22 June 2017
EMA/449274/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mimpara

International non-proprietary name: cinacalcet

Procedure No. EMEA/H/C/000570/X/0055/G

Note

Variation 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, and excretion
AUC	area under the concentration-time curve
AUC0-t	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC0-24hr	area under the serum concentration-time curve from time 0 to 24 hours
cCa	corrected calcium
CaR	calcium-sensing receptor
Ca x P	calcium-phosphorus product
CDC	Centers for Disease Control and Prevention
CEP	Certificate of Suitability of the Ph. Eur
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CL	clearance
CL/F	systemic clearance
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-metabolic bone disease
Cmax	maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DDI	drug-drug interaction
EAP	efficacy assessment phase
EC	European Commission
ECG	electrocardiograph
EDQM	European Directorate for the Quality of Medicines
EPAR	European Public Assessment Report
EU	European Union
ESRD	end-stage renal disease
EMA	European Medicines Agency
EU	European Union
$f_{m,CYP}$	fraction of metabolite formed by CYP enzyme
FTIR	Fourrier transform infrared spectroscopy
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HPT	hyperparathyroidism
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
iPTH	intact parathyroid hormone
K_a	absorption rate constant
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative

KF	Karl Fischer titration
KTZ	ketoconazole
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LLOQ	lower limit of quantitation
LS	least squares
MVOF	minimal value of objective function
NA	Not applicable
NAPRTCS	North American Paediatric Renal Trials and Collaborative Studies
NG/G	nasogastric/gastrostomy
NONMEM	nonlinear mixed effect modeling
PBPK	physiologically-based PK
pcVPC	prediction-corrected visual predictive checks
PDCO	Paediatric Committee
Ph. Eur.	European Pharmacopoeia
PI	prescribing information
PIP	Paediatric Investigation Plan
PTH	parathyroid hormone
PVC	Polyvinyl chloride
Q1, Q3	first quartile, third quartile
Q2/F	distribution clearance
RH	Relative humidity
RO	receptor occupancy
rpm	Revolutions per minute
RSE	relative standard error
r2	goodness-of-fit
SD	standard deviation
SmPC	Summary of Product Characteristics
SSAP	supplemental statistical analysis plan
SOC	standard of care
t1/2	terminal half life
$t_{1/2\beta}$	terminal half life beta
T_{lag}	lag time
t_{max}	time to maximum concentration
TSE	Transmissible spongiform encephalopathy
US	United States
USP-NF	United States Pharmacopeia and The National Formulary
USRDS	United States Renal Data System
V2/F	volume of distribution for the central compartment
V3/F	volume of distribution for the central compartment
w/w	weight for weight

1. Background information on the procedure

1.1. Submission of the dossier

Amgen Europe B.V. submitted on 26 May 2016 a group of variations consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form (granules in capsule for opening) associated with new strengths (1 mg, 2.5 mg and 5 mg) grouped with a type II variation (C.1.6.a) to include use in children aged 28 days to < 18 years in the approved secondary hyperparathyroidism indication. As a consequence, the SmPC is updated to detail information on paediatric patients and to update the safety information. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0008/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0008/2016 was completed.

The PDCO issued an opinion on compliance for the PIP P/0008/2016.

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 MAH 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.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 26 May 2016.
- The procedure started on 16 June 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 September 2016.
- During the meeting on 29 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 13 October 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 11 January 2017.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at 2 sites clinical and analytical facilities located in US between 4 and 7 October 2016. The outcome of the inspection carried out was issued on 28 November 2016.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 23 February 2017.
- During the PRAC meeting on 9 March 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 March 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 10 May 2017.
- The PRAC Rapporteurs circulated the PRAC Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 5 June 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for extension(s) of the marketing authorisation for Mimpara on 22 June 2017.

2. Scientific discussion

2.1. Problem statement

The MAH proposed to introduce for Mimpara a new pharmaceutical form associated with new strengths (1 mg, 2.5 mg and 5 mg hard capsules) for the use in a new proposed indication “secondary HPT in paediatric patients with CKD receiving dialysis”.

2.1.1. Epidemiology

End-stage renal disease is a rare condition in childhood with an estimated worldwide median reported incidence in 2008 of 9 (range: 4 to 18) per million of the age-related population. Published data indicate a median waiting time to kidney transplant of 11 months (first quartile [Q1], third quartile [Q3]: 6, 17 months) among those listed for transplant in European countries (Harambat et al, 2013). No published data exist on the prevalence of paediatric patients with secondary HPT; however, point prevalence estimates using USRDS and DaVita databases for 2015 indicate that < 1000 patients 0 to < 18 years of age on dialysis (491 for haemodialysis and 475 for peritoneal dialysis) will develop secondary HPT (data on file, Amgen). Of these, approximately 300 patients are estimated to be 0 to 5 years of age, 220 aged 6 to 12 years and approximately 430 aged 13 to < 18 years.

2.1.2. Aetiology and pathogenesis

Secondary hyperparathyroidism (HPT) develops in children and adults with chronic kidney disease (CKD). The pathophysiology of secondary HPT is thought to be similar in adults and children. Several factors are involved in the pathogenesis of secondary HPT in CKD. Early alterations in fibroblast growth factor 23, vitamin D metabolism, and calcium and phosphorus regulation lead to a reduction in signalling through the calcium-sensing receptor (CaR) and an increase in PTH secretion, resulting in higher PTH concentrations. Because PTH is the principal physiological regulator of blood calcium concentration, increases in PTH offset physiologic disruptions in calcium. Late in the course of CKD, phosphorus retention and overt hyperphosphatemia, together with skeletal resistance to the calcaemic action of PTH, can also affect calcium metabolism adversely, and further increase PTH secretion among patients with more advanced CKD (Wetmore and Quarles, 2009; Goodman and Quarles, 2008; Slatopolsky et al, 2001; de Francisco et al, 1998). Collectively, these changes in calcium and phosphorus concentrations and vitamin D metabolism contribute to the progression of secondary HPT, which generally worsens in severity over time if left untreated.

2.1.3. Clinical presentation

The development of CKD-mineral and bone disease (CKD-MBD) is manifested by either one or a combination of the following: 1) abnormalities in calcium, phosphorus, PTH, or vitamin D metabolism; 2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and 3) vascular or other soft tissue calcification (KDIGO, 2009). In children, CKD-MBD develops early in the course of CKD, such that a significant portion of children on dialysis have manifestations of CKD-MBD.

The clinical outcome most frequently associated with secondary HPT is the development of high-turnover bone disease, which results in reduced bone mass and increases the risk of bone deformities and fractures in adults and children with advanced CKD. Secondary HPT is also thought to play a role in growth retardation in children, potentially through alterations in bone architecture (including lesions in the epiphyseal growth plate), which interfere with bone formation and lead to impaired bone growth.

2.1.4. Management

Children with ESRD and secondary HPT are prioritized for kidney transplant and often undergo definitive treatment with renal transplant within the first year after starting dialysis.

Currently, there are no approved medical therapies for the management of secondary HPT in paediatric patients with CKD receiving dialysis in the European Union (EU) or the US. A number of drugs have been approved adult patients including Cinacalcet. Current treatment consists of vitamin D sterols, such as calcitriol or synthetic vitamin D analogs. In some circumstances, their use may be limited due to aggravation of hypercalcemia and hyperphosphatemia, conditions associated with increased long-term cardiovascular morbidity and mortality.

2.2. About the product

Cinacalcet is a calcimimetic agent that increases the sensitivity of the CaR to extracellular calcium. Cinacalcet acts as an allosteric modulator of the CaR and regulates PTH secretion by amplifying the sensitivity of the receptor to extracellular calcium, thereby reducing PTH secretion (Nemeth et al, 2004; Nemeth and Bennett, 1998). Cinacalcet is a first-in-class calcimimetic that is synthesized as a hydrochloride salt and is the (R)-enantiomeric form.

For the adult population, cinacalcet has received marketing authorization in 79 countries at the time of this report and is indicated for the treatment of secondary HPT in patients with CKD receiving dialysis. Cinacalcet is not currently approved for use in children, and there is no age-appropriate formulation available commercially, leading to possible off-label use that is not informed by age- and weight-based dosing and titration instructions or data from clinical studies.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The paediatric studies were conducted according to the EU Paediatric Investigation Plan (PIP) and a Written Request (WR) in the US.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as granules in capsule for opening containing 1, 2.5 or 5 mg of cinacalcet (as hydrochloride salt) as active substance.

Other ingredients are:

Capsule contents: pregelatinised starch (maize), microcrystalline cellulose, povidone, crospovidone and silica, dental type.

Capsule shell: iron oxide yellow (E172) (1 mg and 2.5 mg capsules only), indigo carmine (E132) (1 and 5 mg capsules only), titanium dioxide (E171) and gelatin.

Printing ink: iron oxide black, shellac and propylene glycol.

The product is available in high density polyethylene (HDPE) bottles with a foil induction seal and a child resistant polypropylene cap, packed into a carton as described in section 6.5 of the SmPC.

2.4.2. Active Substance

Mimpara 1, 2.5 and 5 mg granules in capsule for opening contain the same active substance, cincacalcet hydrochloride, as that used to manufacture the already authorised film-coated tablets. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications. Therefore, the applicant presented no new information in the dossier to support this line extension application.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Mimpara is presented as granules in capsule for opening containing 1, 2.5 or 5 mg cinacalcet (as hydrochloride salt) as active substance and is packaged in HDPE bottles with a foil induction seal.

The aim of development was to identify a dosage form bioequivalent to the film-coated tablets which is suitable for the paediatric population, in line with the paediatric investigation plan (PIP). Liquid formulations were found to induce mouth numbing and a prolonged bitter taste. Therefore, a capsule formulation was investigated.

A bioequivalence study was conducted to assess the *in vivo* performance of the capsule formulation relative to an equivalent dose of the tablets. One 30 mg tablet was compared with the contents of 6 x 5 mg capsules sprinkled onto apple sauce. The sprinkled formulation was shown to be bioequivalent to the approved tablets. Bioequivalence was not demonstrated for the capsules swallowed whole.

Organoleptic studies showed that the inherent bitterness of the active substance is sufficiently masked when an appropriate quantity of food is used and the mixture is eaten immediately. Instructions to this effect are included in section 4.2 of the SmPC.

All 3 strengths are filled into size 2 hard gelatin capsules distinguishable by colour and imprinting. As the capsules are intended to be opened and sprinkled on food or liquid and not ingested, the use of colourants is acceptable. The proposed capsule strengths provide adequate dosing flexibility for the starting dose. However, the maintenance dose for older children who are not able to swallow could involve opening up to twelve 5 mg capsules on a daily basis. This would result in significant discomfort for the patient and care giver. However, it was agreed that only a small population would be affected since most patients would either

be on a lower dose or able to swallow the approved 30 mg film-coated tablets. The applicant nonetheless committed to evaluating the need for additional 10 or 15 mg strength capsules.

The capsule formulation uses the same intra-granular excipients as the approved tablet presentation. Extra-granular excipients are different given that the capsule blend does not need to be compressed. Therefore, instead of microcrystalline cellulose, crospovidone, magnesium stearate and colloidal silicon dioxide present in the tablet, the sole extra-granular component is silica, dental type, which is an anti-adherent used to ensure complete dose delivery when the capsule contents are sprinkled on food or liquid. 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 2.4.1 of this report.

Initially, concerns were raised by CHMP about the suitability of the capsule dosage form resulting in a major objection. Capsules are generally swallowed whole but should not be in this case since bioequivalence with the tablets was only demonstrated for the capsule contents. In addition, the capsule shells contain colourants which are generally discouraged in paediatric medicines. In addition, assessors had difficulties opening the capsules without breakage which, given the low weight of granules per capsule (4 mg in 1 mg capsule, 10 mg in 2.5 mg capsule, 20 mg in 5 mg capsule), could result in spilling part of the dose or incomplete removal of the granules from the capsule in a real life setting. Therefore, there is a risk of under-dosing patients. As a result, the applicant was requested to consider alternative containers. In order to resolve this concern, the applicant committed to evaluating alternative capsule designs and identifying a capsule with improved properties (easier to open without breakage, reduced risk of contents spilling, and improved dose accuracy). In addition, more detailed instructions on how to open the current capsules, including pictures, have been included in the SmPC. Clear instructions that the capsules are not to be swallowed are included both in the SmPC and on the outer packaging. This was considered acceptable by the CHMP.

The dissolution method is the same as that used for the approved film-coated tablets and is carried out on unopened capsules. The acceptance criteria are the same as for the tablets. The method was originally developed such that it is capable of discriminating between bioequivalent and non-bioequivalent batches of tablets. The dissolution method is applied to the capsules without further development. Given that the composition and manufacturing process of the granules is equivalent to that used for the film-coated tablets, this is considered acceptable.

The wet granulation process is the same as that used for the film-coated tablets. The granules are subsequently blended with amorphous silicon dioxide, screened to ensure suitable particle size and content uniformity and encapsulated. The proposed commercial process is the same as used during clinical development. Holding times for the intermediate powder blend and bulk capsules have been set based on long term stability studies and the associated bulk packaging has been defined.

Compatibility with various food items was assessed. Full recovery of the product was observed 3 hours after mixing with apple sauce, yoghurt, apple juice, or 3 renal milk formulae. Instructions as to how much food to use for mixing are provided in the SmPC.

In addition, compatibility with typical gastrostomy and nasogastric tubes was evaluated, using water, apple juice or the 3 renal milk formulae as carrier liquids. Tubes made from PVC, polyurethane and silicon were investigated and the combination of water with PVC tubing was found to be most acceptable. Again, instructions for use in combination with feeding tubes are provided in the SmPC.

There are currently no standard terms in the EDQM database deemed suitable to describe the present formulation. The applicant originally proposed “hard capsules” but this was considered not to accurately reflect the dosage form by CHMP. The committee was of the opinion that since the granules must be removed from the capsule before consuming, granules should be part of the given pharmaceutical form. “Granules in single dose container” was considered following recommendation from EDQM but it was felt that describing a capsule as a single dose container would be confusing for patients. Since the capsule shouldn’t be swallowed, then a new term was invented which aims to ensure the capsules are opened and the granules sprinkled on food or liquid. The new term is “granules in capsule for opening” which is included in the SmPC and packaging.

The primary packaging is HDPE bottles. The material complies 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 five main steps: wet granulation, milling and drying; sieving and blending; encapsulation; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been evaluated by a number of studies. A continuous process verification approach has been employed, with the process monitored through design to pilot to commercial scale. The applicant proposes to complete validation by manufacturing as suitable number of consecutive batches of common blend which will be used to manufacture batches of capsules of each strength. Based on the demonstrated level of process understanding and manufacturing experience at the commercial site, this is considered acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The amount of water added to the wet granulation is tightly controlled to ensure the correct particle size. Amount and frequency of capsule tapping is also controlled to ensure correct filling of the capsules.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (FTIR and HPLC), assay (HPLC), impurities (HPLC), content uniformity (HPLC), dissolution (HPLC), and moisture content (KF).

The omission of a test for microbiological quality is justified given the low water activity of cinacalcet hydrochloride and the lack of microbial growth seen during development and stability studies. A test for colourants is omitted since the capsules are not to be ingested. The limits for impurities are in line with the ICH Q3B limits.

All tests with the exception of dissolution, appearance and content uniformity are conducted on the capsule contents, essentially, the delivered dose. CHMP considered that the content uniformity test should also be carried out on the contents only to better reflect the dose received by the patient. The applicant committed to modify the relevant analytical method which will be carried out on the contents alone.

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 45 pilot and production scale batches of the 5 mg capsule, and 3 production scale batches each of the 2.5 mg and 1 mg capsules confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Batches complied with the specification in place at the time of testing. During development, the assay limit was tightened as the process and encapsulation accuracy improved.

Stability of the product

A bracketing approach was taken to stability studies with the 2.5 mg capsule omitted. Stability data from 3 production scale batches of the 1 and 5 mg capsules stored for up to under 18 months under long term conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, supportive data on 5 batches of the 5 mg strength stored for up to 60 months under long term conditions was also provided. Samples were tested for the same properties as for release with the omission of identity and content uniformity. A test for microbiological quality was also carried out annually. A slight increase in water content was observed which reached a plateau but had no impact on other properties. All measured parameters remained within specification throughout the studies.

Photostability and forced degradation studies were carried out on the active substance as part of the original film-coated tablet development. These indicate that the active substance is very stable and not photosensitive.

In addition, samples of the capsule contents were exposed to stressed conditions (heat (60 ^{o}C for 2 weeks) and moist heat (50 ^{o}C / 75% RH for 2 weeks). The granules are stable under both sets of conditions.

Based on available stability data and considering the stability of the film-coated tablets (shelf-life 5 years) and the supportive batches, the proposed shelf-life of 48 months without defined storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. 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.

The selected dosage form is not considered optimum by the CHMP for several reasons as discussed in the pharmaceutical development section. Nonetheless, the benefit/risk is still considered positive given the alternative to the proposed capsules for paediatric patients is the off-label use of crushed tablets with significant risk of mis-dosing and considering that detailed instructions, including pictures, have been

included in the SmPC. The applicant committed to investigating alternative capsules which are easier to open without breaking and would ensure the accurate dosing of patients.

A commitment was also made to evaluate the need for higher strengths (e.g. 10 or 15 mg) for older children needing a high maintenance dose but who are unable to swallow, and would thus require the contents of up to 12 capsules to be administered with the currently available 5 mg capsules.

Finally, the applicant committed to amend the content uniformity release test so that only the contents rather than the entire capsule is tested. This will ensure the result more accurately reflects what is given to the patient.

2.4.5. 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. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP notes that the applicant has agreed with the Committee's recommendations as follows:

- to evaluate alternative capsule designs and identify a capsule with improved properties (easier to open without breakage, reduced risk of contents spilling, and improved dose accuracy). A variation introducing the new capsule should be submitted.
- to evaluate the need for higher strength capsules (10 or 15 mg) for older children on a high maintenance dose who are unable to swallow tablets.
- to modify the content uniformity release test such that only the granules are tested rather than the contents and capsule shells. The method should be validated and the relevant variation submitted.

2.5. Non-clinical aspects

2.5.1. Pharmacology

The pharmacology of cinacalcet was thoroughly evaluated during the original approval procedure for Mimpara. Cinacalcet acts on the parathyroid gland by increasing the calcium-sensing receptor (CaSR) sensitivity to extracellular calcium. The primary role of the CaSR is control of parathyroid hormone (PTH) secretion in response to extracellular calcium concentration. Cinacalcet acts as an allosteric modulator of the CaSR, resulting in reduced circulating PTH concentrations. Proof of concept was shown in rat models of secondary HPT (5/6 nephrectomy (Nx); antibiotic-induced renal failure).

The safety pharmacology program covered the central nervous system (CNS), cardiovascular, respiratory, renal, gastrointestinal, and glucose homeostatic systems. Cinacalcet at 200 mg/kg produced decreased spontaneous motor activity in mice. This effect was attributed to hypocalcaemia resulting from the

pharmacological effect of the drug. Increased gastric motility was observed in mice at a dose of 200 mg/kg. Cinacalcet administered intravenously at 20 mg/kg in guinea pigs produced a transient increase in airway resistance and one guinea pig died as the result of bronchoconstriction 6 minutes following dosing.

Studies performed to determine potential interaction with a selection of receptors, channels and enzymes, suggested a potential, small risk for receptor interactions in the clinical situation. Considering the low safety margins in most safety pharmacology and toxicology studies, the presence of secondary pharmacological events cannot be excluded.

No new non-clinical pharmacology studies were submitted in support of the present application. This is acceptable.

2.5.2. Pharmacokinetics

The non-clinical pharmacokinetic aspects of cinacalcet were thoroughly evaluated during the original approval procedure for Mimpara. Oral bioavailability was generally low, less than 10% in rats and approximately 20% in humans. Cinacalcet was highly protein bound (93% to 99%) in all species. Studies with radiolabelled drug showed that cinacalcet is widely distributed in tissues without marked accumulation. Cinacalcet was excreted into the milk of lactating rats and crossed the placental barrier in rabbits. *C*inacalcet is metabolised extensively in mice, rats, monkeys and humans. Studies with specific CYP inhibitors suggested CYP3A4 and CYP1A2 as the major contributors of cinacalcet metabolism in humans. Both hepato-biliary and urinary elimination are major routes of elimination.

No new non-clinical pharmacokinetic studies were submitted in support of the present application. This is acceptable.

2.5.3. Toxicology

Previously conducted toxicology studies

The toxicological profile of cinacalcet was characterized during the original approval procedure for Mimpara. In repeat-dose toxicity studies up to 1 month (dog), 6 months (rat) and 1 year (monkey), hypocalcemia resulting from the pharmacological effect of cinacalcet was the dose-limiting toxicity. Conventional *in vitro* and *in vivo* genotoxicity studies, and 2-year rodent carcinogenicity studies, did not indicate a genotoxic or carcinogenic potential for cinacalcet. Reproductive toxicology studies showed no effect on fertility in rats. Embryotoxicity (lower foetal body weights) was observed in rats and rabbits at doses associated with maternal toxicity. There was no evidence for a teratogenic potential; however, the margins to human clinical exposure were small.

In the original MAA, two 1-month juvenile toxicity studies in rats and dogs were included. The age of the animals covered a human age range of 2-12 years. The maximum doses used were low and did not reach the MTD. Rats showed bone density changes in the femur at $\geq$ 1.5 mg/kg. In dogs, intramural left ventricular arterial hypertrophy was noted in a few animals in all dose groups, including the control, with increasing severity seen among dogs administered 1.5 or 5.0 mg/kg at the end of the recovery period only. One male in the high dose group had multifocal left ventricular myocardial fibrosis. The relationship of these findings to the test article was considered unclear. The exposure to cinacalcet at the highest dose (5 mg/kg) was 0.1-fold that of the adult human dose.

New juvenile toxicity studies

To support the presently sought paediatric indication, the Applicant conducted two new juvenile toxicity studies in Beagle dogs. The first study was a 14-day dose-range finding study using doses of 10, 30 and 100 mg/kg/day. The highest dose, 100 mg/kg/day, was judged to be the maximum tolerated dose (MTD) based on clinical signs related to hypocalcaemia as well as the magnitude of decrease in serum ionized calcium.

In the second, 6-month pivotal toxicity study, the same doses (10, 30 and 100 mg/kg/day) were used. The dogs were aged 10 weeks at the start of treatment, corresponding to an approximate human age of 2 years. A 3-month recovery period was included. The main findings from the study are summarized below:

Mortality

One female dog at 100 mg/kg/day was euthanized on Day 88 due to lack of appetite and growth. The dog had been on drug holiday between Days 64-70, but failed to regain appetite and body weight when drug treatment was reinitiated.

Clinical signs

Tremor, emesis and decreased activity were observed at all dose levels. These effects are considered due to cinacalcet-induced hypocalcaemia. As a consequence of vomiting, dogs treated at ≥ 30 mg/kg/day showed dehydration and thin body condition.

Body weight and food consumption

Body weight gain and body weight were reduced ranging from 11% to 33% in dogs treated at ≥ 30 mg/kg/day; males being somewhat more affected than females. Food consumption was generally reduced, although exact figures were not possible to calculate.

Haematology, serum chemistry and urinalysis

Slightly decreased red blood cell parameters and increased platelets were observed in dogs treated at ≥ 30 mg/kg/day. The Applicant related this finding to decreases in body weight secondary to decreased food consumption and lymphoid changes in the thoracic cavity. It is argued by the Applicant that an extended restoration of red blood cell levels after recovery from malnutrition or weight loss is a phenomenon known from clinical observations in undernourished children and is also related to the long life span of red blood cells. This explanation is considered acceptable.

Total serum calcium and ionized calcium were decreased, and phosphorus increased, at all dose levels. There was a trend for increased serum levels of PTH at all dose levels, as evaluated at the end of study. Urinary calcium oxalate crystals were present at all dose levels.

Target organs of toxicity

Bone (femur, radius) was identified as the main target organ of toxicity. Minimal growth plate thickening of the calcification zone in the femur was observed at all dose levels, and in the radius at 100 mg/kg/day. Investigation *ex vivo* using pQCT showed slightly decreased bone mineral content (BMC), bone mineral density (BMD) and total and cortical mean area in the distal femur metaphysis and diaphysis at ≥ 30 mg/kg/day. The periosteal circumference was slightly lower compared with controls. There were no effects on bone resorption markers in serum; however, bone-specific alkaline phosphatase (BAP) was slightly decreased at ≥ 30 mg/kg/day.

Other findings

Minimal to moderate lymphoid hyperplasia of thoracic (tracheobronchial, mediastinal) lymph nodes and the bronchus associated lymphoid tissue (BALT) in the lung was present at all dose levels. In addition, minimal to

slight mononuclear cell infiltration was seen in the esophagus at all dose levels. These findings were interpreted by the Applicant as secondary to vomiting and aspiration of vomitus. Changes in the tracheobronchial and mediastinal lymph nodes and related findings were not fully reversible after the 3-month recovery period. The Applicant argues based on a literature review on the influence of emesis on local irritation of the esophagus as well as on aspiration pneumonitis. Moreover, a literature based remark that regression of reactive lymphoid hyperplasia might be of extended duration due to various factors was made.

Based on non-clinical studies conducted by the Applicant, a connection of emesis with the incidence of bronchointerstitial inflammation and mediastinal lymph node enlargement was made. In addition, it was remarked that, of various species investigated within the scope of the non-clinical development in studies of up to 2 year duration, the dog was the only one that developed this kind of changes. Taking all data into consideration, the Applicant's explanation is considered acceptable.

