tachyarrhythmias		0.4	0.8			
			0		0		
	Sudden death		0.2	0.2			
			0.3		0		
Cardiac failure			3.2	2.5			
			3.0		0.6		
Muscle related events	Muscle spasm		11.5	6.6			
			6.5		5.9		
GI events	Nausea		10.7	6.2		Secondary endpoint of mean number of days of vomiting or nausea per week in the first 8 weeks was not different: rate ratio 1.2 95%CI (0.89, 1.49)	
			18.3		22.6		
	Vomiting		8.9	5.1			
			13.3		13.8		
	Diarrhoea		10.7	8.6			

Effect	Short Description	Unit	Etel-calcetide	PLB	Cinacalcet	Uncertainties/ Strength of evidence	References
			6.2		10.3		

Balance

Importance of favourable and unfavourable effects

The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry reported over 450,000 patients with ESRD who were receiving renal replacement therapy with most patients receiving dialysis (Pippias et al, 2015). Secondary HPT is common and a major burden in this population.

Treatment with etelcalcetide is indicated for patients with chronic kidney disease on haemodialysis therapy with secondary HPT. These patients have extreme high levels of PTH thought to be associated with metabolic disturbances in calcium and phosphorus homeostasis including pathological changes in bone turnover. In addition, negative effects are anticipated on vascular calcification, left ventricular hypertrophy, and the risk of cardiovascular events.

Etelcalcetide given on top of existing therapies such as phosphate binders and vitamin D sterols demonstrated a clear significant reduction of elevated levels of PTH compared to placebo. In a comparison study to cinacalcet, lower PTH levels were observed with etelcalcetide with the chosen titration scheme and point in time of evaluation of efficacy. Normalisation of extreme levels of PTH is considered to have positive effects on bone turnover, in particular when the levels of calcium and phosphorus are also reduced (as expressed in calcium x P product). These were also numerically reduced with etelcalcetide treatment. Reductions in some bone markers were shown in exploratory analyses. Although no efficacy assessment on clinical relevant endpoints of bone fractures has been performed, within the safety analyses a lower number of fractures was found for etelcalcetide in comparison to placebo, comparable to cinacalcet. However, number of events were limited and do not allow to draw conclusions.

Too low levels of calcium, secondary to aggressive PTH reduction, could compromise treatment of lowering PTH for the individual patient, as this may be associated with specific safety issues. Decreases in serum calcium occurred frequently (64-69%) and slightly more than with cinacalcet, while in 23-36% of the patients treatment had to be discontinued temporarily to normalise calcium levels and a substantial proportion of these patients were down-titrated, likely also to be associated with a relative faster titration scheme for etelcalcetide. In terms of treatment management this did not mitigate the improved effect on PTH over time in comparison to cinacalcet. Permanent discontinuations were sparse. Safety issues related to low calcium levels of neuromuscular irritability were observed more frequently with etelcalcetide than placebo. Also, adverse events of cardiac repolarisation, in particular QT prolongation, were observed as expected due to lower calcium levels. However, any potential harmful effects in associated adverse events of ventricular arrhythmias, syncope, convulsions, and sudden deaths were very sparse, and did not allow for any final conclusions. A slightly higher incidence of cardiac failure with etelcalcetide treatment, which is an identified risk with cinacalcet, was found, but no conclusions could be drawn due to limited numbers and the potential presence of unidentified and confounding factors. In this respect, exclusion of vulnerable patient groups (history of certain cardiac disorders in the past 6 months such as myocardial infarction, CHF III or IV,

ventricular arrhythmia) from these studies, limits extrapolation of these findings to daily clinical practice. Also, data on death can be considered inconclusive due to low numbers and confounding potential, but did not raise further concerns.

The long term studies provided data indicating maintenance of effect and safety, which is considered important for a treatment intended for a long period of time.

An absence of interactions may be considered to favour etelcalcetide treatment in comparison to cinacalcet. Also i.v. injection of etelcalcetide which can be performed during dialysis may potentially improve adherence in comparison to the oral use of cinacalcet that may lead to gastrointestinal complaints and poor compliance.

Benefit-risk balance

Reaching the treatment goals of secondary HPT management in CKD patients on haemodialysis, i.e. maintenance of PTH levels within a target range, avoidance of hyperphosphatemia and maintaining calcium in the normal range, is challenging, and sufficient control of these parameters is often not achieved. Particularly in patients with persistently high PTH values and high Ca levels the dose of Vitamin D sterols can often not be further increased. Cinacalcet is currently registered to be used alone or as add-on to standard therapy including phosphate binders, vitamin D analogues or both.

Etelcalcetide demonstrates a consistent and substantial effect on PTH compared to current standard therapy including phosphate binders and vitamin D sterols. Furthermore, a significant increased effect on PTH reduction compared to cinacalcet was observed with the chosen titration scheme. A decrease in calcium, related to the mechanism of action was also found slightly more frequently than with cinacalcet, indicating a slightly more forceful treatment management with etelcalcetide. Although this potentially compromises efficacy, this can be considered manageable with temporarily discontinuation of treatment.

Further, adverse events related to low calcium levels and also other safety issues were observed infrequently and the safety profile is considered acceptable. Etelcalcetide as an i.v. administered product is well tolerated, which is important for long term therapy.

Compared with the approved oral calcimimetic agent Mimpara (cinacalcet), the absence of interaction potential of etelcalcetide due to lack of metabolism via CYP enzymes and bypassing of the gastrointestinal tract may be regarded as an advantage.

Reduction of the pill-burden by using an i.v. drug may be of relevance for patients who already take many drugs; this also impacts on treatment compliance. Patients receive etelcalcetide within dialysis sessions under supervision of medical staff which may be also an advantage as regards safety monitoring. However, no substantial differences in AEs were seen in comparison to cinacalcet.

It was suggested that the i.v. formulation (as compared to the orally administered cinacalcet) might mitigate the treatment-related AEs of nausea and vomiting by bypassing the intestinal tract. However, etelcalcetide was not different from cinacalcet in the mean number of days of vomiting or nausea per week in the first 8 weeks of treatment.

Discussion on the benefit-risk assessment

Reductions of PTH levels due to etelcalcetide treatment on top of existing therapy of phosphate binders and vitamin D sterols were found in two placebo controlled studies, and as a consequence, secondary reductions

of calcium and phosphorus were also observed. Importantly, a comparison has also been made to the calcimimetic cinacalcet. Cinacalcet has been approved based on its ability to reduce PTH in similar patients as now studied with etelcalcetide and is currently used in clinical practice. The clinical use of cinacalcet is currently mainly limited to postpone or avoid the need of parathyreoidectomy in patients with reduced life expectancy and patients awaiting kidney transplantation. It was demonstrated that etelcalcetide showed a significantly increased effect on PTH reduction in comparison to cinacalcet taking into account the chosen titration scheme and time period of efficacy assessment. This was supported by a (not formally statistically tested) numerical reduction in calcium and phosphorus and exploratory endpoints of bone markers. However, the relative faster titration scheme resulted in a slightly higher need for dose interruptions and downtitrations. This and concomitant treatment adjustments during these interruptions did not substantially influence the observed increased reduction of PTH for etelcalcetide versus cinacalcet and are considered manageable with the current SmPC recommendations. Although it does not become completely absent, the need for dose changes reduces over time. Furthermore, no apparent safety issues were associated with these dose interruptions.

Further, in the placebo controlled studies approximately half of the patients reached a treatment target of < 300 pg/mL in PTH after 6 months of treatment. However, the clinical relevance of such a target PTH level is not established. In the BONAFIDE study that was performed post-approval with cinacalcet, a level of less than 300 pg/mL was associated with decreases in markers of bone turnover and improved bone histology. Such numerical reductions in bone markers for high bone turnover have also been observed in the present etelcalcetide studies. However, the clinical implications of these findings for the long term remain unclear.

There is currently no specific recommendation for a target PTH level due to a lack of robust evidence for the association between PTH level and risk for mortality, CV death, and fractures. Also, any RCTs showing achievement of specific PTH levels resulting in improved outcome are lacking. The KDIGO 2009 guideline currently recommends to target PTH levels below 2 to 9 times above the upper limit of the normal range. The best evidence of any clinical implications of PTH reduction comes from the post-approval EVOLVE study with cinacalcet. This study did not meet its clinical primary CV endpoint (time to all-cause mortality, myocardial infarction, hospitalisation for unstable angina, heart failure or a peripheral vascular event), although secondary and additional sensitivity analyses suggested a beneficial effect. Diverging expert opinions exist in the field whether or not the study should be regarded as positive. Also, the secondary endpoint evaluating effects on bone in terms of fracture risk (which could be considered the most important clinical effect of reducing PTH) was not found to be significantly reduced. The study was, however, hampered by high dropout rates in both treatment groups and patients in the placebo arm who were prescribed cinacalcet as a component of their regular treatment.

Therefore, any conclusions for the clinical implications of etelcalcetide treatment in reduction of PTH levels remain difficult to draw. The current dossier complies with current treatment practice and guidelines of reduction of extreme levels of PTH, which also acknowledge the limitations of this approach. It should be considered that such data have not been requested pre-or post approval for cinacalcet either. Taking this into account it is not considered necessary to ask for long term outcome data of etelcalcetide.

The safety profile identified is as expected for calcimimetics and comparable to what has been found for cinacalcet, except that due to the relative larger PTH lowering (dose) effect with etelcalcetide slightly more patients showed decreases in their calcium levels. This can be considered as one of the reasons for the slightly higher frequencies of dose interruptions and down-titrations with etelcalcetide compared to cinacalcet.

Adverse events that could be associated with a reduction of serum calcium levels did not show any differences between etelcalcetide and cinacalcet with respect to the frequency of treatment discontinuation due to AEs as this was sparsely observed. Somewhat more adverse events related to hypocalcaemia were found with etelcalcetide as compared to cinacalcet, in particular in relation to neuromuscular irritability. However, events related to cardiac repolarisation, which could potentially be harmful were infrequent in the current dossier. This is in itself reassuring but also limits estimation of this risk, also in comparison to cinacalcet. In this respect, exclusion of certain vulnerable patients with CV disease during these studies somewhat limits extrapolation of these findings to daily clinical practice, knowing that CKD patient frequently have (a history of) CV disease. Therefore, these potential risks have been included in the RMP and several warning statements have been included in the SmPC which is acceptable.

A potential serious risk of treatment with etelcalcetide is prolonged suppression of PTH levels below 100pg/mL, which is known to be associated with adynamic bone disease. No cases of adynamic bone disease were seen in the pivotal studies so far, but follow up may be too short yet.

Overall, the benefits of etelcalcetide in the treatment of secondary HPT in CKD patients are considered to outweigh the risks.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Parsabiv in the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that etelcalcetide is qualified as a new active substance.