Reversibility
All findings were reversible except for thin body condition and decreased red blood cell mass at $\geq$ 30 mg/kg/day, body weight decrease in females, changes in the tracheobronchial and mediastinal lymph nodes, and decreased BMD and total and cortical mean area of the femur in females at $\geq$ 30 mg/kg/day.

Toxicokinetics
Exposure to cinacalcet was comparable (< 1.5-fold different) between male and female juvenile dogs. There was a slight accumulation of drug at weeks 12 and 26 relative to week 4. The exposure in terms of AUC_{0-24} at 100 mg/kg/day was 527 hr*ng/mL (combined sexes) at week 26. The margin to adult human AUC_{0-24} at a maximum dose of 180 mg/day is 0.8-fold.

NOAEL
The NOAEL was 10 mg/kg/day.

2.5.4. Ecotoxicity / environmental risk assessment

The Applicant submitted an environmental risk assessment (ERA) as part of the original MAA for Mimpara in 2003. This ERA had been conducted in accordance with the draft EMA guidance available at the time (CPMP/SWP/4447/00 draft, 24 July 2003). Following review of the original ERA, the MAH agreed to a post approval commitment (FUM003) to conduct Phase II Tier A testing following CHMP/SWP/4447/00 draft, 20 January 2005. The 2005 draft guidance contained different testing guidance from the draft 2003 (especially with regard to aquatic effects studies) to determine environmental risk.

This Phase II Tier A testing was completed and submitted to the Agency on 30th September 2005. The CHMP adopted a positive conclusion on acceptability of the ERA, and fulfilment of FUM003, on 15th December 2005 stating: *"The environmental risk assessment is acceptable and the conclusion that cinacalcet will not represent a significant risk for the environment following its prescribed usage in patients is endorsed. Follow-up measure 003 should be considered fulfilled."*

The Applicant has provided calculations of predicted environmental concentration (PEC) surface water for the previously approved indications in adults as well as the proposed paediatric indication. The calculation for the paediatric indication is not agreed with. The parameter *DOSE*ai should be the maximum daily dose consumed per patient, not the average. Thus, DOSEai should be 180 mg instead of 17.5 mg. This results in a $PEC_{surfacewater}$ of 0.0005319 µg/L.

In accordance with the ERA Q&A guidance (EMA/CHMP/SWP/44609/2010), if a product can be prescribed for the treatment of more than one indication, the $PEC_{surfacewater}$ values for all the sought indications should be calculated. The correct calculation is as follows: 0.022 + 0.605 + 0.00605 + 0.0005319 = 0.633 µg/L. This is well above the trigger value of 0.01 µg/L and thus a Phase II, Tier A environmental fate and effects analysis is requested. Since this was already provided in the original MAA for Mimpara, no further action is considered necessary.

2.5.5. Discussion on non-clinical aspects

The new juvenile toxicity study in dogs covers the age range of 2-12 years in a human child. Previously conducted 28-day rat and dog studies, using lower doses, also covered this age range. In the initially sought indication children younger than 2 years were included; thus it may be argued that there is no specific toxicological coverage for the period 0-2 years.

The difficulties of conducting studies in animals of corresponding age to humans in the period 0-2 years are acknowledged. In the case of cinacalcet, the toxicological profile has been established in previous repeat-dose toxicity studies in young adult animals, as well as in juvenile rats and dogs. The main finding in all previous studies, as well as in the two new juvenile toxicity studies in dogs, was hypocalcaemia due to the pharmacological action of cinacalcet. The consequences of hypocalcaemia are well-known and it is considered unlikely that studies in younger animals would identify any additional or unexpected toxic effects. Thus the new juvenile toxicity studies in dogs, together with the previously conducted toxicology package, are considered sufficient to support the currently sought paediatric indication of cinacalcet.

The most important findings from the pivotal 6-month study were growth retardation (decreased body weight and body weight gain) and effects on bone, including minimal growth plate thickening of the calcification zone in the femur, at clinically relevant exposure levels. These effects are likely related to cinacalcet-induced hypocalcaemia. Since serum calcium and body weight will be followed in the clinic, potential adverse effects on growth will be monitorable.

There were no findings in the heart of dogs treated up to 100 mg/kg/day for 6 months. Since the dose, exposure and duration were higher/longer than in the previously conducted juvenile dog study where equivocal heart findings were observed, it is agreed with the Applicant that cinacalcet is not toxic to the heart of juvenile dogs.

Red cell mass was decreased at $\geq$ 30 mg/kg/day in the 6-month juvenile dog study. Similar findings were observed in adult monkeys. The mechanism is not clear; however, no effects on red blood cells have been observed in the paediatric clinical trials.

Lymphoid changes in the thoracic cavity of dogs were interpreted as local non-specific responses to emesis-associated aspiration.

The low exposure margins are stated by the Applicant to be due to the fact that healthy animals are more sensitive to the hypocalcaemic effects of cinacalcet. This relates to the greater effect of PTH on calcium reabsorption in intact kidneys relative to secondary HPT patients with little or no kidney function, who also have elevated PTH and serum calcium. The Applicant's explanation seems plausible.

The Applicant was asked to propose appropriate wording regarding the new dog studies, including main findings and exposure margins, for section 5.3 of the SmPC. The text proposed by the Applicant was acceptable, with a minor revision.

2.5.6. Conclusion on non-clinical aspects

There is no objection to an approval of Mimpara from a non-clinical point of view

2.6. Clinical aspects

2.6.1. Introduction

GCP

Study 20070293 underwent a GCP inspection. The inspection identified deficiencies in documentation of investigational product (IP) administration and sample handling that called into question the overall reliability of data from Study 20070293. Specifically, the inspectors found that labelling and packaging of investigational product was not performed in accordance with Good Manufacturing Practice (GMP). The Inspectors concluded that protocol compliance with regard to IMP administration could not be confirmed during the inspection due to inability to reproduce IMP labels, and insufficient dosing documentation. Since the protocol required administration of six capsules or one tablet per subject respectively, the Inspector considered it essential that the correct number of IMP units was dosed. Further, there were also issues affecting PK Sample analysis. As the bioanalytical site, couldn't demonstrate consistent application of acceptance criteria the reported PK sample concentrations of study samples analysed are in question for 12 subjects.

During the procedure the applicant has performed a new bioequivalence study (20160428) in line with the requirements as outlined in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**. Bioequivalence has been shown between treatment A and B i.e between 6x5 mg capsule and the 30 mg tablet (see results below).

The MAH 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.

- ***Tabular overview of clinical studies***

Table 1 (a). Summary Table of completed Cinacalcet Clinical Studies and Cross-study Analyses in the Paediatric Marketing Application

Study No. (PIP/WR No.)	Study Design	Age Range	Subjects Enrolled
Controlled Safety and Efficacy Studies			
20070208[a] (PIP Study 6, WR Study 2)	Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet in paediatric subjects with CKD and secondary HPT receiving dialysis	6 to 18 years	43 22 cinacalcet, 21 placebo
20130356 (PIP Study 9, WR Study 4)	Phase 3, open-label, randomized, SOC-controlled study to assess the efficacy and safety of cinacalcet in paediatric subjects with CKD and secondary HPT receiving dialysis	6 to 17 years	55 27 cinacalcet + SOC (25 received cinacalcet), 28 SOC
Uncontrolled Efficacy and Safety Studies			
20110100[b] (WR Study 3)	Phase 2, open-label, single-arm study with cinacalcet + SOC to assess the safety, tolerability, and PK of cinacalcet in paediatric subjects of age 28 days to < 6 years with CKD and secondary HPT receiving dialysis	12 to 65 months	18
20140159[b,c] (WR Study 4 extension)	Phase 3, single-arm extension study of Studies 20130356 and 20110100 to assess longer term safety and tolerability of cinacalcet	8 to 18 years[d]	18
Other Efficacy and Safety Studies			
20090198 (PIP Study 7)	Retrospective chart review to describe the use of cinacalcet in paediatric subjects of age 0 to < 6 years with secondary HPT and CKD receiving dialysis	7 to 57 months	23
20120116[b] (WR commitment)	Prospective cohort study using NAPRTCS registry to describe the use and safety of cinacalcet in paediatric	0.1 to 25.5 years	538

	patients receiving dialysis		
Bayesian extrapolation study[e] (PIP Study 10)	Efficacy and safety modelling/extrapolation to infer both a treatment effect and safety profile of cinacalcet use in paediatric subjects with secondary HPT	6 to 18 years and adults	1207 paediatric: 71 adult: 1136

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Study No. (PIP/WR No.)	Study Design	Age Range	Subjects Enrolled
Clinical Pharmacology Studies			
20030227[b,f]	Phase 1, open-label, single-dose to assess the safety, tolerability, PK, and PD of cinacalcet in paediatric subjects with CKD receiving dialysis	6 to 16 years	12
20090005 (PIP Study 4, WR Study 1)	Phase 1, open-label, single-dose study to assess tolerability, PK and PD after a single dose in younger paediatric subjects	8 to 61 months	14
122055[e,g] (PIP Study 5)	Population PK and PK/PD modelling to simulate repeated-dose administration in paediatric subjects from birth to < 6 years	8 months to 17 years and adults	387 (PK) paediatric: 67 adult: 320[h] 648 (PK/PD) paediatric: 84 adult: 564[h]
122086[e,g] (PIP Study 8)	PBPK modelling to simulate PK in paediatric subjects < 1 year of age	8 months to 17 years and adults	139 paediatric: 33 adult: 106[h]
Biopharmaceutic Study			
20160428 (PIP Study 3)	Phase 1, randomized, open-label, 2-period, 2-treatment, single-dose, crossover bioequivalence study in healthy adult subjects	19 to 59 years	44

CKD = chronic kidney disease; HPT = hyperparathyroidism; NAPRTCS = North American Paediatric Renal Trials and Collaborative Studies; PBPK = physiologically-based pharmacokinetic; PD = pharmacodynamics; PIP = Paaediatric Investigation Plan; PK = pharmacokinetics; SOC = standard of care; WR = Written Request

[a] Study 20070208 was submitted to the EU Authorities as a post approval measure (PAM EMA/H/C/570/P46 028) in October 2014.

[b] This study is not a PIP binding element .

[c] Based on interim analysis (data cutoff date 29 April 2016). For Study 20140159 available data is discussed in the dossier. The study has since completed (last patient last visit is 15 March 2017); final CSR is ongoing.

[d] As of day 1 in Study 20140159
[e] Cross-study analyses
[f] Study 20030227 was submitted to the EU Authorities in a Type II variation (EMEA/H/C/000570/II/0015, approved 27 March 2009) to update section 5.2 of the Summary of Product Characteristics (SmPC) with information regarding the PK profile of cinacalcet in paediatric patients aged 6-17 years with CKD receiving dialysis following a single 15 mg dose (Mimpara SmPC, 2015)
[g] Report number
[h] For model development and validation (validation only for PBPK modelling)

Study 20130356 enrolled 55 subjects, 27 randomised to cinacalcet and 28 to SOC.

A total of 18 subjects were enrolled into study 20110100: 8 before the partial clinical hold (cohort 1), and 10 after the partial clinical hold (cohort 2). One subject in cohort 1 did not receive cinacalcet; all other subjects received at least 1 dose and were included in the Safety Analysis Set.

2.6.2. Pharmacokinetics

Comparative Bioequivalence study 20070293

The applicant presented an open-label, randomized, single-dose, 3-period, 3-treatment crossover study to assess the comparative Bioavailability of 5 mg Cinacalcet Capsules to the 30 mg Commercial Formulation Cinacalcet tablets in healthy adult volunteers. An inspection was carried out of the conduct of the clinical study 20070293, in accordance with the article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC. The study was considered invalid due to GCP violations was discovered with deficiencies in the administration of IP and the documentation processes. Further there were also deficiencies in bioanalysis of the plasma samples, however as the study is considered as invalid this is not further pursued. The applicant conducted a new bioequivalence study (20160428) in order to support the validity of the results of the first study. Accordingly, the concerns regarding the analytical part of study 20070293 were not further pursued.

Comparative Bioequivalence study 20160428

A new bioequivalence study with an open-label, randomized, single-dose, and crossover design to assess the bioequivalence of paediatric cinacalcet capsule (administered as six of the 5-mg cinacalcet capsules) with 30 mg commercial cinacalcet tablet in 44 healthy adult volunteers was performed.

The results showed that the geometric least square mean point estimates (90% CIs) for the ratios of capsule contents versus tablet were 0.947 (0.861, 1.042) for AUCinf, 0.945 (0.861, 1.039) for AUClast, and 0.998 (0.885, 1.126) for Cmax, and were within the pre-specified criteria of 0.80 and 1.25.

For commercial use in the paediatric population, 1 mg, 2.5 mg, and 5 mg capsule strengths are planned. However, the study 20160428 only 5mg capsules were tested but it was confirmed that the general biowaiver criteria according to the BE guideline are fulfilled for the 1mg and 2.5mg capsule strengths.

Clinical PK studies

Study **20030227** was a Phase I, Open-Label, Non-Randomized, Single-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Cinacalcet HCl in Paediatric Subjects aged 6 to < 18 years with Chronic Kidney Disease Receiving Dialysis.

The subjects received a single, oral, 15-mg dose (1/2 of a 30-mg tablet, corresponding to a mean dose of 0.39 mg/kg (range: 0.28 mg/kg to 0.81 mg/kg)) of cinacalcet and were followed for 72 hours after dosing for the study assessments. Enrolled subjects were stratified by age into 4 cohorts of 3 subjects each: 6 to 8, 9 to 11, 12 to 14, and 15 to 17 years. Subjects had an age range of 6 to 16 years (mean: 11.33 years) and a body mass index range of 15.6 kg/m2 to 25.6 kg/m2 (mean: 19.85 kg/m2).

Mean exposure in 4 age cohorts did not consistently increase with decreasing age. However, an overall trend of greater exposure in younger subjects was observed in individual Cmax and AUC0-t values. In addition, although a trend of increasing exposure with decreasing body weight also was observed, these data should be interpreted with caution given the single 15 mg dose of cinacalcet administered and the small subject numbers (N = 3/cohort) evaluated.

More recent data (study 20090005, see below) indicate that the trend of increasing exposure is owed mainly to the decreasing body weight at younger age and that weight corrected dose could prevent this effect. This is supported also by simulations from a PK model where no clinically relevant differences were observed in both PK and PD attributes of cinacalcet, but still, a trend of highest cinacalcet plasma levels in the youngest patients at any dose level was seen. The clinical relevance of this trend is not clear and the high intra-individual variability as well as the small sample size need to be considered. An increased vulnerability in younger children can, however, not be completely excluded which should be considered regarding the extrapolation approach in children 28 days to < 6 years of age. Choice of a rather conservative starting dose in children (approx. ½ of the adult starting dose in mg/kg bw) is welcome and mitigates concerns with this regard.

Study **20090005** (PIP study 4, phase I study) was an Open-label, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Cinacalcet HCl in Paediatric Subjects Aged 28 Days to < 6 Years With Chronic Kidney Disease Receiving Dialysis.

Doses were weight-adjusted to be 0.25 mg/kg and rounded to the nearest whole number. Doses from 1.8 mg to 5.4 mg were administered. Mimpara granules will be available in 1 mg, 2.5 mg and 5 mg capsules. In clinical practice, no such precise dosing as in study 200900005 will be possible or is proposed. For pharmacokinetic characterisation, the accurate dosing approach is welcome as the dose/exposure relationship can reliably be determined in this way. It is, however unknown if the aspired dose in this PK study could be sustained through the “mixing” process with purified water or sucrose syrup.

Two children < the age of 1 year seems to have been included in the study (see Table 9-2).

Table 9-2. Baseline Demographics
Safety Analysis Set in Study 20090005

	Age Group 28 days to < 3 years (N = 4)	Age Group ≥ 3 years to < 6 years (N = 8)	Total Subjects (N = 12)
Age (months)			
n	4	8	12
Mean	18.8	51.5	40.6
SD	12.1	6.2	18.0
Median	16.5	51.0	46.0
Min, Max	8, 34	44, 61	8, 61

Weight (kg)			
n	4	8	12
Mean	10.128	16.100	14.109
SD	2.585	3.366	4.205
Median	9.905	14.700	13.850
Min, Max	7.20, 13.50	12.30, 21.50	7.20, 21.50

N = Number of subjects in the analysis set; SD = standard deviation
Source: Table 14-2.1, Table 14-2.2

Pharmacokinetic Results

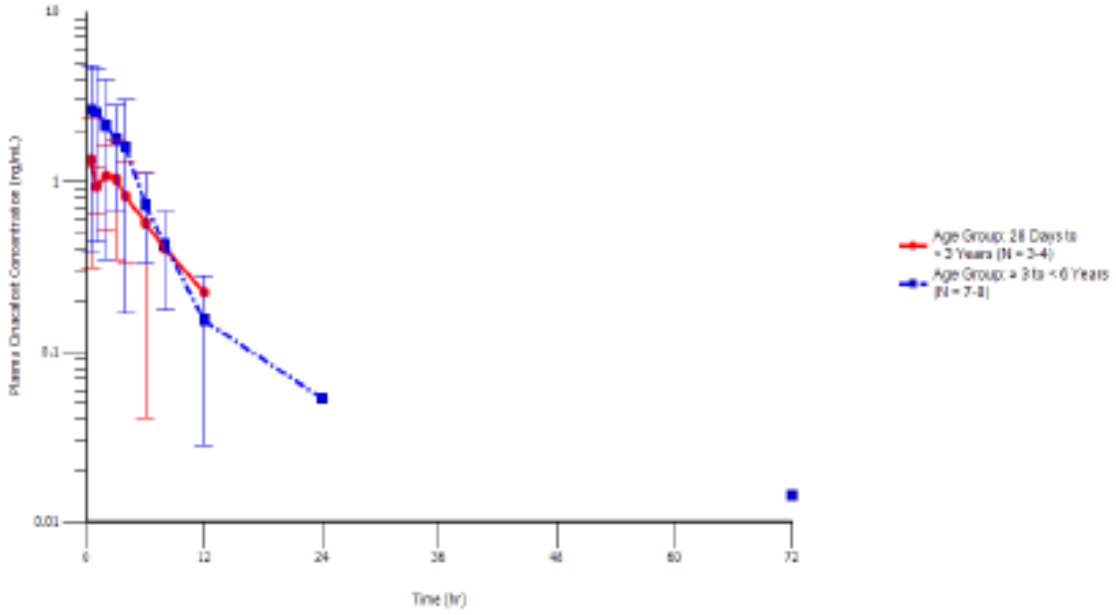
Cinacalcet was rapidly absorbed, with a median tmax of 1 hour (range: 0.50 to 4.0 hours; Table 3 and Figure 6). Mean plasma cinacalcet Cmax and AUC values were slightly higher (1.6- to 2.3-fold) in subjects ≤3 to < 6 years old compared to subjects 28 days to < 3 years old, but were within the range observed for subjects 28 days to < 3 years old. Therefore, given the extensive overlap and the high inter-subject variability, these results suggest that there is no clinically meaningful difference in cinacalcet exposure between the age groups. The limited number of subjects (especially in the younger cohort) has to be taken into account.

Table 3. Descriptive Statistics of Pharmacokinetics Parameter Estimates for Cinacalcet in Plasma after Oral Administration of 0.25 mg/kg Cinacalcet to Pediatric Subjects < 6 Years Old with CKD Receiving Dialysis

Parameter	t_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr•ng/mL)	AUC_{inf} (hr•ng/mL)	$t_{1/2,z}$ (hr)
Subjects 28 Days to < 3 Years Old					
N	4	4	4	4	4
Mean (SD)	NR	1.51 (0.820)	7.21 (5.27)	8.31 (6.28)	2.73 (0.952)
Median	0.75	1.36	6.04	6.68	2.60
Min - Max	0.50 - 3.1	0.797 - 2.51	2.84 - 13.9	3.29 - 16.6	1.83 - 3.87
CV%	NR	54.5	73.1	75.7	34.9
Subjects ≥ 3 to < 6 Years Old					
N	8	8	8	7	7
Mean (SD)	NR	3.50 (2.09)	14.1 (9.49)	12.9 (8.60)	4.26 (3.09)
Median	1.0	3.97	13.7	9.66	2.95
Min - Max	0.50 - 4.0	0.818 - 5.75	3.52 - 28.6	3.90 - 25.4	2.06 - 10.6
CV%	NR	59.9	67.3	66.5	72.6
All Subjects < 6 Years Old					
N	12	12	12	11	11
Mean (SD)	NR	2.83 (1.98)	11.8 (8.74)	11.3 (7.86)	3.70 (2.57)
Median	1.0	2.18	8.96	9.66	2.95
Min - Max	0.50 - 4.0	0.797 - 5.75	2.84 - 28.6	3.29 - 25.4	1.83 - 10.6
CV%	NR	70.0	74.1	69.8	69.4

AUC = area under the plasma-concentration-time curve; AUC_{inf} = AUC from time zero to infinity; AUC_{last} = AUC from time zero to time of last quantifiable concentration; CKD = chronic kidney disease; C_{max} = maximum observed plasma concentration; CV% = coefficient of variation; NR = Not reported; SD = standard deviation; $t_{1/2,z}$ = terminal half-life associated with λ_z; t_{max} = time to maximum concentration.
Source: Table 11-1 of Study 20090005

Figure 6. Mean (±SD) Plasma Cinacalcet Concentration-Time Profiles by Age Group after Oral Administration of Cinacalcet at 0.25 mg/kg to Pediatric Subjects < 6 Years of Age with CKD Receiving Dialysis



Log-linear Scale

CKD = chronic kidney disease

Study **20110100** (Phase II) was an Open-label, Single-arm Study to Assess the Safety and Tolerability of Cinacalcet HCl in Addition to Standard of Care in Paediatric Subjects Age 28 Days to < 6 years With Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis where PK sampling was a secondary objective. This study was not a PIP binding measure. Pharmacokinetic and PTH blood samples were collected on day 1 (predose and postdose), week 1, 4, 8, 12, 16, and 20. At week 12, subjects had a PK assessment over a 24 hour period at predose, and postdose. Dosing of investigational product in Study 20110100 was temporarily suspended following a fatality in Study 20070208 (described further in the safety section of this overview, data cut-off for the interim analysis was 01.March 2013).

As notified by the Applicant in August 2016, study 20110100 was recently closed due to difficulties with recruitment and a short summary of efficacy and safety results was provided. In the initial submission, neither interim nor final PK results were reported for the individual study, interim results were pooled with the results from other paediatric studies and included in the cross-study comparisons (see below); interim PK and PD data were also included in the population PK and PK/PD analysis. No AUC, C_{max} and t_{max} values were reported. It is not clear how many PK samples from different time points are available as it is not reported how many samples were collected. This study is the only source of repeat dose PK of cinacalcet in children and an individual interpretation of PK development over time is of interest.. Individual Plasma Cinacalcet HCl concentration-time profiles varied considerably between individual subjects and cohorts. Also, dose- and weight-normalized AUClast and Cmax show large variability. According to the Applicant, cinacalcet exposures (based on Cmax and AUClast) at week 12 appeared to generally increase with the increase in dose. Results indicate that the PK/PD relationship is similar across age groups, when taking into account baseline characteristics. However, the sample size is limited and conclusions might therefore not be very robust. In

addition, the applicant did not inform on PK/PD relationship at steady state and if it could be different in paediatric patients compared to adults.

Study **20070208** (PIP study 6, Phase III) was a Randomized, Double-Blind, 30-week, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet in Paediatric Subjects with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis were PK sampling was an exploratory objective. Blood samples for pharmacokinetic (PK) analysis were collected pre-dose in all subjects and between 1 and less than 3 hours post-dose (half of hemodialysis subjects) or 3 to 24 hours post-dose (half of hemodialysis subjects) during the double-blind phase. This study was terminated early due to a fatality and after consultation with regulatory authorities. A total of 380 study samples were analysed between 15 December 2011 and 20 June 2013. It is reported, that 22 subject received cinacalcet in the study and that 227 samples were analysed. However, results were not reported for the individual study but only used for POP PK and PK/PD modelling and simulation efforts (study 122055). According to the Applicant observed cinacalcet concentrations were within the expected range of exposures for this population. The cinacalcet concentration data from Study 20070208 was pooled with the results from other paediatric studies and included in the population PK and PK/PD analyses. No PK parameters (AUC, C_{max} and t_{max}) were reported.

Comparison of Cinacalcet Exposure in Adult and Paediatric Subjects

Four different PK studies using different cinacalcet (starting) doses (mg/kg) in different age groups (children and adults) were opposed for the comparison of AUC and C_{max} parameters.

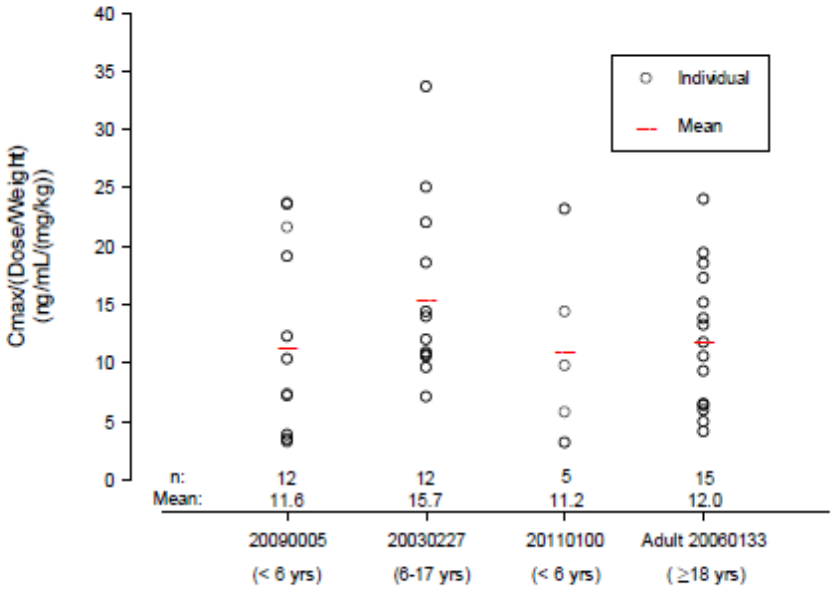
Cinacalcet exposures based on observed dose- and weight-normalized C_{max} and area under the plasma concentration-time curve from time 0 to 24 hours (AUC0-24hr) were compared across 3 paediatric studies in the target population with intensive PK data.

• Study 20090005 and interim results from Study 20110100, age range 28 days to < 6 years (the youngest subject was 8 months old) and;

• Study 20030227, age range 6 to < 18 years old.

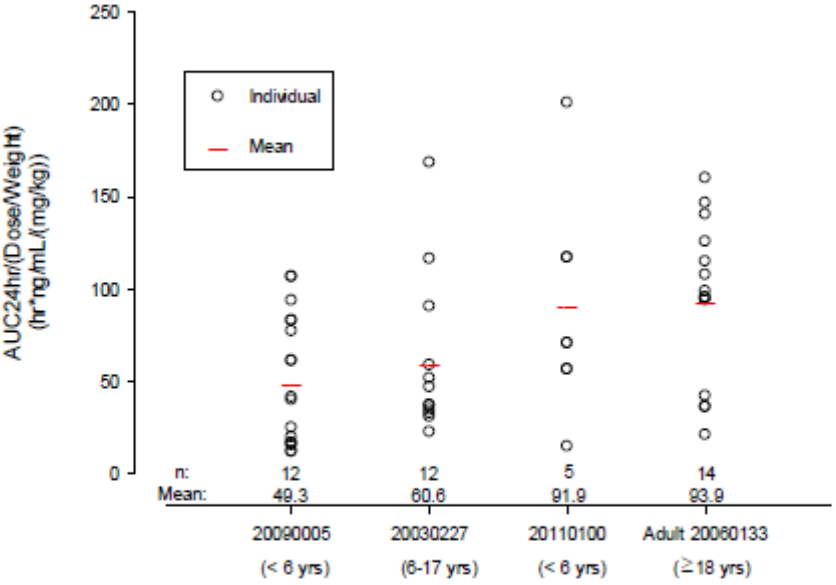
Data from a representative single-dose (30 mg) healthy adult study (20060133) were also included for cinacalcet exposure comparison purposes. Of note, the PK of cinacalcet is the same in healthy adults and adult subjects with CKD and secondary HPT receiving dialysis (Study 990163; renal impairment study). Dose- and weight-normalized C_{max} and AUC_{0-24hr} values (after first dose) in paediatric subjects with CKD and secondary HPT receiving dialysis and in healthy adult subjects largely overlapped and mean values were similar (< 1.31-fold and < 1.91-fold difference, respectively; Figure 9 and Figure 10), indicating that the PK of cinacalcet are similar between adults and paediatric subjects. The dose- and weight-normalized C_{max} and AUC_{0-24hr} values (after first dose) were also similar (< 1.40-fold and < 1.87-fold difference, respectively) between the paediatric age groups (28 days to < 6 years old, 6 to < 18 years old) and across the paediatric studies, demonstrating that cinacalcet PK is also similar across the paediatric age range. The comparisons of dose- and weight-normalized PK data across the adult and paediatric subjects indicate dose-linearity over the dose range evaluated. In addition, these results also support the consistency in cinacalcet PK regardless of renal function status and disease status between paediatric and adults subjects.

Figure 9. Comparison of Dose- and Weight-Normalized Cinacalcet C_{max} Across Pediatric and Adult Subjects (Studies 20090005, 20030227, 20110100, 20060133)



Age range: 28 days to < 6 years old for Studies 20090005 and 20110100; 6 to < 18 years old for Study 20030227.

Figure 10. Comparison of Dose- and Weight- Normalized Cinacalcet AUC_{0-24hr} Across Pediatric and Adult Subjects (Studies 20090005, 20030227, 20110100, 20060133)



Age range: 28 days to < 6 years old for Studies 20090005 and 20110100; 6 to < 18 years old for Study 20030227.

Source: \\usto-pfsx-cf04b\pkdm_bdrepository\AMG073_Sensipar\Comparison between adults and pediatrics pharmacokinetic parameter\graphs\Study comparison_EU Final.JNB

The mean AUC_{0-t} and C_{max} values following weight corrected cinacalcet doses in study 20030227 (mean dose of 0.39 mg/kg, range: 0.28 mg/kg to 0.81 mg/kg), study 200900005 (a single 0.25 mg/kg dose of cinacalcet supplied as a 5 mg capsule) and study 20110100 (starting dose 0.20 mg/kg) were within the range of values observed following a single 30-mg dose of cinacalcet administered to healthy adult subjects in study 20060133 (30 mg once daily is an approximate weight-based dose of 0.4 mg/kg in an average adult (weight of 70 kg)). Cross-study comparison of PK parameters shows comparable PK values (C_{max}, AUC) in different age groups of paediatric patients and adults at different doses/body weight. Considering the wide range of AUC and C_{max} the significance of mean values is somewhat low, the high inter-individual variability seems constant across all age groups and the distribution of individual data points (Figure 9 and 10) is in a comparable range. Still, this makes the choice of an adequate starting dose somewhat complicated. It is therefore considered acceptable to propose a conservative starting dose (0.2mg/kg) from a PK (and a safety) point of view.

PK results from study 20070208 were not included in the the figures 8 & 10 above but were included in the pop PK/PD analysis.

Pk data in children using the new capsule formulation

There are pk data (Cmax and AUC) demonstrating the similarity in cinacalcet pharmacokinetic (PK) exposures between tablet vs. capsule formulations in adult and paediatric subjects.

Population PK analysis

Cinacalcet plasma, serum intact parathyroid hormone (iPTH) and corrected calcium (cCa) concentration-time data were collected from 4 paediatric clinical studies (20070208, 20110100, 20030227, and 20090005) and 4 adult clinical studies (20000172, 20000187, 970241 and 980126). Cinacalcet was administered orally with doses ranging from 1 to 200 mg. The PK, iPTH and cCa concentration-time data from the above-mentioned 8 studies were pooled for the population PK and PKPD analysis. Cinacalcet pharmacokinetics was described by a two-compartment model with delayed first-order absorption and first order elimination processes. The PK model has been updated to included body weight with fixed exponents to standard allometric scaling factors (0.75 on CL and 1 on V_2). The popPK model has the potential to be further improved, i.e. by handling of BQL data. However, the GOF plots and the VPCs show that the model is reasonable and thus, the simulations on exposure for the start doses can be simulated out to guide that the choice of start dose in children 3-18 years. The simulations indicate that the apllicants suggested start dose gives a similar or lower exposure compared to the exposure after 30 mg start dose in adults.

PKPD analysis

The interaction between cinacalcet, iPTH and cCa were described by a semi-mechanistic PKPD model. The model included the role of PTH in calcium regulation, the feedback of calcium onto PTH production via the calcium sensing receptor (CaSR), and the activity of cinacalcet plasma levels in increasing the sensitivity of the CaSR to calcium via the cooperative binding model. Age, weight, race, sex, and phosphorus were assessed and none of them were identified as predictors of PD variability. The updated population PK model, including the added allometric scaling of volumes and clearances, was used as the driver for the PD effects. Data from 5 additional subjects from Study 20110100 were also included in the PK/PD model update. The simulations from the PKPD model indicate that the chosen start doses in children are safe but there are still issues with the PD part of the model.

From the provided GOF and VPC plots in the PKPD report (122055b), clear trends of misspecification can be seen throughout. The applicant has explained that there are several limitations including that the PKPD model does not account for changes in supplements like calcium and vitamin D (allowed by the protocol), which impacts changes in calcium and PTH. The limitations described by

MAH and the clear misspecification from the PKPD model mean that it is not possible to draw accurate conclusions from these simulations. Thus, the choice of start dose will need to be based on the simulated exposures from the popPK model alone.

PBPK analysis

The PBPK platform including peadiatric module (SimCYP version 14.1) was used. The ontogeny was updated according to Upreti and Wahlstrom (2016). The ontogeny was further supported using external although limited pk data for the CYP enzymes involved in cinacalcet metabolism. The used platform is however not deemed qualified to be used for children below 2-3 years of age.

The PBPK cinacalcet model was first established in adults using a two compartment distribution model. The PBPK simulation study design mimicked the clinical study design with regard to number of patients, dose and study length (n = 82, 30 mg and 24 h, respectively).

Refinement of the cinacalcet compound file was achieved through sensitivity analysis; the sensitivity analysis was used to optimize fm, CYP by comparison of the simulated change in cinacalcet AUC upon co-administration with KTZ to the observed change in cinacalcet AUC from the clinical DDI study with KTZ. The updated cinacalcet PBPK model in adults do show reasonable prediction. However based on the performed sensitivity analysis there are aspects that could be improved to provide a better prediction.

The refined cinacalcet compound file was used in all subsequent paediatric PBPK simulations. This PBPK model was then used to predict plasma concentration-time profiles for paediatric patients aged 28 days to 18 year. Initial predictions were carried out at a 0.20 mg/kg dose of cinacalcet, the starting dose used in Amgen Study 20110100 and the expected starting dose for future cinacalcet paediatric studies. The simulations for children below 18 years of age show that the PK of cinacalcet is not adequate predicted for absorption and the elimination phase.

Even if the PBPK simulations provide a conservative estimate of expected exposures in children the use of PBPK in this context for cinacalcet is too uncertain as the PBPK model in children do not show adequate performance as well as the Qualification aspects in young children (below 3 years) is too limited to use PBPK for extrapolation.

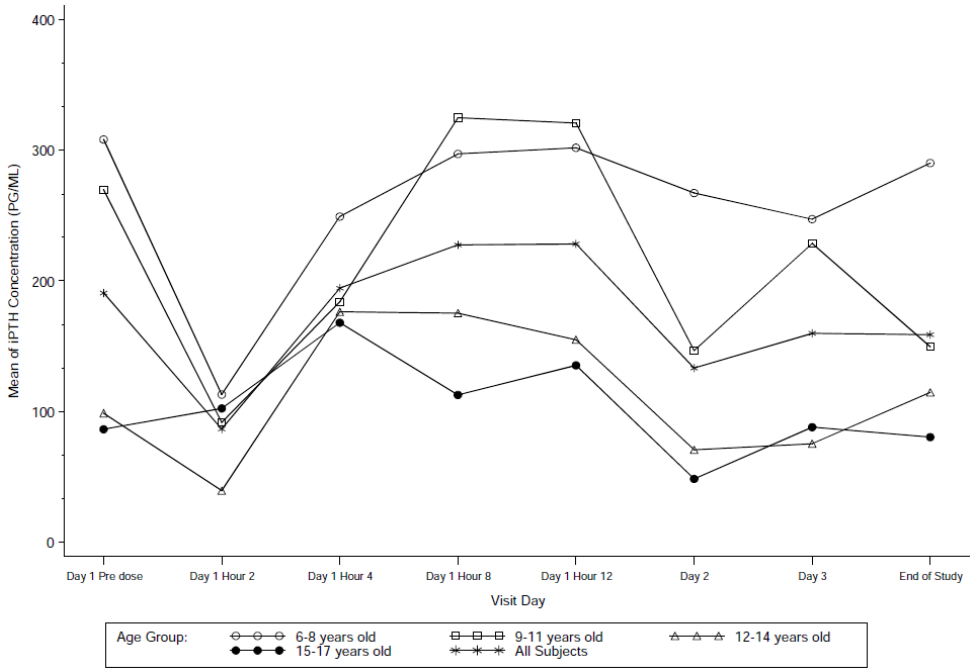
2.6.3. Pharmacodynamics

Efficacy was not a component of the phase 1 single-dose studies; however, the effects of cinacalcet on serum calcium and iPTH were evaluated.

Study 20030227: *A Phase I, Open-Label, Non-Randomized, Single-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Cinacalcet HCl in Pediatric Subjects (6-18 years) with Chronic Kidney Disease Receiving Dialysis (n=12).*

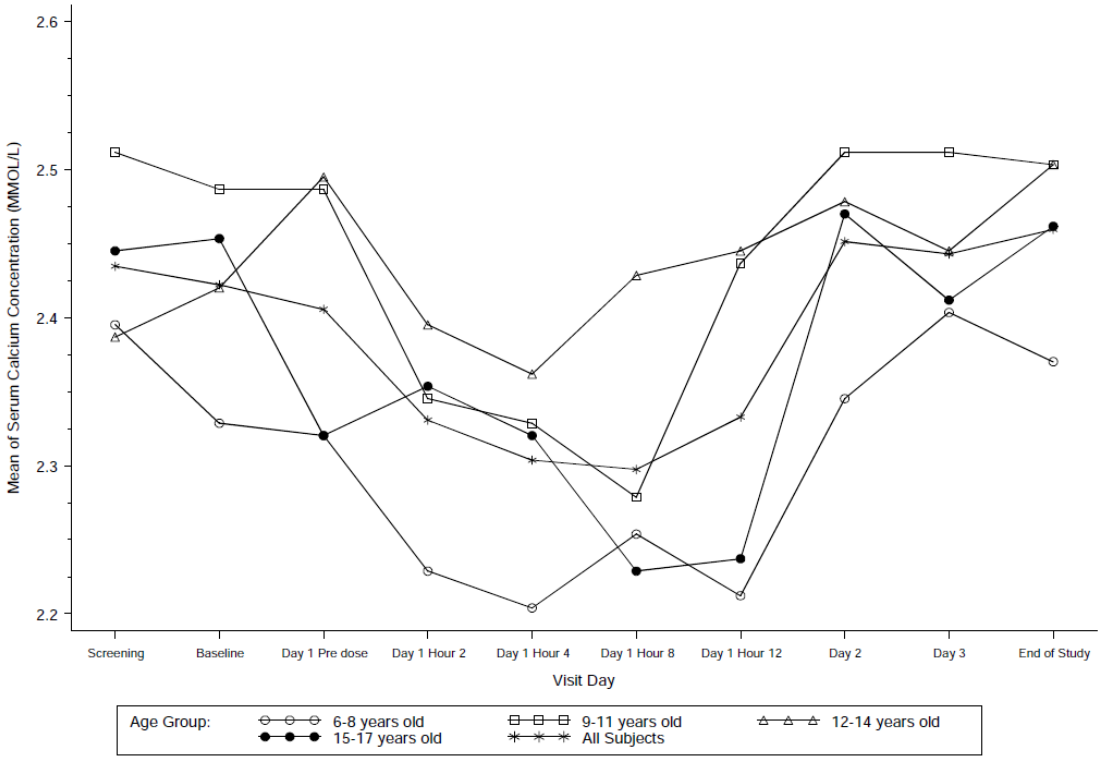
Subjects received a single, oral, 15 mg dose. Mean serum PTH concentrations initially decreased from baseline up to 4 hours post dose, increased to above baseline between 4 to 12 (peak at 8 hours) hours post dose, and returned to baseline levels by day 2 as seen in figure 1 below.

Figure 1. Mean iPTH Concentration - Time Profiles for Each Age Group



Mean decreases from baseline in serum calcium concentration were observed from 2 to 12 hours post dose; returning to baseline levels by day 2 (figure 2)

Figure 2. Mean Calcium Concentration - Time Profiles for Each Age Group

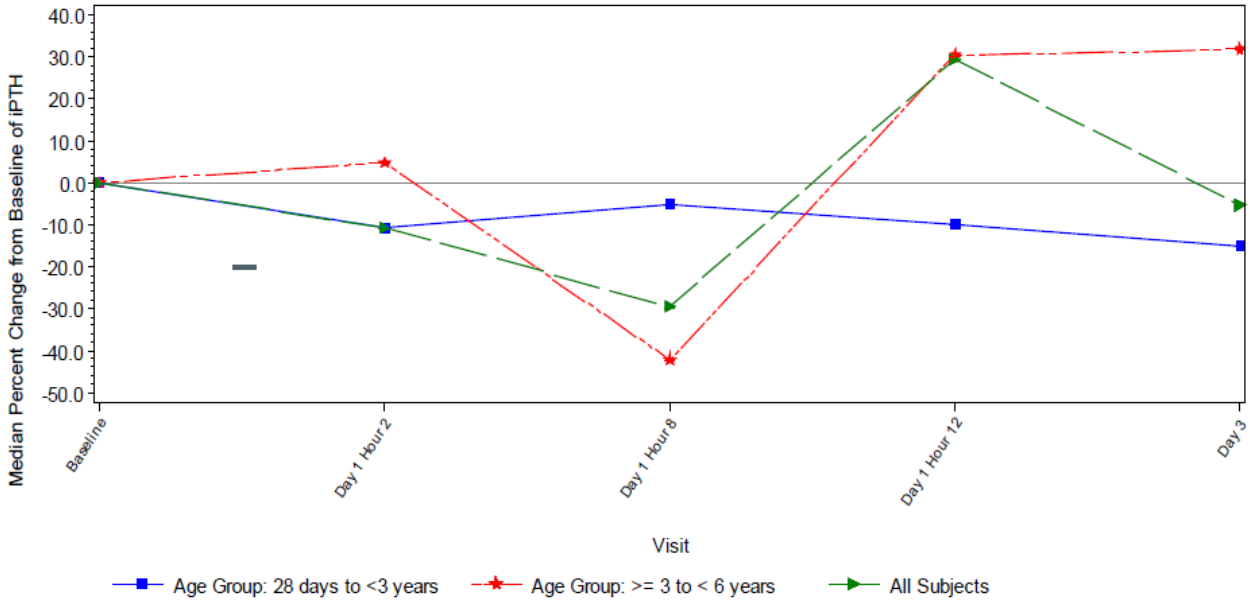


An apparent trend of increasing cinacalcet exposure with decreasing age was noted in this study, possibly related to less body weight. The data provided supported using a dose of 0.2 mg/kg as a starting dose in multi-dose paediatric studies with cinacalcet. The dose is up-titrated according to response. The maximum dose was lowered to 2.5 mg/kg/day (instead of 4.2 mg/kg/day) following a fatality in study 20070208.

Study 20090005: *An Open-label, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Cinacalcet HCl in Pediatric Subjects Aged 28 Days to < 6 Years With Chronic Kidney Disease Receiving Dialysis (n=12)*

Baseline PTH values varied widely since there were no inclusion criteria for minimum PTH levels. One subject had PTH post baseline values that were significantly higher than those observed for other subjects. Following a single oral dose of 0.25 mg/kg cinacalcet, reductions in serum PTH concentrations from baseline were observed at the 2 hours and 8 hours post dose sampling times. Concentrations of serum PTH transiently increased to above baseline at 12 hours post dose (+29.4%), and returned to near baseline levels by day 3 (-5.4%). Median percent PTH reductions were more pronounced at 8 hours post dose in subjects ≥ 3 years to < 6 years old (-42.2%) than in subjects 28 days to < 3 years old (-5.2%), but this observation should be interpreted with caution given the small subject numbers (N = 3 and N = 2, respectively).

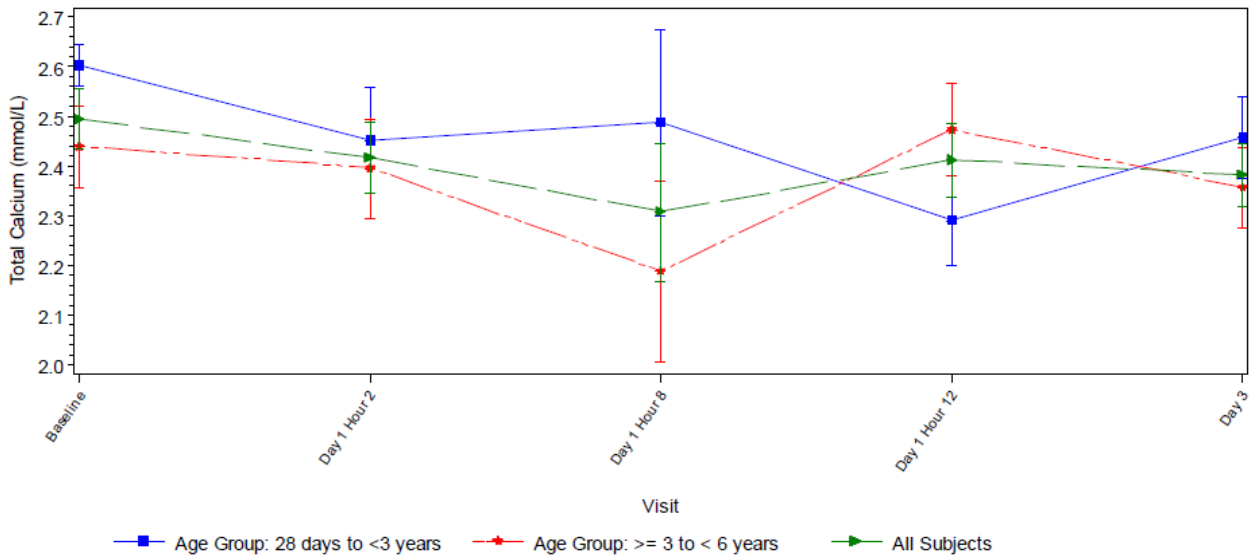
Figure 3. Median PTH Percent Change from Baseline after Oral Administration of Cinacalcet at 0.25 mg/kg to Paediatric Subjects < 6 Years Old with CKD Receiving Dialysis (Study 20090005)



CKD = chronic kidney disease; PTH = intact parathyroid hormone Note: Day 3 = 48 hours postdose.

After administration of cinacalcet, large intersubject variations in PTH concentration were observed, and median percent reductions in plasma PTH concentration appeared to correlate with changes in cinacalcet concentration immediately after dosing. As cinacalcet concentration declined towards undetectable levels, PTH concentration transiently increased and returned to baseline levels by day 3. Slight reductions in serum calcium were observed, followed by a return to baseline. The overall pattern of changes from baseline in mean serum calcium and PTH concentrations was similar for both age groups.

Figure 4. Mean (±SE) Total Serum Calcium Over Time by Age Group and for All Subjects (Study 20090005)



The results from the study 20090005 (< 6 Years) showed only a tendency to slight reductions in serum calcium were observed. Large inter-subject variations in PTH concentrations were observed. A tendency to initial decrease followed by an increase at 12 hours was observed in age group 3-6 years but not in children <3 years. The decrease in PTH was most pronounced at 8 hours in contrast to Study 20030227 which showed a peak in PTH at the same endpoint.

2.6.4. Discussion on clinical pharmacology

The MAH has performed a PK/PD and a PBPK model to predict the pharmacokinetics of cinacalcet in paediatric patients down to 28 days and less than 1 year respectively, as clinical data in this age range is limited.

The sought indication was for children > 28 days. However, the youngest subject recruited and evaluated in any trials was 7 months old. Extrapolation on the basis of modelling- and simulation was performed using pop PK, PKPD and PBPK analyses. The PK/PD analysis was deemed too uncertain. The PBPK was suggested to be used to predict PK in young children as the clinical PK data is very limited in this age group. Even if the PBPK simulations provide a conservative estimate of expected exposures in children the use of PBPK in this context for cinacalcet is too uncertain as the PBPK model in children does not show adequate performance.

The simulations from the popPK model can be used to guide a safe start dose in children down to 3 years of age and while the popPK model can be further improved, it appears passable for this purpose. There remain significant uncertainties that reliable and reasonable dosing recommendations can be derived, especially for the younger age cohorts. As the extrapolation exercises do not provide reliable results for all age groups, the target population might need to be adapted accordingly.

Thus, the dose recommendation below the age of 3 is not supported. The applicant has updated the dosing table in the SmPC accordingly and appropriate weight cut off based on 3 years of age is included.

2.6.5. Clinical efficacy

Dose-response studies and main clinical studies

The primary clinical studies contributing to the evaluation of the efficacy of cinacalcet for the treatment of secondary HPT in paediatric patients with CKD receiving maintenance dialysis therapy are as follows:

I. Study 20070208 was a phase 3, randomized, double-blind, placebo-controlled study in paediatric subjects 6 to < 18 years of age (final analysis).

II. Study 20130356 was a phase 3, randomized, open-label, active-controlled study in paediatric subjects 6 to < 18 years of age (final report submitted with responses, per European Union Paediatric Investigation Plan [EU PIP]).

Supportive data are also provided from the following sources:

III. Study 20090198 was a retrospective chart review that evaluated biochemical markers and safety in children who were < 6 years of age at the time of initiation of cinacalcet treatment (final analysis).

IV. a Bayesian extrapolation study to infer the treatment effects of cinacalcet using pooled data collected from phase 3 adult studies (20000172, 20000183, and 20000188) along with data from paediatric Studies 20070208 and 20130356

V. a phase 2, open-label, single-arm study to assess the safety and tolerability of cinacalcet in addition to standard of care (SOC) in paediatric subjects age 28 days to < 6 years with CKD and secondary HPT receiving dialysis (Study 20110100, final report submitted with responses)

VI. a phase 1, open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of cinacalcet in paediatric subjects age 6 to 18 years with CKD receiving dialysis (Study 20030227; final analysis)

VII. a phase 1, open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of cinacalcet in paediatric subjects age 28 days to < 6 years with CKD and secondary HPT receiving dialysis (Study 20090005, final analysis)

VIII. Study 20140159 Single-arm Extension Study to Characterize the Long-term Safety of Cinacalcet Hydrochloride in the Treatment of Secondary Hyperparathyroidism in Paediatric Subjects With Chronic Kidney Disease on Dialysis

In addition, a cumulative 3 year interim analysis of data collected by the NAPRTCS Dialysis registry on the use of cinacalcet in dialysis participants aged <21 years was submitted and is discussed in the safety section.

Study IV. is assessed in the pharmacokinetic AR and studies VI. and VII. in the pharmacodynamics section.

Main studies

Study 20070208

(Randomized, double-blind, placebo-controlled study in subjects 6 to < 18 years)

Methods

This multicenter study consisted of a 30-week randomized, double-blind, placebo-controlled phase followed by a 30-week open-label phase. All subjects, regardless of treatment assignment received standard of care with vitamin D sterols (calcitriol and its analogs), calcium supplements, and phosphate binders at the discretion of the investigator.

In addition to standard of care, in the double-blind phase, subjects were randomized 1:1 to receive either cinacalcet or placebo. Eligibility was assessed during a 40-day screening period.

The hypothesis for this study was that cinacalcet would reduce PTH by at least 30% in a larger proportion of paediatric CKD subjects with secondary HPT receiving hemodialysis or peritoneal dialysis compared to placebo.

This study was terminated early due to a fatality, see following sections.

Study participants

Eligible subjects were between the ages of 6 to less than 18 years old who had CKD and secondary HPT treated with either hemodialysis or peritoneal dialysis for ≥ 2 months.

Eligible subjects must have had:

- screening iPTH level > 300 pg/mL (31.8 pmol/L) from the central laboratory
- screening serum calcium ≥ 8.8 mg/dL (2.2 mmol/L) from the central laboratory
- serum phosphorus ≥ 4.0 mg/dL (1.3 mmol/L) if age 6 to less than 12 years and ≥ 3.5 mg/dL (1.1 mmol/L) if age 12 to less than 18 years from the central laboratory
- for patients already receiving vitamin D sterols (either calcitriol or a synthetic analog thereof), a stable dose within the preceding 2 months from randomization
- for patients taking a growth hormone, a stable dose defined as no change > 20% within the preceding 2 months prior to randomization

Treatments

Cinacalcet was prepared for oral administration as both capsules for sprinkling and film coated tablets for swallowing. Capsules were developed for the investigational clinical program for paediatric subjects and are not commercially available. Placebo tablets and capsules were presented in identical dosage form.

In both the double-blind and open-label phases, subjects received investigational product orally once daily at **a starting dose of ≤ 0.20 mg/kg** based on dry weight, and the dose was titrated upward according to plasma iPTH and serum calcium levels and subject safety information every 4 weeks. The **maximum dose was 4.2 mg/kg**, not to exceed a total dose of 180 mg for any subject, the labelled recommended adult maximum dose. During the double-blind phase, subjects were randomized to receive cinacalcet or placebo. During the open-label phase, all subjects received cinacalcet.

In the proposed product information, the recommended starting dose is ≤ 0.20 mg/kg. The proposed maximum dose is 2.5 mg/kg/day, which is lower than in the study 20070208, 4.2mg/kg/day.

Outcomes/endpoints

Primary endpoint was defined as achievement of a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP.

Secondary Endpoints were:

- achievement of a mean iPTH value ≤ 300 pg/mL (31.8 pmol/L) during the EAP
- percent change in corrected total serum calcium from baseline to the mean value during the EAP
- percent change from in serum phosphorus from baseline to the mean value during the EAP
- percent change in Ca x P from baseline to the mean value during the EAP
- growth velocity calculated from baseline to week 30, and from week 30 to week 60
- percent change in ionized calcium from baseline to the mean value during the EAP.

Exploratory Endpoints were:

- absolute change in BALP, NTx, CTx, and P1NP from baseline to the week 11, 29, and 59 visits
- percent change in BMD measured at the mid-shaft radius from baseline to week 30 and to week 60, for subjects who participated in the optional dual-energy X-ray absorptiometry scans
- bioavailable and total testosterone levels in male subjects at day 1 and week 29

- Tanner stage at day 1, week 30, and week 60
- plasma cinacalcet concentrations by visit

Sample size

A completed phase 3 clinical trial in the adult dialysis population revealed that among subjects who had baseline iPTH ≥ 300 pg/mL, (31.8 pmol/L), approximately 64% of cinacalcet subjects compared to 13% of placebo subjects achieved a ≥ 30% reduction in mean iPTH from baseline during the EAP using the last observation carried forward method. A similar difference between treatment arms in proportion of subjects achieving such reduction was anticipated in the paediatric dialysis population. The proportions were estimated to be 60% and 15% for the cinacalcet and placebo groups respectively. Using a 2-sided Fisher's exact test at an alpha level of 0.05, a sample size of 100 (50 per treatment group) would provide 99% power to detect the proposed difference. In addition, the study was also sufficiently powered for a smaller treatment difference; the power would be 88% if the observed proportions were 45% and 15%, respectively.

Even though the study was terminated early it was still sufficiently powered. A sample size of 44 (22 per treatment group) would provide 82% power to detect the proposed difference (60% for the cinacalcet group and 15% for the placebo group) with a 2-sided Fisher's exact test at an alpha level of 0.05.

The study was sufficiently powered even though terminated early, however due to the early closure there are more patients with incomplete data that will affect the power.

Randomisation

Subjects between the ages of 6 to less than 18 years of age who met eligibility requirements for the study were randomized at a 1:1 ratio to placebo (control) or cinacalcet (active).

Randomization was stratified by age group (6 to less than 12 years and 12 to less than 18 years of age at the time of randomization.

Dose levels

Summary of adjusted daily doses in the Double-Blind Phase - Study 20070208 (Safety Analysis Set)

	Placebo (N = 21)	Cinacalcet (N = 22)
Initial actual weight adjusted daily dose (mg/kg/day)		
N	21	22
Mean	0.00	0.18
SD	0.00	0.06
SE	0.00	0.01
Median	0.00	0.18
Q1, Q3	0.00, 0.00	0.12, 0.21
Min, Max	0.0, 0.0	0.1, 0.3
Maximum actual weight adjusted daily dose (mg/kg/day)		
N	21	22

Mean	0.00	0.99
SD	0.00	1.26
SE	0.00	0.27
Median	0.00	0.41
Q1, Q3	0.00, 0.00	0.26, 1.55
Min, Max	0.0, 0.0	0.1, 5.7
Average actual weight adjusted daily dose taken during EAP (mg/kg/day)		
N	9	5
Mean	0.00	1.54
SD	0.00	2.04
SE	0.00	0.91
Median	0.00	0.78
Q1, Q3	0.00, 0.00	0.29, 1.28
Min, Max	0.0, 0.0	0.3, 5.1

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N = Number of subjects in the analysis set
Safety analysis set: randomized subjects who received at least one dose of IP
If number of tablets returned were unknown, then subjects were assumed to have received Cinacalcet for the entire dosing period
The dry weight at baseline was used to calculate weight adjusted dose.

Statistical methods

The general statistical hypothesis tested was:

H0: P cinacalcet = P placebo vs. H1: P cinacalcet ≠ P placebo,

where P is the proportion of subjects achieving the primary endpoint, H0 is the null hypothesis that the proportions are the same in the 2 treatment groups (cinacalcet and placebo), and H1 is the alternative hypothesis that there is a difference between the proportions.

Several analysis sets were defined:

- Full Analysis Set, All randomized subjects with at least 1 post-randomization assessment.
- Safety Analysis Set, All randomized subjects who received at least 1 dose of investigational product.
- Per Protocol Analysis Set, All randomized subjects who completed the protocol without important protocol deviations and had at least 1 measurement during the EAP.
- PK/Pharmacodynamic Analyses Set, All subjects with PK data collected at the protocol-specified sampling time points.
- Completer Set, All subjects who completed 30 weeks of the study or at least 12 weeks of study before undergoing kidney transplant.
- Open-Label Safety Analysis Set, All subjects who enrolled in the open-label phase and received at least 1 dose of investigational product.

No interim analysis was planned. Following a fatality in this study, an unplanned interim analysis was performed with a data cutoff of 01 March 2013. The distribution of the unblinded results from the interim analysis was limited to representatives from appropriate departments of the cinacalcet paediatric development team involved in the analysis of the data. With the exception of 2 principal investigators involved in the study design, investigators, site staff, and Amgen representatives interacting with the study sites remained blinded. The results of the interim analysis were provided to United States (US) and European Union (EU) regulators to aid in their evaluation of the cinacalcet paediatric development program.

The last observation carried forward method was used in the analysis of the primary and secondary efficacy endpoints, except for the secondary efficacy endpoint of growth velocity. For subjects who were missing an efficacy measurement during the EAP, the mean of the last 2 available post baseline values in the dose-titration phase were used. If only 1 post baseline value was available, the single value was used.

Cochran-Mantel- Haenzel (CMH) test stratified by baseline age group at 2-sided significance level of 0.05 was used to analyse the primary endpoint.

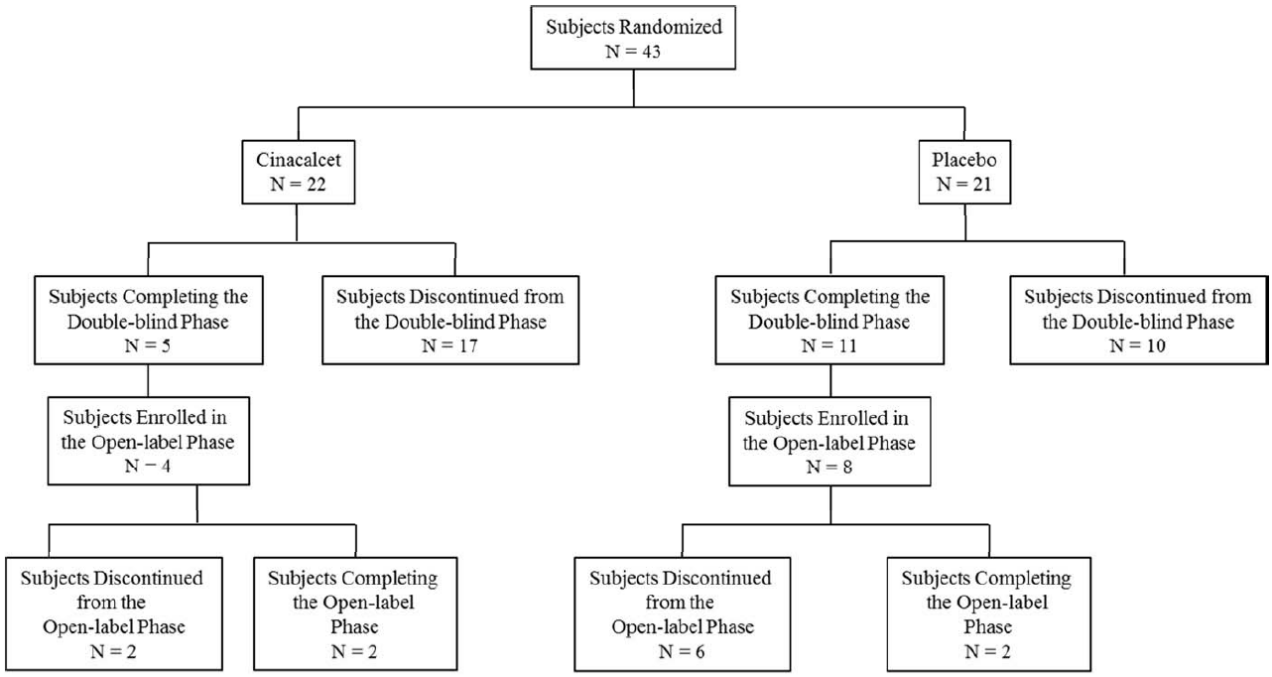
ANCOVA using baseline age group as a covariate or CHM, with multiplicity adjustment using Holm's method, was used for the secondary endpoints.

Four sensitivity analyses were planned:

- Analysis of primary and secondary endpoints based on the per protocol analysis set
- Analysis of primary and secondary endpoints using subjects who complete the EAP
- Analysis of primary and secondary endpoints using data only from visits (EAP or prior to EAP) where subjects are still on IP
- Analysis of proportion of subjects achieving a mean iPTH $\leq$ 300 pg/mL (31.8 pmol/L) during the EAP based on subjects with screening iPTH value $\geq$ 350 pg/mL (37.1 pmol/L)

Results

Participant flow



The most common reason for investigational product discontinuation in the double-blind phase both the cinacalcet group (40.9%) and the placebo group (33.3%) was administrative decision due to the early termination of the study, followed by kidney transplant (27.3% of subjects in the cinacalcet group and 9.5% of subjects in the placebo group). All of these, except one subject in the placebo group, terminated study treatment during the month of January 2013 when the partial clinical hold occurred. Although more subjects in the cinacalcet arm were impacted by study termination, it was considered by chance since the decision and timing of partial-clinical hold was unrelated to individual subject treatment assignment or outcome.

The most common reason for investigational product discontinuation in the *open-label phase* was administrative decision due to the early termination of the study (58.3%).

Table. Subject Disposition in the Double-Blind Phase

	Placebo (N = 21)	Cinacalcet (N = 22)	Total (N = 43)
Study disposition			
Total completed the titration phase	14 (66.7)	10 (45.5)	24 (55.8)
Total completed the DB phase	11 (52.4)	5 (22.7)	16 (37.2)
Total discontinued the study during the DB phase	10 (47.6)	17 (77.3)	27 (62.8)
Ineligibility determined	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	0 (0.0)	1 (4.5)	1 (2.3)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Full consent withdrawn	3 (14.3)	1 (4.5)	4 (9.3)
Administrative decision	5 (23.8)	7 (31.8)	12 (27.9)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (4.5)	1 (2.3)
Protocol-specified criteria	2 (9.5)	6 (27.3)	8 (18.6)
Parathyroidectomy	0 (0.0)	0 (0.0)	0 (0.0)
Kidney Transplant	2 (9.5)	6 (27.3)	8 (18.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (4.5)	1 (2.3)

Baseline data

Table. Demographics and Baseline Characteristics (Enrolled Subjects)

Characteristic	Placebo (N = 21)	Cinacalcet (N = 22)	Total (N = 43)
Age (years)			
Mean (SD)	13.2 (2.9)	13.3 (3.6)	13.2 (3.3)
Sex (n [%])			
Male	11 (52.4)	10 (45.5)	21 (48.8)
Female	10 (47.6)	12 (54.5)	22 (51.2)
Race (n [%])			
White	15 (71.4)	16 (72.7)	31 (72.1)
Black or African American	6 (28.6)	5 (22.7)	11 (25.6)
Other	0 (0.0)	1 (4.5)	1 (2.3)
Ethnicity (n [%])			
Hispanic or Latino	5 (23.8)	3 (13.6)	8 (18.6)
Non-Hispanic or Latino	16 (76.2)	19 (86.4)	35 (81.4)
Baseline iPTH (pg/mL)			
N	21	22	43
Mean (SD)	795.8 (537.9)	757.1 (440.1)	776.0 (484.8)
Median	684.0	676.0	680.0
Minimum, maximum	300, 2246	309, 2407	300, 2407
Baseline corrected total serum calcium (mg/dL)			
N	21	22	43
Mean (SD)	9.88 (0.62)	9.91 (0.54)	9.90 (0.58)
Median	9.80	10.05	9.90
Minimum, maximum	9.0, 11.3	8.9, 10.8	8.9, 11.3
Baseline serum phosphorous (mg/dL)			
N	21	22	43
Mean (SD)	6.37 (1.48)	6.68 (1.78)	6.53 (1.63)
Median	6.00	6.70	6.00
Minimum, maximum	4.5, 10.6	3.7, 12.1	3.7, 12.1

SD = standard deviation; iPTH = intact parathyroid hormone.

Numbers analysed

Table. Analysis Data Sets (Enrolled Subjects)

	Placebo (N = 21) n (%)	Cinacalcet (N = 22) n (%)	Total (N = 43) n (%)
Efficacy (Full) Analysis Set [a]	21 (100)	22 (100)	43 (100)
Safety Analysis Set [b]	21 (100)	22 (100)	43 (100)
Per Protocol Analysis Set [c]	4 (19)	3 (13.6)	7 (16.3)
Completer Set [d]	12 (57.1)	8 (36.4)	20 (46.5)
Open-Label Safety Analysis Set [e]	6 (28.6)	4 (18.2)	10 (23.3)

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N = The number of enrolled subjects
[a] Efficacy (Full) Analysis Set: All randomized subjects with at least one post-baseline assessment will be included.
[b] Safety Analysis Set: Subjects who received at least one dose of investigational product will be included.
[c] Per Protocol Analysis Set: Subjects who completed the protocol without important protocol deviations and have at least one measurement in the EAP will be included.
[d] Completer Set: Subjects who complete 30 weeks of study or 12 weeks of study before undergoing kidney transplant
[e]Open-Label Safety Analysis Set: Subjects who received at least one dose of investigational product in the open-label will be included.

The number of subjects still in the study decreases over time, mainly due to the early termination of the study.

Table 14-1.99.1. Subject Disposition Over Time in the Double-Blind Phase (All Randomized Subjects)

	Placebo (N = 21) n (%)	Cinacalcet (N = 22) n (%)	Total (N = 43) n (%)
Subjects randomized	21 (100.0)	22 (100.0)	43 (100.0)
On study at week 4	19 (90.5)	21 (95.5)	40 (93.0)
On study at week 8	19 (90.5)	19 (86.4)	38 (88.4)
On study at week 12	18 (85.7)	18 (81.8)	36 (83.7)
On study at week 16	15 (71.4)	14 (63.6)	29 (67.4)
On study at week 20	14 (66.7)	11 (50.0)	25 (58.1)
On study at week 24	14 (66.7)	8 (36.4)	22 (51.2)
On study at week 26	11 (52.4)	7 (31.8)	18 (41.9)
On study at week 28	11 (52.4)	5 (22.7)	16 (37.2)

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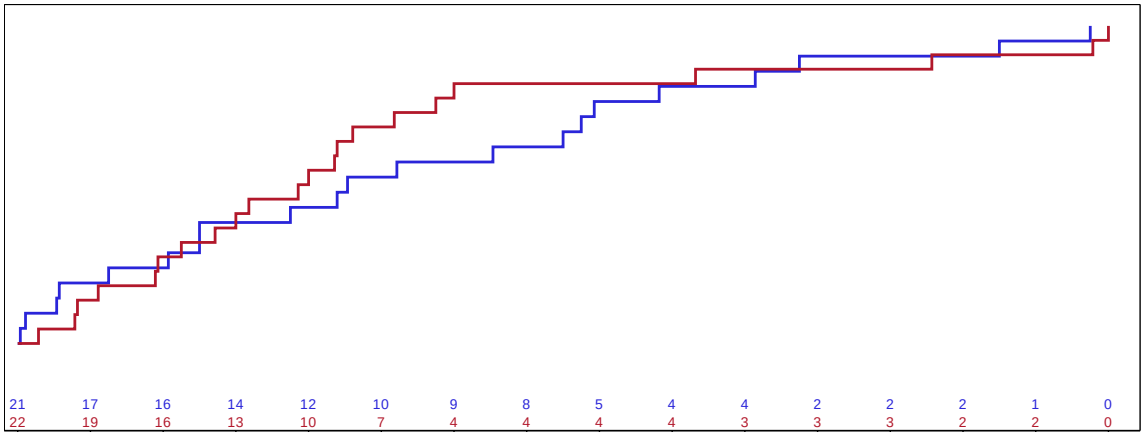
Program: /userdata/stat/calci/sHPT/c20070208/analysis/final/tables/program/t-ds-sum-visit.sas
Output: t14-01-099-001-ds-sum-visit.rtf (Date Generated: 16MAY14:03:09:31) Source Data: adam.adsl

There seems to be an imbalance between treatments in time to discontinuation: 11 (52%) of the placebo treated patients were on study at week 28 compared to only 5 (22.7%) of the cinacalcet treated patients. Although a numeric imbalance in IP discontinuation was observed between treatment groups, the primary reasons for discontinuation (study termination and kidney transplant) were unrelated to treatment received or treatment outcomes.

Figure 1. Time to Discontinuation of Investigational Product in Study 20070208



Treatment groups are based on the randomized treatment.

Outcomes and estimation

Primary endpoint analysis:

Table 14-4.1.1. Results from Stratified Cochran-Mantel-Haenszel Test for the Proportion of Subjects Achieving ≥ 30% Reduction in Mean iPTH from Baseline to the Efficacy Assessment Phase (Full Analysis Set)

	6 - < 12 years		12 - < 18 years		Total	
	Placebo (N=5)	Cinacalcet (N=6)	Placebo (N=16)	Cinacalcet (N=16)	Placebo (N=21)	Cinacalcet (N=22)
Efficacy assessment phase	1 (20.0)	6 (100.0)	4 (25.0)	5 (31.3)	5 (23.8)	11 (50.0)

	CMH Statistic (Chi-square)		Odds Ratio (Cinacalcet/Placebo)		Difference (Cinacalcet-Placebo)[a]	
	Value	p-value	Value	95% CI	Value	95% CI
Test statistic	3.043	0.081	2.41	(0.59, 9.89)	26.19%	(-1.53%, 53.91%)

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N = Number of subjects in the full analysis set
Full analysis set: all subjects who were randomized and with at least one post-baseline assessment
[a] Based on the difference in proportions between treatment groups.
CMH test is stratified by the age group.

Program: /userdata/stat/calci/sHPT/c20070208/analysis/final/tables/program/t-lb-cmh-pth-ge30pct.sas
Output: t14-04-001-001-lb-cmh-pth-ge30pct-eap-full.rtf (Date Generated: 23MAY2014:08:32) Source Data: adam.adsleff

Table 10-1. Proportion of Subjects Achieving ≥ 30% Reduction in Mean iPTH From Baseline to the Efficacy Assessment Phase Excluding iPTH Values Collected After Investigational Product Suspension (Full Analysis Set)

	6 - < 12 years		12 - < 18 years		Total	
	Placebo (N = 5) n (%)	Cinacalcet (N = 6) n (%)	Placebo (N = 16) n (%)	Cinacalcet (N = 16) n (%)	Placebo (N = 21) n (%)	Cinacalcet (N = 22) n (%)
Efficacy assessment phase	1 (20.0)	6 (100.0)	3 (18.8)	6 (37.5)	4 (19.0)	12 (54.5)

	CMH Statistic (Chi-square)		Odds Ratio (Cinacalcet/Placebo)		Difference (Cinacalcet - Placebo)[a]	
	Value	p-value	Value	95% CI	Value	95% CI
Test statistic	5.735	0.017	4.26	(0.99, 18.30)	35.50%	(8.76%, 62.24%)

iPTH = intact parathyroid hormone; CMH = Cochran-Mantel-Haenszel; CI = confidence interval.
Full analysis set: all subjects who were randomized and with at least 1 post-baseline assessment
All data collected 7 days after the clinical hold (31 January 2013) were excluded.
[a] Based on the difference in proportions between treatment groups
Source: *Table 14-4.99.1*.

The first table (14-4.1.1) reports the results of the primary pre-specified analysis, the resulting treatment difference are 26.19% (p=0.081) and the modified primary analysis, which included lab values up to 7 days after the partial clinical hold (administrative suspension of investigational product) results in a treatment difference of 35.50% (p=0.017).

Study 20130356

Final analysis of the study 20130356 was provided as a part of the responses to the Day 120 questions.

Methods

This was a phase 3, randomized, multicenter, open-label, controlled study. Cinacalcet was evaluated in paediatric subjects between the ages of 6 and < 18 years, with secondary hyperparathyroidism (HPT) and chronic kidney disease (CKD) who were receiving either haemodialysis or peritoneal dialysis. Subjects were randomized into 1 of 2 treatment groups; administration of cinacalcet daily in addition to standard of care (SOC) treatment group, or a SOC treatment group. Randomization was stratified by age group (6 to < 12 years and 12 to < 18 years). All subjects received SOC which could include therapy with vitamin D sterols, calcium supplementation, and phosphate binders. Subjects randomized to the cinacalcet group received daily cinacalcet over weeks 1 to 20. Subjects in both treatment groups who completed the 20-week treatment period were eligible to enroll in an open-label extension study (Study 20140159) for further safety follow-up.

Study participants

This study was conducted at 20 centers in Belgium, Czech Republic, France, Greece, Germany, Hungary, Lithuania, Poland, Portugal, Russia, Ukraine, and the US. The first subject was enrolled on 07 November 2014.

A total of 55 subjects were randomized in the study and are included in this report; 27 in the cinacalcet +SOC group and 28 in the SOC group. Two subjects randomized in the cinacalcet + SOC group who did not receive investigational product were included in the cinacalcet + SOC group (as randomized) for the full analysis set, and in the SOC group (as treated) for the safety analysis set. Subjects who completed at least 12 weeks of treatment before undergoing renal transplant or parathyroidectomy were considered to have completed the study (not discontinued) according to the protocol; 36 subjects (65.5%) completed the study (16 cinacalcet + SOC [59.3%], 20 SOC subjects [71.4%]). The primary reason for subjects discontinuation was decision by sponsor (6 cinacalcet + SOC subjects [22.2%], 7 SOC subjects [25.0%]), which includes 10 subjects who discontinued due to study closure on 24 June 2016. Twenty-three subjects (85.2%) in the cinacalcet + SOC group (8 subjects between 6 and <12 years and 15 subjects were between 12 and <18 years) and 26 subjects (92.9%) in the SOC group (9 subjects between 6 and <12 years and 17 subjects were between 12 and <18 years) completed at least 12 weeks of the study.

As of 31 July 2015, a total of 28 subjects were randomized in the study, 13 in the SOC group and 15 in the cinacalcet + SOC group. Two subjects who were randomized to the cinacalcet + SOC group did not receive investigational product. One of these subjects was randomized and withdrawn from the study on the same day (decision by sponsor); this subject was analyzed according to the SOC group in the safety analysis set. The second subject was randomized on 29 July 2015, but no investigational product record was entered as of the interim analysis data cutoff date 31 July 2015 (investigational product was held per protocol due to elevated liver function test results). This subject remained in the study and was analyzed in the cinacalcet + SOC group.

Treatments

The protocol specified doses for use in this study were: 2.5, 5, 10, 15, 30, 60, 90, 120, and 180 mg. The maximum dose of cinacalcet administered at any time during the study was 2.5 mg/kg/day based on the subject's dry weight measured at the screening week-2 visit or 180 mg daily, whichever was lower.

Capsules: Each capsule contained 5 mg of cinacalcet

Tablets were provided in a strength of 30 mg.

Standard of care therapy included the use of vitamin D sterols, calcium supplementation, and phosphate binders.

On day 1, the subject's ionized calcium had to be at or above threshold of ≥ 1.05 mmol/L prior to initiation of treatment. The initial dose of cinacalcet was 0.20 mg/kg/day, and dose adjustments for subjects receiving cinacalcet were assessed at each weekly visit during the treatment period. The daily dose of cinacalcet was only increased at monthly titration visits (week 4, 8, 12, or 16) based on iPTH, corrected calcium levels, ionized calcium and subject safety information. At all weekly visits (including week 4, 8, 12, and 16), the dose was maintained, reduced or withheld based upon the specified criteria.

Outcomes/endpoints

The primary endpoint is proportion of subjects who achieve a ≥ 30% reduction from baseline in mean plasma iPTH during the efficacy assessment period (EAP), defined as weeks 17 to 20

Secondary endpoints are:

- proportion of subjects who achieve a mean iPTH ≤ 300 pg/mL (31.8 pmol/L) during the weeks 17 to 20
- percent change in iPTH from baseline to the mean value during the weeks 17 to 20
- change in corrected total serum calcium from baseline to the mean value during weeks 17 to 20
- change in serum phosphorus from baseline to the mean value during weeks 17 to 20

Sample size

Using the Fisher's exact test at a 2-sided alpha level of 0.05, a sample size of 48 (24 per treatment group) would provide 80% power to detect a difference of 42% in this endpoint (assuming response rates of 62% and 20% in cinacalcet and standard-of-care group, respectively).

Randomisation

Subjects were randomized by the interactive voice response (IVR) / interactive web response (IWR) system in a 1:1 ratio to 1 of the following 2 treatment groups, administration of cinacalcet daily in addition to SOC therapy or SOC therapy. Randomization was stratified by age group (6 to < 12 and 12 to < 18 years of age).

Statistical methods

The general statistical hypothesis to be tested is:

H0: P cinacalcet + SOC = P SOC vs H1: P cinacalcet ≠ P SOC

where P is the proportion of subjects achieving the primary endpoint, H0 is the null hypothesis that the proportions are the same in the two treatment groups (cinacalcet and SOC), and H1 is the alternative hypothesis that there is a difference between the proportions. The comparison of the proportion of subjects achieving the primary endpoint between treatment groups was planned to be performed applying the Haybittle-Peto boundary ($\alpha = 0.001$) to preserve the overall Type 1 error rate. However, due to the limited available data, this analysis was not performed. The final analysis will be performed at $\alpha = 0.05$.

Analysis sets defined are the Full Analysis Set (FAS) used for the primary and secondary endpoints. The FAS includes all randomized subjects. Each subject will be analysed according to the treatment group to which they are randomized. The Completer Set includes all subjects who complete 20 weeks of the study or complete at least 12 weeks of the study before undergoing kidney transplant. The Per Protocol Set (PP) is defined as all randomized subjects who completed the protocol without key important protocol deviations (IPDs) or non-compliance.

The comparison of the proportion of subjects achieving the primary endpoint between the two treatment groups will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline age group (6 - <12 years old or 12 -<18 years old) as determined at randomization. For subjects who do not have a iPTH value during the EAP, the mean of the last two available post-baseline values collected at protocol-specified

visits in the dose-titration phase will be used. If only one post-baseline value is available, this single value will be used. If no post-baseline value is available, the subject in considered a non-responder.

A hierarchical testing procedure will be used to test the primary and biochemical secondary endpoints. The primary endpoint will be tested at a 2-sided significance level of 0.05. The four secondary endpoints will be tested using Holm's method (Holm's 1979) at 0.05 (2-sided) should the primary endpoint achieve a significant result. The overall family-wise type 1 error among the primary and secondary endpoints is controlled at 0.05 by using the above testing procedure.

Sensitivity analyses will be performed for primary and secondary endpoints using the following the completer set and per protocol set.

Results

Disposition of patients

Table 9-1. Subject Disposition With Discontinuation Reason (Enrolled Subjects)

	SOC (N = 28) n (%)	SOC + Cinacalcet (N = 27) n (%)	Total (N = 55) n (%)
Investigational product accounting			
Subjects who never received investigational product	0 (0.0)	2 (7.4)	2 (3.6)
Subjects who received investigational product	28 (100.0)	25 (92.6)	53 (96.4)
Subjects who completed investigational product	19 (67.9)	16 (59.3)	35 (63.6)
Subjects who completed 12 weeks of investigational product	25 (89.3)	22 (81.5)	47 (85.5)
Age 6 to < 12 years	9 (32.1)	8 (29.6)	17 (30.9)
Subjects who discontinued investigational product[a]	9 (32.1)	10 (37.0)	19 (34.5)
Protocol deviation	0 (0.0)	1 (3.7)	1 (1.8)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	0 (0.0)	1 (3.7)	1 (1.8)
Decision by sponsor[b]	6 (21.4)	4 (14.8)	10 (18.2)
Study closure	6 (21.4)	4 (14.8)	10 (18.2)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Requirement for alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)
Protocol-specified criteria	3 (10.7)	4 (14.8)	7 (12.7)
Renal Transplant	3 (10.7)	2 (7.4)	5 (9.1)
Parathyroidectomy	0 (0.0)	0 (0.0)	0 (0.0)
Treatment non-compliance	0 (0.0)	2 (7.4)	2 (3.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Study completion accounting			
Subjects who completed study	20 (71.4)	16 (59.3)	36 (65.5)
Subjects who completed study or 12 weeks of treatment before receiving renal transplant or parathyroidectomy[c]	20 (71.4)	16 (59.3)	36 (65.5)
Subjects who discontinued study	8 (28.6)	11 (40.7)	19 (34.5)
Subject who completed 12 weeks of study	26 (92.9)	23 (85.2)	49 (89.1)
Age 6 to < 12 years	9 (32.1)	8 (29.6)	17 (30.9)
Withdrawal of consent from study	1 (3.6)	5 (18.5)	6 (10.9)
Decision by sponsor[b]	7 (25.0)	6 (22.2)	13 (23.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

N=Number of subjects enrolled; SOC = standard of care
Percentages based on N
All enrolled subjects completed the EOIP and EOS forms except subject 35625004001 who was randomized to SOC + cinacalcet arm and discontinued study the same day as randomization; the subject was unwilling to take syrup-based medications. EOIP form was inactivated and EOS reason was collected as decision by sponsor.
[a] Discontinued study treatment period for SOC subjects
[b] Subjects who discontinued investigational product or study due to study closure in 2016 are summarized under the decision by sponsor category.
[c] Subjects who completed at least 12 weeks of treatment before undergoing kidney transplant or parathyroidectomy are counted as completed study instead of discontinued study according to protocol

Baseline data

Table 9-3. Baseline Demographics (Enrolled Subjects)

	SOC (N = 28)	SOC + Cinacalcet (N = 27)	Total (N = 55)
Sex - n (%)			
Male	13 (46.4)	15 (55.6)	28 (50.9)
Female	15 (53.6)	12 (44.4)	27 (49.1)
Ethnicity - n (%)			
Hispanic/Latino	4 (14.3)	0 (0.0)	4 (7.3)
Not Hispanic/Latino	24 (85.7)	27 (100.0)	51 (92.7)
Race - n (%)			
Black (or African American)	4 (14.3)	5 (18.5)	9 (16.4)
White	23 (82.1)	19 (70.4)	42 (76.4)
Mixed race	0 (0.0)	1 (3.7)	1 (1.8)
White, Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (3.7)	1 (1.8)
Other	1 (3.6)	2 (7.4)	3 (5.5)
Age (years)			
n	28	27	55
Mean	12.4	12.8	12.6
SD	3.5	3.9	3.6
Median	12.0	14.0	13.0
Q1, Q3	10.0, 15.5	9.0, 16.0	10.0, 16.0
Min, Max	6, 17	6, 17	6, 17
Age group - n (%)			
6 - < 12 years	9 (32.1)	9 (33.3)	18 (32.7)
12 - < 18 years	19 (67.9)	18 (66.7)	37 (67.3)

N=Number of subjects enrolled; min = minimum; max = maximum; Q = quartile; SD = standard deviation
Percentages based on N
Source: Table 14-2.2

Numbers analysed

A total of 55 subjects were randomized in the study, 27 in the cinacalcet + SOC group and 28 in the SOC group. Two subjects who were randomized to the cinacalcet + SOC group but did not receive investigational product were included in the cinacalcet + SOC group (as randomized) for the full analysis set, and were included in the SOC group (as treated) for the safety analysis set.

The number of patients included in the per protocol analysis set were 13 in the cinacalcet + SOC group and 25 in the SOC group. The completer set consisted of 35 patients, 15 in the cinacalcet + SOC group and 20 in the SOC group. It should be noted that there is a high rate of exclusion from the Cinacalcet + SOC treatment arm compared to the SOC treatment arm in the PP analysis set.

Outcomes and estimation

The proportion of subjects achieving ≥ 30% reduction from baseline in mean plasma iPTH during weeks 17 to 20 was 22.2% (6 of 27 subjects) in the cinacalcet + SOC group and 32.1% (9 of 28 subjects) in the SOC group (p =0.42, stratified by age); the difference ([cinacalcet + SOC] – [SOC]) in the proportions was -9.9%

(95% confidence interval [CI] -33.3%, 13.4%) (Table 10-1). A summary of the median percent change in iPTH from baseline at scheduled visits, by treatment group, is provided in Figure 10-1.

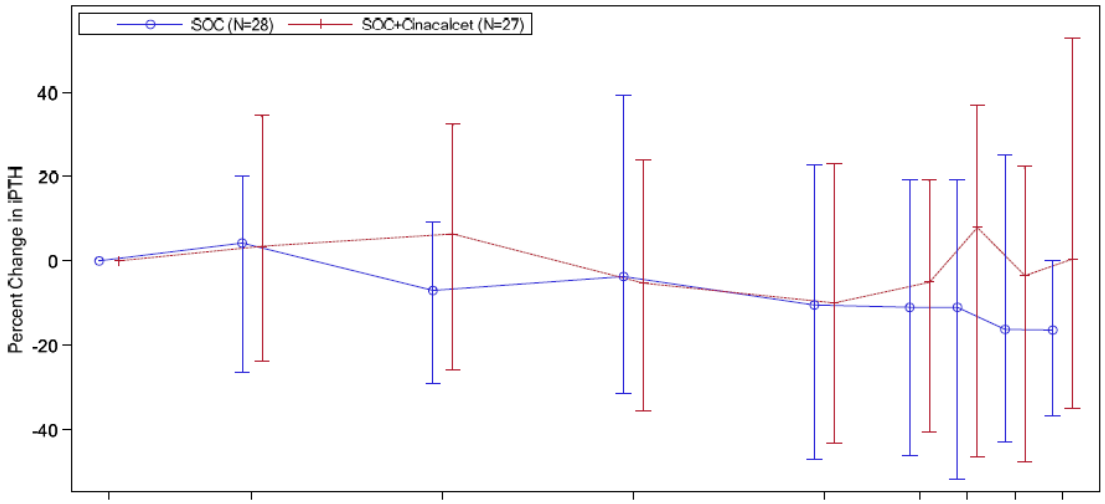
The primary endpoints did not achieve statistical significance; therefore, as pre-specified, the secondary endpoints were not statistically tested. Results of the secondary endpoints also did not show clear treatment effects of cinacalcet on PTH, serum calcium, or serum phosphorus. Results for the primary and secondary endpoints are listed below; nominal p-values are presented without multiplicity adjustment.

Table 10-1. Results From Stratified Cochran-Mantel-Haenszel Test for the Proportion of Subjects Achieving ≥ 30% Reduction in Mean iPTH From Baseline During Weeks 17 to 20 – Last Value Carried Forward (Full Analysis Set)

	6-<12 years		12-<18 years		Total	
	SOC (N=9) n (%)	SOC+Cinacalcet (N=9) n (%)	SOC (N=19) n (%)	SOC+Cinacalcet (N=18) n (%)	SOC (N=28) n (%)	SOC+Cinacalcet (N=27) n (%)
Week 17 and 20	4 (44.4)	1 (11.1)	5 (26.3)	5 (27.8)	9 (32.1)	6 (22.2)
	CMH Statistic (Chi-square)		Odds Ratio (SOC+Cinacalcet /SOC)		Difference (SOC+Cinacalcet - SOC)[a]	
	Value	p-value	Value	95% CI	Value	95% CI
Test statistic	0.658	0.42	0.614	(0.188, 2.003)	-9.9%	(-33.3%, 13.4%)

N = Number of subjects in the analysis set
[a]Based on the difference in proportions between treatment groups.
CMH test is stratified by the age group

Figure 10-1. Median (IQR) Percent Change in iPTH From Baseline at Scheduled Visits by Treatment Group (Full Analysis Set)



SOC (N=28)	28	27	27	24	24	17	16	18	19
SOC+Cinacalcet (N=27)	25	24	21	20	19	16	14	14	11

iPTH = intact parathyroid hormone; IQR = interquartile range; SOC = standard of care

Table 10-3. Summary of Secondary Endpoints (Full Analysis Set)

Primary and Secondary Endpoints[a]	SOC (N=28)	Cinacalcet + SOC (N=27)	Treatment Difference (95% CI) Nominal p-value
Proportion of subjects achieved mean iPTH ≤ 300 pg/mL during weeks 17 to 20 - n (%)	5 (17.9%)	2 (7.4%)	-10.4% (-27.7%, 6.8%) 0.25
Percent change in iPTH from baseline to the mean value during Weeks 17 to 20 - %	-11.3% (-33.7%, 11.0%)	7.7% (-15.9%, 31.3%)	19.0% (-12.5%, 50.5%) 0.23
Change in corrected serum calcium from baseline to the mean value during Weeks 17 to 20 - mg/dL	0.06 (-0.19, 0.31)	-0.28 (-0.55, -0.01)	-0.34 (-0.70, 0.01) 0.059
Change in serum phosphorus from baseline to the mean value during Weeks 17 to 20 - mg/dL	-0.09 (-0.60, 0.43)	0.67 (0.14, 1.21)	0.76 (0.04, 1.48) 0.039

iPTH = intact parathyroid hormone; SOC = standard of care
[a] Last value carried forward (LVCF) imputation was applied
Source: Tables 14-4.3.1, Table 14-4.4.1, Table 14-4.5.1, Table 14-4.6.1

Growth velocity was an exploratory endpoint for this study. The mean (95% CI) estimated growth velocity from baseline to week 20 was 3.67 (1.16, 6.18) cm/year for subjects in the cinacalcet + SOC group and 3.42 (1.20, 5.65) cm/year for subjects in the SOC group. Growth velocity was not significantly different between treatment groups (p = 0.88), after adjusting for age.

The mean (SD) duration of exposure in the cinacalcet + SOC group was 112.8 (41.0) days. The mean (SD) actual weight adjusted daily dose of cinacalcet taken was 0.398 (0.467) mg/kg/day during weeks 17 to 20. The mean (SD) maximum actual weight-adjusted daily dose was 0.55 (0.484) mg/kg/day.

Dosing rules based on weekly assessments of calcium using protocol specified ionized calcium thresholds resulted in a high rate of dose interruptions and dose reductions that precluded dose titration to achieve adequate cinacalcet exposure and iPTH reduction in most subjects. Dose reduction and interruptions occurred even in situations where the corrected serum calcium value would have allowed dose maintenance or increase. During the entire treatment period, 23 of 25 subjects (92.0%) had ≥ 1 dose withheld or reduced, and 19 of 25 subjects (76.0%) had ≥ 1 dose of cinacalcet withheld. Reasons for dose withholding included: per protocol (11 subjects [44.0%]), noncompliance (10 subjects [40.0%]), and adverse event (6 subjects [24.0%], and other (4 subjects [16.0%]).

Upon investigation of the reason for the lower than expected efficacy of cinacalcet, it was noted that the mean dose of cinacalcet during the EAP in Study 20130356 was approximately 80% lower than the mean dose during the EAP in Study 20070208.

In the day 120 LoQ, the MAH was asked to clarify if criteria for dose adjustments in study 20130356 were similar to the recommendations proposed in the SmPC section 4.2 for paediatric patients and discuss any possible differences.

Dose increases and dose reductions/withholding were managed in Study 20130356 using protocol-specified criteria. In this study, dose adjustments and withholding were based on plasma intact parathyroid hormone (iPTH), ionized calcium and corrected serum calcium levels, and the subject's safety status. Dose increases were allowed every 4 weeks. The dose was increased if the plasma iPTH was ≥ 300 pg/mL, provided the subject did not meet any criteria for dose maintenance, dose reduction, or dose withholding, there was no evidence of noncompliance, and the subject had not reached the maximum allowed dose. If cinacalcet treatment had been stopped for more than 14 days, the protocol required that subjects restart treatment at the recommended starting dose.

Study 20090198

Study 20090198 was a multicentre, retrospective, observational chart review.

A total of 23 paediatric subjects were identified for retrospective collection of data for this study. Medical charts were reviewed in an effort to describe changes in biochemical markers and the occurrence of safety events in children from birth to < 6 years of age with secondary HPT and CKD receiving dialysis who were treated off label with cinacalcet.

Data collection for these subjects was discontinued for the following reasons: cinacalcet use was terminated (8 subjects), kidney transplant (6 subjects), the data collection period ended (7 subjects), or for other reasons (2 subjects). The reasons for terminating cinacalcet use were the following: administrative decision (4 subjects), death (2 subjects), noncompliance (1 subject), or adverse drug reaction (1 subject).

The primary objective of the study was to describe changes in biochemical markers (intact PTH [iPTH], calcium, and phosphorus concentrations) in paediatric subjects with CKD and secondary HPT on dialysis following initiation of cinacalcet treatment.

Other objectives of the study included:

- To describe the safety and tolerability of cinacalcet.
- To describe the method of administration of cinacalcet (e.g., crushing or splitting of tablets), route, dose, and frequency.
- To describe the use of other medications (e.g., vitamin D sterols, phosphate binders, 1,25 dihydroxyvitamin D, growth hormone, erythropoietin).
- To describe markers of bone turnover and bone mineral density if available.

Methods

Data were obtained from subject medical charts from paediatric nephrologists in hospital and community-based practices, as well as dialysis centers registered in various existing networks. This study consisted of retrospective data collection both prior to initiating treatment with cinacalcet (baseline) and after initiating treatment with cinacalcet (treatment) in all subjects.

For the estimation of biochemical parameters, data obtained prior to initiating treatment (baseline) and 1, 2, and 3 months after initiating treatment with cinacalcet, if available, were collected. Time points were

approximate. Acceptable variation was ± 2 weeks for the month 1, 2, and 3 time point. Additional data of interest (e.g., biochemical parameters) were collected beyond 3 months after initiation of treatment with cinacalcet for as long as the subject continued to receive treatment and was < 6 years of age.

To identify possible adverse drug reactions to cinacalcet, retrospective record review for safety data continued for as long as the subject continued to receive treatment with cinacalcet and was ≤ 7 years of age.

Baseline data collection/abstraction included demographics and medical and surgical history. In addition, the following data were abstracted from subject medical charts for baseline and during the period of treatment with cinacalcet: weight, height or length, Tanner stage, vital signs, medical and surgical history, kidney transplant status, hospitalizations, medication use, biochemistry (e.g., iPTH, calcium, and phosphorus).

During the treatment period, cinacalcet use (dose, frequency, route, and method of administration) was recorded.

Number of Subjects Included in Study: 23

Sex: 14 males, 9 females

Age: Mean age (SD), 32.6 months (15.1)

The youngest subject recruited and evaluated in any of the clinical trials was 7 months old.

Ethnicity (Race): 13 white or Caucasian, 4 black or African Americans, 6 other

Main criteria for inclusion:

- Diagnosed with CKD requiring maintenance dialysis (peritoneal or hemodialysis).
- Diagnosed with secondary HPT.
- Treated with at least 1 dose of cinacalcet at any time prior to 31 August 2009.
- Age from birth to < 6 years at the time treatment with cinacalcet was initiated.

Statistical Methods:

The distribution for key variables such as laboratory parameters and cinacalcet dosing were evaluated for outliers and missing data. Queries were generated for obvious spurious values and inconsistent data. Owing to the retrospective and observational nature of this study, it was anticipated that there would be missing data. No imputation of missing data was carried out.

The following estimates and 95% CIs were provided to address the study primary objectives. All subjects who had at least 1 post-baseline measurement of the respective biomarker were included in the analysis of that time point:

- Percent change in iPTH concentration from baseline to month 1, 2, and 3.
- Proportion of subjects who achieved ≥ 30% reduction in iPTH concentration from baseline to month 1, 2, and 3.
- Percent change in serum calcium concentration from baseline to month 1, 2, and 3.
- Percent change in phosphorous from baseline to month 1, 2, and 3.

Results

Subject Characteristics:

Fifteen study centers identified retrospectively collected data from 23 paediatric subjects who met the eligibility criteria. Data collection for these subjects was discontinued for the following reasons: cinacalcet use was terminated (8 subjects), kidney transplant (6 subjects), the data collection period ended (7 subjects), or for other reasons (2 subjects). The reasons for terminating cinacalcet use were the following: administrative decision (4 subjects), death (2 subjects), noncompliance (1 subject), or adverse drug reaction (1 subject).

The mean (SD) weight and height of subjects at baseline was 12.6 (4.5) kg and 83.3 (11.7) cm, respectively.

Baseline comorbid conditions that occurred in ≥ 10% of subjects were growth retardation (65%), failure to thrive (43%), hypertension (39%), vision impairment (22%), respiratory disease other than asthma and cystic fibrosis (17%), fracture (17%), liver disease (13%), other gastrointestinal disease (13%), other musculoskeletal (13%).

All 23 enrolled subjects had CKD; 4 subjects had a history of kidney transplant.

At baseline, 19 (83%) subjects were receiving peritoneal dialysis and 3 (13%) subjects were receiving haemodialysis. The mean duration from initiation of dialysis to initiation of cinacalcet treatment was 19.47 months.

The mean (SD) iPTH concentration was 1380.7 (800.0) pg/mL indicating inadequately controlled secondary HPT at baseline. Mean serum calcium concentration was within normal limits (i.e., 8.9 to 10.3 mg/dL).

Dose Administration

Fifteen of the 23 enrolled subjects were administered cinacalcet orally. Nineteen subjects received their medication as a crushed tablet; 7 subjects were administered cinacalcet by nasogastric (NG) tube.

The mean (SD) duration of exposure was 274.17 (245.53) days, with a minimum exposure of 34 days and a maximum of 1036 days.

The median (min, max) initial weight-adjusted daily dose was 0.61 (0.1, 1.9) mg/kg/day. The median (min, max) maximum weight-adjusted daily dose over the course of treatment was 1.40 (0.4, 5.6) mg/kg/day. Seventeen of 23 (74%) subjects had at least 3 months of cinacalcet treatment. A review of dose administration by individual subject showed variable dosing regimens with doses ranging from 2.5 mg to 60 mg.

Clinical Laboratory Evaluations

Cinacalcet treatment was assessed by the changes in biomarkers indicative of secondary HPT.

Biochemical indices were collected at monthly intervals. Height and weight measurements were also collected monthly.

The Research Project Plan (RPP) for this study targeted changes in biomarkers over a 3-month period; however, data were available for most subjects beyond 3 months. Summary statistics for the group were generated if the number of subjects with data was greater than 5 at any time point.

Intact Parathyroid Hormone (iPTH)

Intact PTH is summarized for all 23 enrolled subjects by mean changes from baseline, mean percent changes from baseline, and the proportion of subjects with ≥ 30% reduction from baseline. One subject (19848001001) had a low baseline iPTH value (101.8 pg/mL). Upon query by the sponsor, the site confirmed that the sample had been collected prior to initiation of cinacalcet and further, that the baseline sample had been possibly diluted 10-fold. The subject's iPTH values were 1201.9 pg/mL and 1398.0 pg/mL at Month 1 and Month 3, respectively.

Because the reliability of the baseline value for this subject was uncertain, summaries of iPTH results excluding data from this subject were also provided.

Mean Change from Baseline in iPTH

Mean (SD) iPTH concentrations ranged from 1312.3 (612.9) pg/mL at month 1 to 562.4 (478.2) pg/mL at month 6. Mean iPTH concentrations decreased from baseline at every time point except month 4. The mean (SD) decreases ranged from -86.8 (815.9) pg/mL at month 1 to -743.8 (910.1) pg/mL at month 6.

A mean increase over baseline of 90.7 (1011.2) pg/mL was observed at month 4. The exclusion of data from Subject 19848001001 resulted in greater mean decreases from baseline at month 1 (-156.6 pg/mL), month 3 (-634.4 pg/mL), month 5 (-400.2 pg/mL), and month 6 (-1056.0 pg/mL). Mean changes from baseline at months 2, 4, and 7 were the same in both datasets.

Mean iPTH (mg/dL) at Selected Time Points (Enrolled Subjects)

	Cinacalcet (N = 23)
Baseline	
n	21
Mean	1380.7
SD	800.0
SE	174.6
Median	1416.0
Q1, Q3	727.0, 1878.0
Min, Max	102, 2845
Month 1	
n	18
Mean	1312.3
SD	612.9
SE	144.5
Median	1318.5
Q1, Q3	1011.0, 1722.0
Min, Max	128, 2345
Month 6	
n	7
Mean	562.4
SD	478.2
SE	180.8
Median	374.0
Q1, Q3	226.0, 1143.0
Min, Max	10, 1231

Table. Proportion of Subjects who Achieved ≥ 30% Reduction From Baseline in iPTH (Enrolled Subjects)

	Cinacalcet (N=23)[a]	95% C.I.
Month 1	6/18 (33)	(0.13 , 0.59)
Month 2	5/12 (42)	(0.15 , 0.72)
Month 3	7/12 (58)	(0.28 , 0.85)
Month 4	2/5 (40)	(0.05 , 0.85)
Month 5	3/7 (43)	(0.10 , 0.82)
Month 6	6/7 (86)	(0.42 , 1.00)
Month 7	3/5 (60)	(0.15 , 0.95)

N = number of subjects enrolled.
95% C.I. is obtained using exact method based on binomial distribution.
Subject 19848001001 had substantial increase in iPTH compared to baseline that might be caused by improper dilution of the iPTH assay
[a] Time points up to the last with 5 or more subjects available were included; data were not available for every subject at every timepoint.

Serum Calcium

Total and ionized calcium were assessed by mean changes from baseline and mean percent changes from baseline.

Total Calcium

Mean (SD) calcium concentrations ranged from 8.72 (1.11) mg/dL at month 1 to 9.76 (1.13) at month 2. Mean decreases from baseline in total calcium were observed at every time point except month 2. The largest mean (SD) decreases from baseline were -0.59 (0.83) mg/dL observed at month 1 and -0.61 (0.72) mg/dL observed at month 5. The mean (SD) percent decreases from baseline at these same time points were -6.45% (8.98%) and -6.23% (6.91%), respectively. In general, mean serum calcium concentrations remained within normal limits during treatment (i.e., 8.9 to 10.3 mg/dL).

Corrected calcium values were available for 4 subjects only; therefore, summary statistics are not provided.

Table. Mean Total Calcium (mg/dL) at Selected Time Points (Enrolled Subjects)

	Cinacalcet (N = 23)
Baseline	
n	23
Mean	9.47
SD	0.83
SE	0.17
Median	9.50
Q1, Q3	8.96, 9.90
Min, Max	8.0, 11.4
Month 1	
n	20
Mean	8.72
SD	1.11
SE	0.25
Median	8.80
Q1, Q3	7.95, 9.75
Min, Max	6.4, 10.4
Month 6	
n	11
Mean	9.09
SD	0.82
SE	0.25
Median	8.90
Q1, Q3	8.60, 9.80
Min, Max	7.9, 10.7

Ionized Calcium

Ionized calcium data were available for 8 subjects.

Mean (SD) changes from baseline in ionized calcium were observed at every time point, ranging from a decrease of -0.15 (0.15) mg/dL at month 1 to an increase of 1.57 (2.83) mg/dL at month 2. By month 3, mean concentrations were approaching baseline levels. The mean (SD) percent change from baseline at month 2 was 34.97% (65.36%).

Intact PTH, Calcium, and Ionized Calcium Data through 17 Months

One subject (19848001001) had iPTH, calcium and ionized calcium data available through 17 months.

Phosphorus

Phosphorus was assessed by mean changes from baseline and mean percent changes from baseline.

Mean decreases from baseline in phosphorus were observed at every time point. The largest mean (SD) decrease from baseline was -1.48 (2.32) mg/dL observed at month 2. The mean (SD) percent decrease from baseline at this same time point was -20.79% (30.52%).

Mean percent increases from baseline were observed at month 1, month 5, month 6, and month 7, which was inconsistent with the mean decreases from baseline observed at these time points. This difference is likely the result of substantial increases over baseline for 2 subjects (19826003001 and 19866012001). In general, mean serum phosphorus concentrations remained within normal limits during treatment (i.e., 4.5 to 8.0 mg/dL).

Creatinine

Mean creatinine concentrations remained relatively unchanged over baseline at month 1 and month 2. Thereafter, mean (SD) increases from baseline were observed at all time points, ranging from 0.15 (1.76) mg/dL at month 3 to 2.06 (1.89) mg/dL at month 7. Mean (SD) percent increases over baseline ranged from 8.09% (33.35%) at month 3 to 53.14% (62.39%) at month 7.

Hemoglobin

Mean (SD) decreases from baseline in hemoglobin concentrations were observed at months 1, 4, 5, 6, and 7 ranging from -0.06 (2.17) g/dL at month 6 to -0.79 (2.36) g/dL at month 4.

Biochemical Markers for Bone Turnover

Bone biomarker measurements were only recorded in medical charts for 2 subjects: osteocalcin concentration in 1 subject (3 records) and bone-specific alkaline phosphatase concentration in 1 subject (2 records).

Radiographic Evaluation of Bone Mineral Density

Radiographic assessment of bone was not recorded in any of the subject medical charts.

Weight

Mean changes from baseline in weight were observed at every time point except month 3. The largest mean (SD) change in weight of -0.8 (1.1) kg was observed at month 4. The mean (SD) weight at baseline was 12.6 (4.5) kg.

Mean height (length) increased from baseline at every time point. By month 3, mean (SD) height increased over baseline by 3.2 (3.5) cm. The mean (SD) height at baseline was 83.3 (11.7) cm

MAH Conclusions: This chart review showed that cinacalcet in a mean dose range of 0.81 to1.87 mg/kg/day (SD 0.54-1.30) used in children < 6 years of age with CKD and secondary HPT had expected effects on biochemical markers of secondary HPT.

In summary, the study 20090198 was a retrospective, observational chart review in 23 paediatric subjects from birth to < 6 years of age (mean age 32.6 months). The subjects received Cinacalcet off-label. The mean baseline iPTH concentration was 1380.7 pg/mL indicating inadequately controlled secondary HPT, however, baseline total serum calcium concentrations were within normal limits.

Nineteen subjects received their medication as a crushed tablet; 7 subjects were administered cinacalcet by nasogastric (NG) tube.

Both dose strength and frequency of administration varied among subjects. The median (min, max) maximum weight-adjusted daily dose over the course of treatment was 1.40 (0.4, 5.6) mg/kg/day (the currently proposed paediatric max dose is 2.5 mg/kg/day.

Mean iPTH concentrations generally decreased and ranged from 1312.3 (612.9) pg/mL at month 1 to 562.4 (478.2) pg/mL at month 6. About half of the subjects had iPTH value at month 6.

Mean decreases from baseline in total calcium were observed. The largest mean (SD) decreases from baseline were -0.59 (0.83) mg/dL observed at month 1 and -0.61 (0.72) mg/dL observed at month 5.

In general, mean serum phosphorus concentrations remained within normal limits during treatment (i.e., 4.5 to 8.0 mg/dL).

Although a research plan was developed prospectively for this chart review, this review shares similar limitations to other retrospective observational analyses, i.e., propensity for missing data, accuracy and completeness of data quality, and chart selection determination. Consequently, no firm conclusions of efficacy in patients < 6 years can be drawn.

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

Bayesian Extrapolation Study

Methods

An extrapolation analysis was implemented to leverage data from cinacalcet studies in adults to support the data from paediatric subjects. This approach was justified for the cinacalcet paediatric program since important principles of extrapolation defined by the European Medicines Agency (EMA, 2013) (i.e., similarities in disease progression, response to treatment, and concentration-response between the source and target populations) were met and the feasibility of conducting large studies in the target population was restricted (EMA, 2013; Dunne et al, 2011; Manolis and Pons, 2009).

The Bayesian extrapolation study that was submitted with the Marketing Authorisation Application (MAA) used data from paediatric Study 20070208 (N = 43) and pooled data from adult Studies 20000172, 20000183, and 20000188 (N = 1136) to make inferences on the treatment effect of cinacalcet on intact parathyroid hormone (iPTH). Interim analysis data from paediatric Study 20130356 (N = 28) was also included to make inferences on the treatment effect of cinacalcet on corrected calcium (cCa) in paediatric subjects. This analysis (submitted with the MAA) is referred to as the original Bayesian analysis throughout this response.

As requested and agreed upon in the Day 120 clarification meeting (D120 Clarification Meeting Minutes), the original Bayesian analysis has been repeated for both efficacy and safety endpoints to include all available paediatric data, including the final data from Studies 20070208, 20130356 and 20110100, and interim data from Study 20140159 (data cutoff date 29 April 2016). The efficacy results from the repeated Bayesian

analyses are provided below. This analysis (the repeated efficacy and safety endpoints with all available paediatric data) is referred to as the repeated Bayesian analysis.

The efficacy endpoints for this extrapolation study were the following:

- achievement of a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP
- percent change in plasma iPTH from baseline during the study

In the Bayesian analysis of the efficacy endpoints, data from adult studies were used to derive the prior distributions and paediatric data from Study 20070208 were used as the likelihood. The binary efficacy endpoint, achievement of a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP, was fitted by a Bayesian binomial model and the posterior median and the 95% posterior credible interval of the response rate were provided. A 30% difference in response rates for efficacy (where response was defined as achievement of a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP) between the placebo and cinacalcet groups were considered a clinically meaningful treatment effect size. The Bayesian inference on the response rate for efficacy was based on the posterior probabilities that the true response rate difference was greater than the assumed effect size π = 30% and π = 0%. For the primary analysis, a weight of 5% was applied to the adult data to balance the adult and paediatric contributions; other weights were used as sensitivity analyses to assess the robustness of the prior assumptions.

Data for the binary response efficacy endpoint (achievement of a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP) from the pooled adult studies and all available paediatric data, including the final data from Studies 20070208, 20130356, 20110100 and interim data from Study 20140159, are summarized in Table 1.

Table 2. Summary of Observed Binary Efficacy Endpoint in Pooled Adult Studies and Paediatric Studies (All Paediatric Data Included)

	Response Rate (%)				
	Placebo/SOC		Cinacalcet Group		Difference
Study	n/N	Rate (95% CI[a])	n/N	Rate (95% CI[a])	Rate Difference (95% CI[a])
Adult	59/471	12.5 (9.5, 15.5)	450/665	67.7 (64.1, 71.2)	55.1 (50.5, 59.8)
20070208	4/21	19.0 (2.3, 35.8)	12/22	54.5 (33.7, 75.4)	35.5 (8.8, 62.2)
20130356	9/28	32.1 (14.8, 49.4)	6/27	22.2 (6.5, 37.9)	-9.9 (-33.3, 13.4)
20110100	-	-	12/17	70.6 (48.9, 92.2)	-
20140159	-	-	2/9	22.2 (-4.9, 49.4)	-

CI = confidence interval; n = number of subjects who achieved efficacy endpoint; N = total number of subjects enrolled in the corresponding treatment group; SOC = standard of care
[a] Confidence intervals were calculated based on normal approximation.
Program: /userdata/stat/calci/meta/Extrapolation_2015/analysis/2016_eu_rtq/stats/program/binary/Binary.R
Source: /userdata/stat/calci/meta/Extrapolation_2015/analysis/2015-for_PIP/statdata/ISS_ISE
/userdata/stat/calci/meta/Extrapolation_2015/analysis/2016_eu_rtq/statdata/bayeudm

Table 3. Posterior Probability of ≥ 30% Reduction From Baseline in Mean Intact Parathyroid Hormone During the Efficacy Assessment Phase (Binary Model) (All Paediatric Data Included)

	Response Rate (%)			Probability (%) of True Rate Difference > π			
Weight(ω)	Placebo/SOC (95% CrI)	Cinacalcet (95% CrI)	Difference (95% CrI)	π = 0%	π = 10%	π = 20%	π = 30%
10%	19.6 (12.3, 28.2)	54.4 (46.2, 62.8)	34.7 (23.0, 46.0)	100	100	99.2	79.5
5%	**21.7 (13.4, 32.0)**	**50.3 (40.9, 59.8)**	**28.4 (14.9, 41.1)**	**100**	**99.6**	**88.9**	**40.9**
2%	24.0 (14.4, 36.0)	46.4 (36.3, 56.8)	22.5 (7.0, 36.5)	99.7	94.1	62.5	15.0
1%	25.0 (14.7, 37.8)	44.6 (34.2, 55.6)	19.4 (3.0, 34.8)	98.9	87.6	47.6	9.3
0%	26.3 (15.2, 39.8)	42.7 (31.6, 53.8)	16.2 (-1.2, 32.2)	96.7	76.9	32.5	4.6

CrI = credible interval; SOC = standard of care
The weight of 5% (in bold) was predefined for the primary analysis.
Program: /userdata/stat/calci/meta/Extrapolation_2015/analysis/2016_eu_rtq/stats/program/binary/Binary.R
Source: /userdata/stat/calci/meta/Extrapolation_2015/analysis/2016_eu_rtq/statdata/bayeudm

The results from the Bayesian extrapolation analysis of the longitudinal model for the percent change in iPTH over time supported the results for the binary endpoint in the extrapolation study. The percent change from baseline iPTH for the cinacalcet group had a decreasing trend in the first 12 weeks and then became stable, whereas a slightly increasing trend for the placebo group was observed over the entire study period.

Supportive studies

Study 20110100

A phase 2, open-label, single-arm study to assess the safety and tolerability of cinacalcet in addition to standard of care (SOC) in paediatric subjects age 28 days to < 6 years with CKD and secondary HPT receiving dialysis.

Primary Endpoint:

Proportion of subjects who develop corrected serum calcium levels < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, and < 8.4 mg/dL (2.1 mmol/L) for ages ≥ 2 to < 6 years

Secondary Endpoints:

• Proportion of subjects who develop corrected serum calcium levels < 8.8 mg/dL (2.2 mmol/L) during the study

• PK parameters at week 12 (e.g., maximum plasma concentration (Cmax), area under the curve (AUC), apparent clearance (CL/F), apparent volume of distribution (V/F))

• The percent change of plasma intact parathyroid hormone (iPTH), corrected total serum calcium, serum phosphorous, and Ca x P from baseline to scheduled visits during the study

• Proportion of subjects who have any decreases in iPTH of > 30% from baseline at two consecutive measurements

• Achievement of ≥ 30% reduction from baseline in plasma iPTH during the study

• Proportion of subjects who have any normal iPTH values between 200 and 300 pg/mL at two consecutive measurements

• Achievement of plasma iPTH values < 300 pg/mL (31.8 pmol/L) during the study

Safety Endpoints:

• Nature, frequency, severity, and relationship to treatment of all adverse events, including those of special interest (including hypocalcemia, seizures, and infections), reported during the study

• Subject incidence of hypocalcemia throughout the study

• Changes in laboratory parameters, including clinical chemistry, at scheduled visits

• Changes in vital signs at scheduled visits

• Electrocardiograms (ECGs)

Subjects will remain on study for 26 weeks or until time of kidney transplantation, whichever comes first. All subjects, in addition to receiving cinacalcet, will receive standard of care, which may include vitamin D sterols (25 OH vitamin D and/or 1,25 OH vitamin D and its analogs).

Subjects who complete the 26-week study may be eligible to participate in an extension study (Study 20140159).

Summary of Subject Eligibility Criteria: Subjects between the ages of 28 days to < 6 years of age, who have CKD and SHPT undergoing either HD or PD at the time of screening (subjects 6 months or older should have been receiving dialysis for ≥ 1 month).

Eligible subjects must have:

• Screening plasma iPTH level > 300 pg/mL (31.8 pmol/L) from the central laboratory, and not have received any cinacalcet therapy for at least 30 days prior to start of dosing

• Screening corrected calcium from the central laboratory:

o ≥ 9.4 mg/dL (2.35 mmol/L) if age 28 days to < 2 years

o ≥ 8.8 mg/dL (2.2 mmol/L) if age ≥ 2 to < 6 years

• Serum phosphorus from the central laboratory:

o ≥ 5.0 mg/dL (1.25 mmol/L) if age 28 days to < 1 year

o ≥ 4.5 mg/dL (1.13 mmol/L) if age ≥ 1 to < 6 years

• SHPT not due to vitamin D deficiency, per investigator assessment

Statistical Considerations: There is no formal statistical testing for this study. The analysis for the primary and secondary endpoints will be descriptive in nature.

Descriptive statistics will be used to summarize data for continuous variables (including n, mean, standard deviation (SD) or standard error (SE), median, 25th (Q1) and 75th (Q3) percentiles, minimum and maximum values, and corresponding 95% confidence intervals (CIs), where applicable). For categorical variables, the

number and percentage of subjects in each category will be reported. Results are presented overall and separately for subjects enrolled before (cohort 1) and after (cohort 2) the partial clinical hold.

Results

A total of 18 subjects were enrolled into the study: 8 before the partial clinical hold (cohort 1), and 10 after the partial clinical hold (cohort 2). One subject in cohort 1 did not receive cinacalcet; all other subjects received at least 1 dose and were included in the Safety Analysis Set. Eleven subjects overall (61.1%); 37.5% in cohort 1, and 80.0% in cohort 2; completed at least 12 weeks of treatment. Four subjects (22.2% overall, 2 in each cohort) completed the study: 3 completed 26 weeks, and 1(cohort 1) completed 12 weeks, which was followed by a kidney transplant. Fourteen subjects (77.8%) discontinued the study. The most common reason for discontinuation was administrative decision, which was due to a partial clinical hold in 2013 for cohort 1 (4 subjects) and study closure in June 2016 for cohort 2 (5 subjects).

Demographics: 66.7% of the included subjects were boys and 33.3% girls. The mean age was 35.9 months. Three subjects (16.7%) were within the age range of 28 days to < 2 years, and 15 subjects (83.3%) were within the age range of 2 years to < 6 years. 83.3% were white, 11.1% black and 5.6% other.

Efficacy

For the primary endpoint, no subjects had corrected serum calcium level that met the primary endpoint of a corrected serum calcium of < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, and < 8.4 mg/dL (2.1 mmol/L) for ages ≥ 2 years to < 6 years during the study.

Results from relevant secondary efficacy endpoints are below:

- A higher proportion of subjects in cohort 1 (100.0%) than in cohort 2 (50.0%) achieved ≥ 30% reduction in iPTH. All subjects who completed the study (4 subjects: 2 subjects each per cohort) achieved this threshold of response.
- Overall, 8 subjects (47.1%, cohort 1: 57.1%, cohort 2: 40.0%) achieved > 30% reduction in iPTH from baseline for 2 consecutive measurements; all 4 subjects who completed the study also met this response threshold for 2 consecutive measurements.
- One subject (5.9% overall) achieved plasma iPTH values between 200 and 300 pg/mL (21.2 and 31.8 pmol/L) at any 2 consecutive measurements. Of the subjects in the Full Analysis Set, 52.9% had achieved an iPTH value < 300 pg/mL during the study, and the proportion of subjects achieving this threshold value was similar between cohorts (cohort 1: 57.1% and cohort 2: 50.0%). Three of the 4 subjects (75.0% overall, cohort 1: 50.0% and cohort 2: 100.0%) who completed the study achieved iPTH values < 300 pg/mL.
- Percent change of corrected serum calcium, serum phosphorus, and calcium phosphorus product (Ca x P): Increases in mean percent change in corrected serum calcium levels over time were noted overall (range: -0.10% to 5.88%). Cohort 1 generally had decreases in mean percent changes in corrected serum calcium values (range: -6.86% to 1.94%) compared to baseline whereas cohort 2 generally had increases in mean percent changes in corrected serum calcium values compared to baseline (range: -0.49% to 5.88%).
- For serum phosphorus and Ca x P, initial decreases from baseline were observed. At week 11 and later time points, trends were difficult to observe.

Study 20140159

A Multicenter Single-arm Extension Study to Characterize the Long-term Safety of Cinacalcet Hydrochloride in the Treatment of Secondary Hyperparathyroidism in Paediatric Subjects With Chronic Kidney Disease on Dialysis

Primary Objective: To characterize the long-term safety and tolerability of cinacalcet in paediatric subjects with CKD receiving dialysis

Secondary Objective(s): To characterize the long-term effect of cinacalcet in paediatric subjects receiving dialysis on laboratory parameters associated with chronic kidney disease-mineral bone disease (CKD-MBD)

Exploratory Objective: To characterize the long-term effect of cinacalcet in paediatric subjects on linear and pubertal growth

Subjects from Study 20100100 and 20130356 were eligible to enroll, and receive 28 weeks of treatment with cinacalcet in this extension study. Enrolment has been completed with 28 subjects enrolled. The MAH has provided interim data from the ongoing study.

Table 4. Summary of Subject Incidence of Low Ionized Calcium (Safety Analysis Set)

	Parent Study/Treatment		
	20130356 SOC (N = 9) n/N_1 (%)	20130356 SOC+Cinacalcet (N = 9) n/N_1 (%)	Total (N = 18) n/N_1 (%)
Subject incidence of iCa < 1.05 mmol/L	8/9 (88.9)	6/9 (66.7)	14/18 (77.8)
Subject incidence of iCa < 1.00 mmol/L	6/9 (66.7)	4/9 (44.4)	10/18 (55.6)
Subject incidence of iCa < 0.94 mmol/L	2/9 (22.2)	1/9 (11.1)	3/18 (16.7)

iCa = ionized calcium
Data cut-off date: 29-APR-2016
The safety analysis set includes all subjects who were enrolled and received at least one dose of investigational product.
N=Number of subjects in the analysis set.
Percentages based on N.
N_1= Number of subjects with at least one post-baseline ionized calcium value.

Based on the available data, the following observations were made:

- Review of adverse events, vital signs, and laboratory parameters revealed no new or unexpected safety concerns across the subject population.
  - No clinically relevant differences in the incidences of adverse events of interest were observed for subjects who previously received cinacalcet in the parent study (Study 20130356 cinacalcet + SOC group) compared with subjects initiating cinacalcet in the current study (Study 20130356 SOC group).
  - No unexpected safety concerns were revealed in subjects who previously received cinacalcet in the parent study compared with subjects initiating cinacalcet in the current study.

- A high degree of intersubject variability was observed in laboratory parameters associated with CKD-MBD, regardless of previous exposure to cinacalcet in the parent study.
- Weekly assessments of calcium using protocol-specified ionized calcium thresholds to guide dose adjustment and withholding precluded dose titration to achieve the target iPTH reduction in the majority of subjects.

2.6.6. Discussion and conclusions on clinical efficacy

Two controlled phase 3 studies were performed in paediatric subjects 6 to 18 years. Both trials were conducted in accordance with the PDCO. Both were terminated early, first due to a fatality in the study and the second due to difficulties in recruitment.

The first study 2007208 showed trend to positive efficacy results: A total of 5 out of 21 (24%) of the placebo patients and 11 out of 22 (50%) of Cinacalcet treated patients reached the primary endpoint (p= 0.08), which was the number of patients achieving ≥30% reduction in mean iPTH from baseline to the efficacy assessment phase. When iPTH values collected after investigational product suspension were excluded, the corresponding numbers presented were 4 out of 21 (19%) in placebo and 12 out of 22 (55%) in Cinacalcet treated patients, p=0.017.

The statistical methods are overall adequate for the study design and endpoints, however adequate sensitivity analyses of the dichotomized response endpoint using different single imputation methods (LOCF for some subjects and BOCF for the other) was requested. Since more subjects in the cinacalcet arm discontinued due to study termination and kidney transplant which were unrelated to treatment outcome, using BOCF regardless of reasons will introduce bias against the cinacalcet arm and the approach will generate an over-conservative estimate or treatment effect. The results from all imputation strategies were all directionally consistent with the primary analysis.

The results of the analyses of PTH changes over time based on linear mixed models and different assumptions for handling missing values are directionally consistent with the results of the primary analysis. The variability is substantial; while the mean difference in percent change from BL to EAP is –19, the confidence interval is very broad and it cannot be excluded that the mean change in the placebo group is larger by more than 50% (interpreting the upper bound of the 95% CI). The results are therefore inconclusive.

Table: Summary of efficacy for trial 20070208

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Paediatric Subjects 6 to <18 years with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis	
Study identifier	Eudra CT Number: 2010-023150-37
Design	This multicenter study consisted of a 30-week randomized, double-blind, placebo-controlled phase followed by a 30-week open-label phase. All subjects, regardless of treatment assignment received standard of care with vitamin D sterols (calcitriol and its analogs), calcium supplements, and phosphate binders at the discretion of the investigator.

	Duration of main phase:		Double-blind, placebo-controlled phase of the study, consisted of a 24-week dose-titration period followed by a 6-week EAP. The open-label phase of the study consisted of a 24-week dose-titration period followed by a 6-week open-label maintenance period, in which all subjects received cinacalcet.
	Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Cinacalcet (double- blind and open-label phase)		The investigational product consisted of cinacalcet tablets, cinacalcet capsules-for-sprinkling. Subjects received IP orally once daily at a starting dose of ≤ 0.20 mg/kg based on dry weight, and the dose was titrated upward according to plasma iPTH and serum calcium levels and subject safety information every 4 weeks. The maximum dose was 4.2 mg/kg, not to exceed a total dose of 180 mg for any subject, the labeled recommended adult maximum dose. During the open-label phase, all subjects received cinacalcet.
	Placebo group (double-blind phase)		The IP in this group consisted of placebo tablets or placebo capsules-for sprinkling.
Endpoints and definitions	Primary endpoint	<label>	to demonstrate the efficacy of cinacalcet for reducing the plasma iPTH by ≥ 30%
	Secondary endpoint	<label>	to demonstrate the efficacy of cinacalcet for lowering the plasma iPTH level to ≤ 300 pg/mL (31.8 pmol/L).
	Secondary endpoint	<label>	to demonstrate the impact of cinacalcet on corrected total serum calcium level.
	Secondary endpoint	<label>	to demonstrate the impact of cinacalcet on serum phosphorus level.
	Secondary endpoint	<label>	to demonstrate the impact of cinacalcet on Ca x P.
	Secondary endpoint	<label>	to assess the impact of cinacalcet on growth.
	Secondary endpoint	<label>	to assess percent change in ionized calcium from baseline to the mean value during the efficacy assessment phase (EAP).
Database lock	The first subject was enrolled on 28 June 2011. The study was placed on clinical hold, and the last subject's last visit was on 03 May 2013. Following a fatality the study was subsequently terminated early, and the primary completion date was 30 April 2014.		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Intent to treat (Full analysis set)

Descriptive statistics and estimate variability	Treatment group	Placebo	Cinacalcet HCL
	Number of subject	21	22
	Proportion of Subjects Achieving ≥ 30% Reduction in Mean iPTH From Baseline to the EAP Excluding iPTH Values Collected After Investigational Product Suspension	4 (19%)	12 (54.5%)
	The proportion of subjects achieving a mean iPTH value ⩽ 300 pg/mL (31.8 pmol/L) during the EAP	5 (23.8 %)	6 (27.3)
	The percent change in mean corrected total serum calcium during the EAP		
	LS mean (95% CI)	4.9% (-5.5%, 15.3%)	10.2% (-0.8%, 21.2%)
	the percent change in mean Ca x P during the EAP		
	LS mean (95% CI)	8.0% (-1.8%, 17.7%)	-2.0% (-11.4%, 7.4%)
	growth velocity from baseline to the end of the double-blind phase		
	LS mean (95% CI)	3.3 (1.22) cm/year	3.3 (1.22) cm/year
Effect estimate per comparison	Primary endpoint:	Comparison groups	Cinacalcet vs. Placebo

	Proportion of Subjects Achieving ≥ 30% Reduction in Mean iPTH From Baseline to the EAP Excluding iPTH Values Collected After Investigational Product Suspension	CMH-stratified odds ratio (95% CI)	4.25 (0.99,18.30)
		Difference 95 % CI	8.76%, 62.24%
		CMH Statistic P-value	0.017
	Secondary endpoint: The proportion of subjects achieving a mean iPTH value ⩽ 300 pg/mL (31.8 pmol/L) during the EAP	Comparison groups	Cinacalcet vs. Placebo
		CMH-stratified odds ratio (95% CI)	1.13 (0.25, 4.75)
		Difference 95% CI	-22.58%, 29.51%
		CMH Statistic P-value	0.826
Notes	Due to relatively short duration of the drug exposure and low number of evaluable subjects no conclusions regarding the impact of cinacalcet could be drawn on the following other efficacy endpoints: bone biomarkers, growth velocity, Tanner stage, percent change in bone mineral density, testosterone levels.		

The final results from study 20130356 showed that the efficacy was less than expected, and this has an impact on the benefit-risk assessment.

In Study 20070208 a higher allowed maximum daily dose of 4.2 mg/kg was suggested. The maximum daily dose was 2.5 mg/kg in Study 20130356. The latter failed to meet its primary endpoint. The Applicant was asked to clarify the actual maximum doses mg/kg given in these studies and to discuss in how far limitation of the maximum daily dose could have had an influence on study outcomes:

The mean of the actual maximum weight adjusted daily dose of cinacalcet was 0.99 mg/kg/day in Study 20070208 and 0.69 mg/kg/day in Study 20130356.
In Study 20070208, only 1 subject received a dose above 2.5 mg/kg/day, the maximum allowed daily dose for Study 20130356; while in Study 20130356, no subject received the maximum allowable daily dose of 2.5 mg/kg/day.

The CHMP therefore concurs with the MAH that differences in the protocol-specified maximum dose per se in the 2 studies did not explain the different doses used. The lower than expected dose used in Study 20130356 may have resulted from changes in the dosing algorithm used in this study and not due to a need for dose titration to doses higher than the protocol-specified maximum dose. The MAH has provided information on the weight adjusted daily dose in Mimpara exposed subjects compared to placebo in study 20070208. Starting from week 16, the actual exposure to placebo is higher compared to cinacalcet for the rest of the dose titration period and EAP.

The treatment success (>30% reduction from baseline in mean IPTH during EAP) was achieved by 54% of subjects group in study 20070208. The mean differences are directionally consistent with the primary analysis for the study, which was based on the dichotomized response endpoint of PTH reduction of > 30% from baseline.

Individual patients' data show that there is no substantial difference between the two treatment groups over the time. Consequently, it is not possible to make a clear statement that the iPTH reduction is in favor for cinacalcet arm.

In Study 20130356, no clinically relevant changes in iPTH from baseline over time were observed for subjects who received cinacalcet + SOC compared with subjects who received SOC alone. These findings were consistent with primary analysis for this study. Additionally it should be noted that the difference in mean change during the EAP points towards a favorable effect of SOC.

Although the 'treat-to target' approach (PTH: 100-300 pg/mL) appears to be a meaningful concept in general, in study 20070208 it is very difficult to recognize any trends in favor of the cinacalcet arm. This does not significantly improve in the long run. A related drawback is the fact that in the study 20070208 a greater proportion of cinacalcet-treated patients had at least one PTH level that fell below 100 pg/mL compared to placebo treated subjects. These results are expected due to the effects of calcimimetics to lower PTH. In contrast, in the Study 20130356, the additional dose adoptions rules (Cinacalcet treatment regimen was lower and the decision criteria for dose titration were modified) probably protect against the event to fall below 100 pg/mL (2 subjects in the cinacalcet + SOC group versus 4 subjects in the SOC group). As seen from the provided analysis no clinical relevant changes in iPTH from baseline over the time were observed.

In the day 120 LoI, the MAH was asked to clarify if criteria for dose adjustments in study 20130356 are similar to the recommendations proposed in the SmPC section 4.2 for paediatric patients and discuss any possible differences.

The MAH has clarified the criteria for dose adjustments in study 20130356 and provided a rationale for differences compared to the recommendations proposed in the SmPC section 4.2 for paediatric patients. The optimal wording in SmPC 4.2 needs further discussion.

There are indications that measuring ionised calcium could be more accurate in complex patients such as patients undergoing dialysis. However, measurement of ionised calcium is more expensive and not performed at all sites. It is therefore accepted that corrected calcium is used in the SmPC. The SmPC proposal state that serum calcium levels should be maintained within the normal range. This is endorsed. However, the normal range is differs marked depending on the methods used by the laboratory and age of the child. Therefore, giving exact Ca limits in the SmPC may be misleading. Therefore, guidance for dose adjustment in paediatric patients given in the SmPC is now expressed relative to the age-specific normal range instead of absolute Ca values.

Results from the open-label, single-arm study 26-week study **20110100** (subjects <6 years) show decreases in iPTH and calcium.

In both controlled trials 2007028 and 20130356 cinacalcet was used as a part of a therapeutic regiment including phosphate binders and/or Vitamin D sterols.

The primary endpoint for the 2 controlled studies was the proportion of subjects with ≥ 30% reduction from baseline in mean plasma iPTH during the efficacy assessment phase (EAP), which was defined as the period

between weeks 25 and 30, inclusive, for Study 20070208 and weeks 17 and 20, inclusive, for Study 20130356.

The results of the Bayesian extrapolation study show a tendency to higher response rate when results in the adult population compared to the paediatric population.

Study 20090198 was a retrospective, observational chart review in 23 paediatric subjects from birth to < 6 years of age (mean age 32.6 months). The subjects received Cinacalcet off-label. This study type has several limitations and no firm conclusions of efficacy can be drawn.

Interim data from the ongoing, single arm, open-label, extension study 20140159 showed that low levels of iCa were common. Weekly assessments of calcium using protocol-specified ionized calcium thresholds to guided dose adjustment and withholding precluded dose titration to achieve the target iPTH reduction in the majority of subjects. The study illustrates similar concerns as the controlled studies.

Results from both phase III studies are not appropriate to unequivocally demonstrate efficacy in the proposed indication. In study 20070208 a trend in favor of cinacalcet over placebo could be seen, however. Evaluation of the results from the second pivotal trial, study 20130356, showed that the efficacy was less than expected which was most likely due to inadequate drug exposure in the majority of the subjects. This was supposedly a direct consequence of additional safety measures and a conservative management of the investigational product dosing in order to further minimize the risk of hypocalcaemia.

Based on the pharmacological mechanism, PK extrapolation for a safe starting dose in children above 3 years as well as results from the 20070208 study, it is likely that Mimpara is be effective in lowering PTH in paediatric patients if the dose can be titrated without endangering hypocalcaemia- such as in cases where the use of SOC is limited by hypercalcaemia. An unmet medical need to treat patients who still have elevated PTH levels in spite of optimally titrated standard of care therapy is recognized. Further data should be obtained in a proposed registry study, agreed as a category 3 study.

A restricted indication in the paediatric population in whom sHPT is not “adequately controlled with standard of care therapy” was considered adequate by CHMP, in particular in the context of elevated S-Ca levels. Due to the risk of severe hypocalcaemia in children, the treatment should not be initiated at S-Ca levels at the lower limit of normal. Corrected serum calcium should be monitored, and be above or in the upper range of the reference interval prior to initiation of Mimpara in the paediatric population. Mimpara should not be used in hypocalcaemia in both adults and children and hypocalcaemia is therefore a contraindication in the SmPC.

For children under 3 years, the data is not sufficient to recommend a starting dose with acceptable safety.

2.7. Clinical safety

2.7.1.1. Exposure

On day 121 of the procedure, further data has been provided from study 20130356 and study 20110100 which have been completed. Furthermore the cut-off of the previously submitted 20140159, ongoing study

has been extended from 29 February 2016 to 29 April 2016. The following section has been updated accordingly in order to reflect the current safety results available.

Across the entire cinacalcet paediatric development program, 103 subjects were exposed to cinacalcet in phase 1, 2, and 3 interventional clinical studies (cut-off date for Study 20140159: 29 April 2016; all other studies complete). This includes 5 subjects between 28 days and < 2 years, 24 subjects between 2 and < 6 years, 24 subjects between 6 and < 12 years, and 48 subjects between 12 and < 18 years; 2 subjects were 18 years old at enrolment and are classified into "18 to < 65 years" category (see Table below, footnote). Summaries of cinacalcet exposure across all paediatric clinical studies, in phase 1 studies, in other studies (i.e., the phase 2 and 3 paediatric clinical studies), and in randomized and controlled studies by age group are summarized below.

Table. Summary of Cinacalcet Exposure

Study	Age Group (years)	n	Statistic	Maximum Dose (mg)	Maximum Weight-adjusted Dose (mg/kg)	Duration of Exposure (days)
20090005	28 days to < 6	12	Mean (SD)	3.49 (1.05)	0.25	1
			Range	1.8, 5.4	0.25, 0.25	1, 1
	28 days to < 3	4	Mean (SD)	2.53 (0.66)	0.25	1
			Range	1.8, 3.4	0.25, 0.25	1, 1
	3 to < 6	8	Mean (SD)	3.98 (0.87)	0.25	1
			Range	3.0, 5.4	0.25, 0.25	1, 1
20110100	28 days to < 6	17	Mean (SD)	-	0.73 (0.66)	86.7 (48.0)
			Range	-	0.10, 2.30	10, 166
20090198[a]	0 to < 6	23	Mean (SD)	23.53 (17.04)	1.87 (1.30)	274.2 (245.5)
			Range	5.0, 60.0	0.4, 5.6	34.0, 1036.0
20030227	6 to 18	12	Mean (SD)	15	-	1
			Range	15, 15	-	1, 1
20070208 Double-blind	6 to < 18	22	Mean (SD)	-	0.99 (1.26)	109.7 (65.9)
			Range	-	0.1, 5.7	8, 212
Open-label[c]		10	Mean (SD)	-	0.70 (0.60)[b]	119.2 (75.5)
			Range	-	0.2, 1.9[b]	12, 210
20130356	6 to < 18	25	Mean (SD)	-	0.55 (0.48)	112.8 (41.0)
			Range	-	0.08, 1.85	6, 141
20140159[d]	6 to < 18	18[e]	Mean (SD)	-	0.77 (0.70)	146.7 (46.9)
			Range	-	0.12, 2.33	39, 196
20120116[a,f]	< 21	90	Mean (SD)	30.8 (18.8)	-	-
			Range	3, 120	-	-

- = not reported
[a] Non-interventional study
[b] Prescribed dose

[c] Six subjects had previously received placebo and 4 subjects had previously received cinacalcet
[d] As of interim analysis data cutoff date of 29 April 2016
[e] Nine subjects had previously received standard of care (SOC) only and 9 subjects had previously received cinacalcet + SOC in Study 20130356
[f] mean (SD) and range of first available regimen based on data available in 80 subjects
One subject in paediatric Study 20070208 and 1 subject in paediatric Study 20140159 were 18 years old at enrollment and are classified into "18 to < 65 years" category

Table. Total Subject Exposure to Cinacalcet in Paediatric Clinical Studies[a] by Age Group (ICH E11 Guideline) Safety Analysis Set[b]

	Exposure to Cinacalcet	
	Randomized Controlled Studies[c] n (subject-years)	All Studies n (subject-years)
All Phase 1 paediatric studies	0 (0.00)	24 (0.07)
28 days to <2 years	0 (0.00)	3 (0.01)
2 to < 12 years	0 (0.00)	15 (0.04)
2 to <6 years	0 (0.00)	9 (0.02)
6 to <12 years	0 (0.00)	6 (0.02)
12 to <18 years	0 (0.00)	6 (0.02)
All Phase 2 and 3 paediatric studies – ESRD	47 (14.87)	79 (28.26)
28 days to <2 years	0 (0.00)	2 (0.62)
2 to < 12 years	14 (5.15)	33 (11.11)
2 to <6 years	0 (0.00)	15 (3.63)
6 to <12 years	14 (5.15)	18 (7.48)
12 to <18 years	32 (9.51)	42 (16.04)
18 to <65 years	1 (0.21)	2 (0.48)
Total	47 (14.87)	103 (28.32)
28 days to <2 years	0 (0.00)	5 (0.63)
2 to < 12 years	14 (5.15)	48 (11.15)
2 to <6 years	0 (0.00)	24 (3.66)
6 to <12 years	14 (5.15)	24 (7.50)
12 to <18 years	32 (9.51)	48 (16.06)
18 to <65 years	1 (0.21)	2 (0.48)

n = number of subjects exposed to cinacalcet; ESRD = end-stage renal disease; subject-years = total subject-years of exposure.
[a] Data from completed studies and on-going Study 20140159 with cutoff date as 29 April 2016.
[b] Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
[c] Only randomized controlled treatment phases are included.
One subject in paediatric Study 20070208 and 1 subject in paediatric Study 20140159 were 18 years old at enrollment and are classified into "18 to < 65 years" category
Modified from t14d-05-005-001-exp-cum-byage-ped1.rtf (Date Generated: 26AUG2016:17:18) and t14d-05-005-003-exp-cum-byage-ped3.rtf (Date Generated: 26SEP2016:08:40)

2.7.1.2. Main studies 20070208 and 20130356

Adverse events

Data from the 2 studies were presented side by side and not pooled, because safety measures related to hypocalcaemia monitoring in Study 20130356 resulted in lower exposure in Study 20130356 compared with Study 20070208. In below table, the corresponding numbers from adult studies 20000172, 20000183, and 20000188 are included for comparison.

Table. Summary of Adverse Events in Phase 3 Cinacalcet Paediatric Studies (20070208 and 20130356) (double-blind phase) and Adult Registrational Studies (20000172, 20000183, and 20000188)

	Randomized and Controlled Pool				Adult Registrational Studies	
	Study 20070208[a]		Study 20130356			
	Control[b] (N = 21) n (%)	Cinacalcet (N = 22) n (%)	Control[b] (N = 30) n (%)	Cinacalcet (N = 25) n (%)	Placebo (N = 470) n (%)	Cinacalcet (N = 656) n (%)
Treatment-emergent adverse events	18 (85.7)	18 (81.8)	17 (56.7)	21 (84.0)	440 (94)	599 (91)
Serious adverse event	9 (42.9)	9 (40.9)	2 (6.7)	4 (16.0)	148 (31)	187 (29)
Death	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	15 (3)	14 (2)
Adverse events leading to IP discontinuation[c]	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	37 (8)	96 (15)
Adverse events related to IP	11 (52.4)	8 (36.4)	0 (0.0)	8 (32.0)	116 (25)	283 (43)

IP = investigational product; N = Number of subjects in the analysis set; n = Number of subjects reporting at least 1 occurrence of an adverse event. Percentages are based on N.
[a] Double-blind phase
[b] Study 20070208 control = placebo; Study 20130356 control = standard of care
[c] Adverse events leading to discontinuation in adult registrational studies

In the paediatric randomized and controlled pool, a similar proportion of subjects in the cinacalcet and control groups of the double-blind Study 20070208 had at least 1 adverse event (82% versus 86%, respectively), but not in the cinacalcet and control groups of open-label Study 20130356 (84% versus 57%). The open-label study design of Study 20130356 may have contributed to the difference between studies in adverse event attribution.

Most adverse events were reported for a similar proportion of subjects in the cinacalcet and control groups. In Study 20070208, the most common events reported in the cinacalcet group were vomiting (7 subjects [31.8%]), hypocalcaemia (5 subjects [22.7%]), and nausea (4 subjects [18.2%]); all other events in the cinacalcet group were reported for ≤ 3 subjects. In Study 20130356, the most common adverse events reported in the cinacalcet + SOC group were hypocalcaemia (6 subjects [24.0%]), nausea (3 subjects

[12.0%]), and muscle spasms (3 subjects [12.0%]). All other adverse events in the cinacalcet + SOC group were reported for ≤ 2 subjects.

Adverse events were reported for 9 (90.0%) subjects in the open-label phase of study 20070208. The adverse events reported for more than 1 subject were hypocalcaemia (40.0%, 4/10 subjects); nausea (30.0%, 3/10 subjects); and headache, hypertension, paraesthesia, abdominal pain, and pyrexia (20.0% each, 2/10 subjects).

Serious adverse events

In the paediatric randomized and controlled pool, serious adverse events were reported for 9 subjects (40.9%) in the cinacalcet group and 9 subjects (42.9%) in the placebo group of Study 20070208 and for 4 subjects (16.0%) in the cinacalcet + SOC group and 2 subjects (6.7%) in the SOC group of Study 20130356. The only serious adverse events reported for > 1 subject total across the study cinacalcet groups were hypertension (2 cinacalcet subjects and 1 control subject in Study 20070208), fluid overload (1 cinacalcet subject in each study and 1 control subject in Study 20070208) and peritonitis (1 cinacalcet subject and 0 control subjects in each study). Hypocalcaemia was reported as a serious adverse event for 1 subject (4.5%) in the cinacalcet group (Study 20070208) in the randomized and controlled pool.

Four subjects (2 cinacalcet, 2 control; all in Study 20070208) had serious adverse events considered related to study treatment.

The applicant has provided detailed information regarding the 2 SAE which were considered related to the investigational product. Both cases were related to hypocalcaemia, which is considered to be an expected Adverse Event due to the mechanism of action of cinacalcet. Nonetheless, in one case the severe hypocalcaemia was linked to a fatal case/event (see below under “Deaths”).

During the open-label phase of study 20070208, 4 subjects (40.0%) had serious adverse events. No serious adverse event was experienced by more than 1 subject.

Deaths

One subject experienced a fatal adverse event (reported preferred term: cardiopulmonary failure) during the study 20070208. The fatality occurred in a 14-year-old girl with end-stage renal disease and secondary HPT on peritoneal dialysis

The analysis of lab data showed that the subject had substantial increases in iPTH (≥ 300pg/mL) with concomitant decrease in serum calcium. Although the fatality was determined to be multifactorial, a causal role for hypocalcemia as a result of treatment with cinacalcet could not be excluded, as a lab report that became available after the fatality showed a corrected calcium concentration of 5.3 mg/dL on the morning of the subject’s death.

No death was reported in the final results from study 20130356.

Adverse events of interest

Based on the mechanism of action, the pharmacological profile of cinacalcet, potential class effects of cinacalcet as a CaR agonist, and observations made during the nonclinical and clinical program, the following events of interest were summarized for the paediatric clinical studies:

- Acute pancreatitis
- Cardiac failure
- Convulsions
- Drug-related hepatic disorders – comprehensive search
- Hypersensitivity
- Ischemic heart disease
- Malignant or unspecified tumors
- Effects on cardiac repolarization (Torsade de pointes/QT prolongation, ventricular tachyarrhythmia)
- Fractures
- Hypocalcemia
- Hypotension
- Nervous system disorders
- Nervous system disorders excluding seizures

Numerically more subjects in the placebo group experienced convulsions/seizures and infection compared to Cinacalcet group. Infection was reported for 3 (30.0%) subjects in the open-label phase.

Table. Safety Follow-up Adjusted Incidence Rates for Events of Interest Reported for ≥ 1 Subject (Randomized and Controlled Pool, Safety Analysis Set)

	Study 20070208 Double-blind Phase		Study 20130356	
	Control (N = 21) n (%) / e [r]	Cinacalcet (N = 22) n (%) / e [r]	Control (N = 30) n (%) / e [r]	Cinacalcet (N = 25) n (%) / e [r]
Hypocalcaemia	4 (19.0) / 8.5 [47.1]	5 (22.7) / 7.4 [67.6]	3 (10.0) / 10.1 [29.7]	7 (28.0) / 7.6 [92.6]
Blood calcium decreased	0 (0.0) / 9.7 [0.0]	0 (0.0) / 8.7 [0.0]	1 (3.3) / 10.4 [9.6]	1 (4.0) / 8.6 [11.6]
Hypocalcaemia	4 (19.0) / 8.5 [47.1]	5 (22.7) / 7.4 [67.6]	2 (6.7) / 10.5 [19.0]	6 (24.0) / 7.6 [79.0]
Convulsions/seizure	2 (9.5) / 8.9 [22.4]	0 (0.0) / 8.7 [0.0]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Epilepsy	1 (4.8) / 9.2 [10.8]	0 (0.0) / 8.7 [0.0]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Seizure	1 (4.8) / 9.4 [10.7]	0 (0.0) / 8.7 [0.0]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Hypotension	1 (4.8) / 9.4 [10.6]	2 (9.1) / 8.4 [23.9]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Cardiac Failure	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.7 [11.5]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Cardiopulmonary failure	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.7 [11.5]	0 (0.0) / 10.9 [0.0]	0 (0.0) / 8.7 [0.0]
Hypersensitivity	3 (14.3) / 9.2 [32.6]	2 (9.1) / 8.2 [24.4]	3 (10.0) / 10.0 [30.1]	0 (0.0) / 8.7 [0.0]
Nervous system disorders (excluding seizures)	6 (28.6) / 7.9 [75.6]	6 (27.3) / 7.3 [82.0]	7 (23.3) / 8.9 [78.6]	4 (16.0) / 7.4 [53.7]
Drug related hepatic disorders	0 (0.0) / 9.7 [0.0]	0 (0.0) / 8.7 [0.0]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.4 [11.8]
ALT increased	0 (0.0) / 9.7 [0.0]	0 (0.0) / 8.7 [0.0]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.4 [11.8]
Medication errors	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.1 [12.4]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.6 [11.6]
Overdose	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.1 [12.4]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.6 [11.6]
Product use issues	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.1 [12.4]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.6 [11.6]
Overdose	0 (0.0) / 9.7 [0.0]	1 (4.5) / 8.1 [12.4]	0 (0.0) / 10.9 [0.0]	1 (4.0) / 8.6 [11.6]

ALT = alanine aminotransferase
N = Number of subjects in the analysis set
n = Number of subjects reporting at least one occurrence of an adverse event. Percentages are based on N.
e = Sum across all subjects, the total time to first event or total safety follow-up if no event (years)
r = Safety follow-up adjusted subject rate per 100 subject years (n/e*100)

Hypocalcaemia

The main safety concern of Cinacalcet in the paediatric population is hypocalcaemia. At Day 121, the applicant was requested to analyse whether cases of low calcium levels and hypocalcaemia in clinical studies are more common/ more severe in paediatric population compared to the adult population and discuss

possible rationale for that. This information is discussed in a separate section below where pooled data from all studies are presented.

Haematology

No clinically significant changes were observed in hematology parameters during the study.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically significant changes were observed in vital signs. Bazett-corrected QT interval (QTcB) was recorded in Study 20070208 and Study 20130356 with minor and varying changes recorded,

Discontinuation due to AES

2 subjects (5.7%) from the control group of study 20070208 (placebo) discontinued the study due to adverse events.
In study 20130356 no discontinuation due to adverse events was recorded.

2.7.1.3. Safety in supportive studies:

Please see the efficacy section for a detailed description of the studies.

Study 20110100 (n=18)

Overall, 94.1% of subjects had at least 1 adverse event. The most common adverse events in all subjects were cough, hypertension, upper respiratory tract infection, and vomiting (23.5% each). Nine (52.9%) subjects had a serious adverse event. All serious adverse events were reported for a single subject, except for preferred terms of complication associated with device and hypertension (2 subjects each). No deaths occurred during the study, and no subject discontinued investigational product because of an adverse event.

Results from this study showed no subject developed cCa levels < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, or < 8.4 mg/dL (2.1 mmol/L) for ages ≥ 2 to < 6 years (the primary endpoint).

Study 20090198 (n=23)

Two subjects had adverse drug reactions (i.e., cinacalcet-related adverse events): decreased level of consciousness and intermittent mild hypocalcemia; the decreased level of consciousness event occurred in the setting of marked hypocalcaemia and was considered serious.

One subject reported a SAE of decreased level of consciousness in the setting of marked hypocalcaemia and was considered related to cinacalcet treatment.

Two deaths were recorded in the chart review; neither death was reported by the investigator as related to cinacalcet.

a) A 1-year-old boy died from invasion of systemic aspergillose (systemic aspergillosis) in combination with an arterial hypertonus, which ended in dialysis with a hemorrhagic apoplexy (hemorrhagic stroke).
b) A 3-year-old girl had acute respiratory compromise at home and subsequently died as a result of respiratory failure in a hospital.

Study 20030227 (N=12):

Two subjects (17%) had non-serious adverse events:

1. One subject had adverse events of bacteraemia (grade 2) and pyrexia (grade 1).

2. One subject had an adverse event of QT interval prolongation (grade 1), observed on the end-of-study ECG and obtained 4 days after cinacalcet administration, which the investigator felt was possibly due to chest trauma. None of the adverse events were considered by the investigator to be related to treatment.

All adverse events were mild to moderate in severity.

Six subjects had decreases in serum calcium below the lower limit of normal (2.23 mmol/L for both boys and girls). The low calcium values for these subjects ranged from 2.00 to 2.22 mmol/L.

No serious adverse events were reported and no deaths occurred in this single-dose study.

Study 20090005 (N=12):

Treatment-emergent adverse events were reported for 3 of 12 (25%) subjects, including 1 of 4 (25%) subject 28 days to < 3 years old and 2 of 8 (25%) subjects ≥ 3 years to < 6 years old.

Adverse events reported for 1 subject 28 days to < 3 years old were vomiting, catheter site haemorrhage and device expulsion by the same subject. Adverse events reported for subjects ≥ 3 years to < 6 years old were body temperature increased and hypocalcaemia (treatment-related adverse event of interest), each reported by 1 subject. There were no grade 4 events reported during the study. Grade 3 events included 1 event each of catheter site haemorrhage, device expulsion (chest catheter falling out), and hypocalcaemia. Changes observed in laboratory test results were consistent with the disease states under study. No notable changes from baseline were observed for vital signs measurements or ECG results.

1 subject aged ≥ 3 years to < 6 years old reported hypocalcaemia (treatment-related adverse event of interest). Grade 3 events included 1 event each of catheter site haemorrhage, device expulsion (chest catheter falling out), and hypocalcaemia.

No serious adverse events were reported and no deaths occurred in this single-dose study.

Study 20140159 (N=18) (ongoing)

The primary endpoint for this study was the incidence of adverse events of interest. Nervous system disorders excluding seizures (4 subjects), hypocalcaemia (2 subjects), hypersensitivity, and fracture (each 1 subject) were the only reported adverse events of interest. None of the adverse events of interest were serious adverse events. The adverse events of hypocalcaemia and paraesthesia were considered related to investigational product by the investigator. There were no adverse events of cardiac failure, convulsions, hypotension, torsade de pointes/QT prolongation, ventricular tachyarrhythmia, acute pancreatitis, drug-related hepatic disorders, malignant or unspecified tumours, ischemic heart disease, medical errors, or product use issues. Hypocalcaemia as primary endpoint is discussed under Efficacy.

A fatal event was reported in a 2.5-year, old boy. The fatal event was not deemed to be related to cinacalcet by the investigator. According to the autopsy report, the cause of the death was infection (bronchopneumonia and acute exacerbation of a chronic pyelonephritis).

NAPRTCS Registry study 20120116 (ongoing)

NAPRTCS (North American Paediatric Renal Trials and Collaborative Studies) was established in 1987 to capture information about current practice and trends in the care of paediatric renal allograft recipients in North America. In 1992, the study was expanded to include paediatric patients who receive maintenance haemodialysis or peritoneal dialysis therapy. A cumulative 3 year interim analysis of data collected by the NAPRTCS Dialysis registry on the use of cinacalcet in dialysis participants aged <21 years was submitted. The cumulative data includes available safety information about the differences between patients treated with and without cinacalcet.

Exposure:

At the time of the interim analysis cutoff date of 31 July 2015, 416 patients were enrolled. 73 patients were treated with cinacalcet. Dosing information was available for 67 of the 73 subjects treated with cinacalcet (age range: 2 to 21.4 years). The most frequent dosing schedule was 30 mg once per day, 210 mg per week. This was reported in 27 of the 67 subjects (40%). The median dose was 30 mg (range 7.5 to 120 mg) and the median dose per week was 210 mg (range 45 to 840 mg). No further exposure data is available.

Demographics

Children in the group receiving cinacalcet were older than children that did not receive cinacalcet, with 37 (51%) in the >12 year age group (at last follow-up visit) vs. 130 (38%). Median age at last visit was 15.9 years (range 2.0 – 21.4) in the group that received cinacalcet compared to 12.5 (range 0.2 - 23.6) in the group that did not receive cinacalcet during the study period.

Drug Dosing

Cinacalcet dosing information was available on 67 of the 73 participants treated with cinacalcet. The most frequent dosing schedule is 30 mg once per day (210 mg per week). This was reported in 27 of the 67 participants (40%). The median dose is 30 mg (range 7.5-120 mg) and the median dose per week (mg) is 210 mg (range 45-840 mg).

Safety results:

Overall, 50 subjects were treated for or had a modification of treatment for hypocalcemia a total of 105 times during the cumulative study period. Eleven of these 50 subjects were hospitalized for these events. Ten of 73 subjects (13.7%) who received cinacalcet were treated for or had a modification of treatment for hypocalcemia. Eight of these subjects (11.0%) had a hypocalcemia treatment or modification of hypocalcemia treatment and 7 of 8 subjects had a change in cinacalcet therapy. In subjects not receiving cinacalcet, 42 of 343 (12.2%) had a total of 86 hypocalcemia treatments or modification of hypocalcemia treatment.

A total of 18 of 416 subjects reported 35 seizures. In subjects receiving cinacalcet, 4 of 73 subjects (5.5%) reported 4 seizure episodes; 2 subjects experienced seizures before taking cinacalcet, 1 subject experienced a seizure 2 weeks after taking cinacalcet and 1 subject experienced a seizure while taking cinacalcet. In the 343 subjects that did not receive cinacalcet during the study period, 14 (4.1%) reported a total of 31 seizures.

Eighty-seven of 416 subjects reported 156 hospitalizations due to infection. In subjects receiving cinacalcet, 13 of 73 subjects (17.8%) reported 25 hospitalizations for infection. In subjects that did not receive cinacalcet during the study period, 74 of 343 (21.6%) reported a total of 131 hospitalizations for infection.

Other adverse events were reported for 1 subject (1.7%) receiving cinacalcet (moderate subtotal parathyroidectomy). Ten subjects (2.9%) not receiving cinacalcet reported other adverse events and 7 of the 10 experienced serious adverse events (peritonitis [2 subjects], seizure, gastrointestinal bleed, malignant hypertension, cracked central venous access device, inguinal hernia repair, peritonitis, and acute viral myocarditis).

The interim analysis cutoff date was 31 July 2015. In response to the Day120 LoQ, the Applicant has provided an updated summary of deaths in the study per 01 August 2016. There were 3 fatal cases among the 90 patients treated with cinacalcet. In two of the cases, cinacalcet was stopped cinacalcet more than two months before the death. The cause of death in the third case was complications to acute lymphoblastic leukaemia.

2.7.1.4. Hypocalcaemia (pooled data)

The main safety concern of cinacalcet in the paediatric population is hypocalcaemia. The Applicant was requested to analyse whether cases of low calcium levels and hypocalcaemia in clinical studies are more common/more severe in paediatric population compared to the adult population and discuss possible rationale for that.

Based on the totality of data from the cinacalcet paediatric program, it appears that the incidence of reported adverse events of hypocalcaemia in paediatric patients is greater compared with the adult cinacalcet registrational studies, however the subject incidence was higher for both cinacalcet and control groups in the paediatric studies.

Table. Summary of Hypocalcaemia Severity in Adult Studies (Maximum severity [Hypocalcaemia MedDRA Search Strategy])

	Secondary HPT[a] n (%)		Study 20050182[b] n (%)	
	Placebo (N = 470)	Cinacalcet (N = 656)	Placebo (N = 1923)	Cinacalcet (N = 1938)
Subjects with event	6 (1.28)	30 (4.57)	33 (1.72)	240 (12.38)
Mild	2 (0.43)	8 (1.22)	9 (0.47)	134 (6.91)
Moderate	2 (0.43)	18 (2.74)	18 (0.94)	89 (4.59)
Severe	2 (0.43)	4 (0.61)	6 (0.31)	15 (0.77)
Life threatening	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.10)
Fatal	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)

[a] Pooled pivotal studies for SHPT (20000172, 20000183, 20000188) and extension Study 20010240, Safety Analysis Set; number of subjects (%).
[b] Secondary HPT Study 20050182 (EVOLVE), Safety Analysis Set; number of subjects (%).

Table. Summary of Hypocalcaemia Severity in Paediatric Studies (Maximum Severity [Hypocalcaemia MedDRA Search Strategy])

	Study 20070208			Study 20130356	
	Paediatric Secondary HPT[a] Double-blind Phase n (%)		Paediatric Secondary HPT Double-blind and Open-label Phases[b] n (%)	Paediatric Secondary HPT Safety Analysis Set n (%)	
	Placebo (N = 21)	Cinacalcet (N = 22)	Cinacalcet (N = 28)	Placebo (N = 30)	Cinacalcet (N = 25)
Subjects with event	4 (19)	5 (23)	9 (32)	3 (10)	7 (28)
Severity					
Mild	2 (10)	0 (0)	2 (7)	2 (7)	4 (16)
Moderate	2 (10)	4 (18)	6 (21)	1 (3)	3 (12)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Life threatening	0 (0)	1 (5)	1 (4)	0 (0)	0 (0)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Includes double-blind phase of paediatric Study 20070208.
[b] Includes double-blind and open-label phase of paediatric Study 20070208.

While it is possible that children, who have a greater demand for calcium during their skeletal growth phase, experience a higher incidence of hypocalcaemia, it should be noted there are limitations that affect this comparison. Specifically, in the studies conducted in adults, laboratory abnormalities were generally not collected as adverse events. Per protocol in the paediatric studies, in addition to the clinical symptoms of hypocalcaemia, any clinically important calcium laboratory abnormalities alone could have been reported as adverse events. Of note, laboratory evaluations of calcium were performed more frequently in Study 20130356 than adult studies (weekly monitoring of ionized calcium, monthly monitoring of corrected serum calcium).

Among all paediatric subjects exposed to cinacalcet in clinical studies (all cinacalcet pool; Studies 20070208, 20130356, 20110100, 20140159), a total of 19 subjects (24.1%; 64.5 per 100 subject years) had at least 1 adverse event of hypocalcaemia: 9 subjects (25.7%; 72.2) before the partial clinical hold and 10 subjects (22.7%; 58.8) after the partial clinical hold.

Serious adverse events of hypocalcaemia were reported for 2 subjects: 1 subject (4.5%) in the cinacalcet group in the double-blind phase of Study 20070208 (this subject died of cardiopulmonary failure, as discussed in Section 1.2.2 “Deaths”) and 1 subject (10.0%) in the open label phase. No subject had a serious adverse event of hypocalcaemia in Study 20130356.

In other studies, the incidence of hypocalcaemia included the following:

- In Study 20110100, 1 subject enrolled after the partial clinical hold had hypocalcaemia, considered related to investigational product; signs and symptoms of hypocalcaemia were not evident.

• At the time of interim analysis for Study 20140159, non-serious hypocalcaemia (asymptomatic) was reported for 2 subjects (11.1%), 1 from each parent study (20130356) treatment group, considered by the investigator to be related to investigational product.

• In single-dose Study 20090005, 1 subject (≥ 3 years to < 6 years of age) experienced an adverse event of hypocalcaemia (grade 3) approximately 12 hours after dosing on day 1. The event was considered by the investigator to be related to cinacalcet, and resolved on day 3.

No subjects in Study 20030227 had hypocalcaemia reported as an adverse event

The Applicant was also requested to provide data on hypocalcaemia in different age groups in the paediatric population.

In Study 20070208, 2/6 cinacalcet subjects and 1/5 placebo subject in the age group of 6 to < 12 years experienced hypocalcaemia, and 3/16 subjects from each treatment group in the age range of 12 to < 18 years experienced hypocalcaemia. In Study 20130356, 3/8 cinacalcet + SOC subjects (37.5%) and 2/10 SOC subjects in the age group of 6 to < 12 years experienced hypocalcaemia (preferred term hypocalcaemia or blood calcium decreased). Four out of seventeen cinacalcet + SOC subjects and 1/20 SOC subject experienced hypocalcaemia in the 12 to < 18 years age group.

Among all subjects exposed to cinacalcet, 1/15 subjects in the age group of 2 to < 6 years experienced an adverse event of hypocalcaemia. In the age group of 6 to < 12 years, 9/18 subjects experienced adverse events of hypocalcaemia (preferred term hypocalcaemia [n = 8] and blood calcium decreased [n = 1]). In the age group of 12 to < 18 years, 9/44 subjects experienced adverse events of hypocalcaemia.

A summary of the incidence of low corrected serum calcium values by age group (28 days to < 6 years, 6 to < 12 years, and 12 to < 18 years) for the all cinacalcet pool is provided in the table below.

Table 7. Summary of Subject Incidence of Low Corrected Serum Calcium by Age Group All Cinacalcet Pool (Safety Analysis Set)

	Before Partial Clinical Hold			After Partial Clinical Hold				
	Study 20070208 n (%)	Study 20110100 n (%)	Total n (%)	Study 20110100 n (%)	Study 20130356[a] n (%)	Study 20140159[b] n (%)	Total n (%)	Overall n (%)
Ages 28 days to < 6 years[c]								
Subjects with ≥ 1 post-baseline cCa value - N1	0	7	7	10	0	0	10	17
cCa < 8.4 mg/dL for age ≥ 2 years to < 18 years or < 9.0 mg/dL for age ≥ 28 days to < 2 years	0 (-)	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	0 (0.0)	0 (0.0)
cCa < 8.0 mg/dL	0 (-)	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	0 (0.0)	0 (0.0)
cCa < 7.5 mg/dL	0 (-)	0 (0.0)	0 (0.0)	0 (0.0)	0 (-)	0 (-)	0 (0.0)	0 (0.0)
Ages 6 to < 12 years								
Subjects with ≥ 1 post-baseline cCa value - N1	8	0	8	0	8	2	10	18
cCa < 8.4 mg/dL for age ≥ 2 years to < 18 years or < 9.0 mg/dL for age ≥ 28 days to < 2 years	5 (62.5)	0 (-)	5 (62.5)	0 (-)	5 (62.5)	1 (50.0)	6 (60.0)	11 (61.1)
cCa < 8.0 mg/dL	4 (50.0)	0 (-)	4 (50.0)	0 (-)	2 (25.0)	1 (50.0)	3 (30.0)	7 (38.9)
cCa < 7.5 mg/dL	1 (12.5)	0 (-)	1 (12.5)	0 (-)	1 (12.5)	0 (0.0)	1 (10.0)	2 (11.1)
Ages 12 to < 18 years								
Subjects with ≥ 1 post-baseline cCa value - N1	20	0	20	0	17	7	24	44
cCa < 8.4 mg/dL for age ≥ 2 years to < 18 years or < 9.0 mg/dL for age ≥ 28 days to < 2 years	6 (30.0)	0 (-)	6 (30.0)	0 (-)	3 (17.6)	0 (0.0)	3 (12.5)	9 (20.5)
cCa < 8.0 mg/dL	3 (15.0)	0 (-)	3 (15.0)	0 (-)	1 (5.9)	0 (0.0)	1 (4.2)	4 (9.1)
cCa < 7.5 mg/dL	2 (10.0)	0 (-)	2 (10.0)	0 (-)	1 (5.9)	0 (0.0)	1 (4.2)	3 (6.8)

2.7.2. Discussion and Conclusions on clinical safety

Across the entire cinacalcet paediatric development program, 103 subjects were exposed to cinacalcet in phase 1, 2, and 3 interventional clinical studies (cut-off date for Study 20140159: 29 April 2016; all other studies complete). This includes 5 subjects between 28 days and < 2 years, 24 subjects between 2 and < 6 years, 24 subjects between 6 and < 12 years, and 48 subjects between 12 and < 18 years; 2 subjects were 18 years old at enrolment and are classified into "18 to < 65 years" category.

In the first pivotal **study 20070208**, 81.8% of subjects in the cinacalcet group and 85.7% of subjects in the placebo group had at least 1 adverse event, with the most common events in the cinacalcet group being vomiting (7 subjects [31.8%]), hypocalcemia (5 subjects [22.7%]), and nausea (4 subjects [18.2%]).

A higher proportion of paediatric subjects in the cinacalcet group compared to the placebo group had corrected total calcium concentrations < 8.4 mg/dL (31.8% in the cinacalcet group and 14.3% in the placebo group) and < 7.5 mg/dL (13.6% in the cinacalcet group and 0% in the placebo group).

All subjects enrolled in this study was aged 6 to <18 years. Two serious events of hypocalcaemia were reported, one in the double-blind phase and second the open-label phase in patients receiving cinacalcet.

The study 20070208 was terminated early due to a fatality in the cinacalcet group. At the time of event onset, the 14-year old patient was on 90 mg of cinacalcet. A causal role for hypocalcemia could not be excluded. The paediatric program was subsequently placed on partial clinical hold for 14 months. Study 20130356 was initiated after the paediatric program was reinitiated.

Results from the second pivotal **study 20130356**, which was open label, show that the group receiving cinacalcet had more adverse events and serious adverse events than the group without cinacalcet. No new signals or unexpected safety concerns were observed during the study. It is noted that mean the average weight-adjusted daily dose of cinacalcet taken during week 17 to 20 time periods were approximately 80% lower than the mean dose taken during the EAP (week 25 to 30) in Study 20070208 (conducted before the partial clinical hold).

The proportion of treatment emerged AEs were comparable in both studies in the cinacalcet arms, as were the AEs related to IP, despite the considerably lower doses in study 20130356. There were, however, more serious adverse events recorded in study 20070208 (where higher doses were administered). The dose response relationship as regards safety is not entirely clear. There are not enough data available for a robust conclusion due to the small sample size of both phase III studies. It is also noted that comparability of trials is problematic considering the differences in study designs (20070208: RCT; 20130356 open-label, controlled trial).

Results from the open-label, single-arm study 26-week **study 20110100** (subjects <6 years) show no new safety concerns. This study was designed as a safety and tolerability study. No subjects had corrected serum calcium level that met the primary endpoint of a corrected serum calcium of < 9.0 mg/dL (2.25 mmol/L) for ages 28 days to < 2 years, and < 8.4 mg/dL (2.1 mmol/L) for ages ≥ 2 years to < 6 years during the study. Two subjects (11.8%; 1 subject each per cohort) in the Calcium Analysis Set, both within the 2 to < 6-year age range, had corrected serum calcium levels that were < 8.8 mg/dL (2.2 mmol/L).

Decreases in serum calcium below the lower limit were reported in both **single-dose phase 1 studies.**

In the NAPRTCS Registry **study 20120116,** cinacalcet was used to treat older participants who have been on dialysis for longer time that was seen in the group not receiving cinacalcet. Crude rates of seizures, change in hypocalcemia treatment and hospitalization for infection are similar between cinacalcet users and non-users.

The main safety concern of Cinacalcet in the paediatric population is hypocalcemia. Based on the totality of data from the cinacalcet paediatric program, it appears that the incidence of reported adverse events of hypocalcaemia in paediatric patients is greater compared with the adult cinacalcet registrational studies, however the subject incidence was higher for both cinacalcet and control groups in the paediatric studies. While the risk of hypocalcaemia in paediatric subjects is anticipated to be the same based on available knowledge about cinacalcet and the similarities in disease state in adults and children, it cannot be fully determined whether hypocalcaemia is more severe in children based on available data. There was a fatality in a hypocalcaemic patient in the paediatric clinical program, which lead to partial hold of the clinical development program. Hypocalcaemia has now been added as a contraindication for the use of cinacalcet in both adult and paediatric patients. In addition, text in SmPC section 4.2 and 4.4 includes wording against initiating treatment with cinacalcet unless serum calcium is above or in the upper range of the age-specified reference interval in the paediatric population.

In total, two deaths occurred during the cinacalcet paediatric interventional studies; 1 in Study 20070208 (see subsection “Deaths” under the headline “Main studies 20070208 and 20130356”) and 1 in the ongoing extension study 20140159 (see “study 20140159 above). Although the fatality in study 20070208 was determined to be multifactorial, a causal role for hypocalcemia as a result of treatment with cinacalcet could not be excluded. In study 20140159, on the other hand, the fatal event was not deemed to be related to cinacalcet by the investigator.
In the non-interventional cinacalcet paediatric studies, 10 deaths were recorded. 5 of the subjects had received cinacalcet. Two deaths were recorded in Study 20090198 (systemic fungal infections and respiratory failure). Neither death was reported by the investigator as related to cinacalcet (please refer to headline “Study 20090198”).
In the NAPRTCS registry study (Study 20120116), 3 fatal cases among subjects having received cinacalcet were recorded. The causes of death were haemorrhagic pancreatitis for 1 subject and are unknown for the other 2 subjects (1 subject collapsed and was unable to be resuscitated and no details were provided for the other death, which occurred in a subject with acute lymphoblastic leukaemia-multiple complication). They first 2 subjects were known to have stopped cinacalcet more than two months before the death. The cause of death in the third case was complications to acute lymphoblastic leukaemia.

No formal drug-drug interaction studies were conducted in paediatric patients with CKD and secondary HPT receiving dialysis. No update of section 4.5 of the SmPC is foreseen. In study 122055 patient- and disease-descriptors/covariates were evaluated as predictors of key PK parameters. These covariates included: demographic factors, organ function biomarkers, disease characteristics and concomitant medications. Treatment regimens for sHPT are rather similar between adults and paediatric patients, concomitant medications include vitamin D, phosphate binders and calcium supplements. However, especially in very young children drug management could differ as additional medication might be indicated to support weight gain or other conditions specific for infants.
The main difference in the treatment of secondary hyperparathyroidism between adults and the paediatric population is the treatment of possible growth retardation and the underlying comorbidities. The applicant has provided a discussion covering the most common used therapeutics to treat the comorbid conditions contributing to growth retardation and has also discussed the potential for interaction with the metabolism of cinacalcet.

The most common medications used to treat comorbidities in relation to growth retardation in the paediatric population will most likely be found in the area of Anemia, Vitamin D Deficiency, undernutrition, metabolic Acidosis or renal bone disease. The typical standard medication used, as outlined by the applicant, will most likely not interfere with Cinacalcet metabolism. This is especially true for the treatment of growth retardation with recombinant growth hormone or the treatment of undernutrition or Anemia via dietary supplements such as Vitamins or caloric supplements. Other medications used such as Erythropoetin are not metabolized by CYP enzymes. Furthermore the treatment of other comorbidities in relation to growth retardation will most likely not be expected to interact with cinacalcet via CYP mediated drug interactions, since alternative pathways such as CYP2R1 and CPY27B1, and CYP24AI exist or the medication applied are metabolized via chemical reactions, as discussed by the applicant as part of the responses to Day180 questions. Other therapies such as vitamin D, phosphate binders, and calcium supplementation have been evaluated in the clinical studies of cinacalcet with no known drug-drug interactions with cinacalcet. In conclusion, the activity of CYP3A4 and 2D6 reaches levels similar to those of adults by approximately 2-3 years of age. The main differences with regards to the treatment of hyperparathyroidism between both treatment groups therefore lies in the treatment of possible growth retardation and the underlying comorbidities. The applicant´s argumentation line provided as part of the responses to Day180 questions as to why interactions with Cinacalcet treatment are most likely not to occur can be followed, especially since treatment regimens directed at secondary hyperparathyroidism and associated comorbidities can be considered comparable between adults and paediatric patients and are already covered with appropriate statements in section 4.4 and 4.5 of the SmPC.

2.8. Risk Management Plan

Safety concerns

Important identified risks	hypocalcemia
	convulsions/seizures
	hypersensitivity reactions (including rash, urticaria, and angioedema)
	hypotension and/or worsening heart failure
	QT prolongation and ventricular arrhythmias secondary to hypocalcemia
Important potential risks	fracture
	acute pancreatitis
	possible drug-related hepatic disorders
	nervous system disorders (excluding seizure)
	neoplastic events
	medication errors with cinacalcet granules in capsules for pediatric use
Missing information	pregnant or breastfeeding women

Pharmacovigilance plan

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Registry study, in collaboration with IPDN, to evaluate the risk of hypocalcaemia (eg, clinical characteristics, laboratory variables [PTH, Ca, and P], hospitalization due to hypocalcaemia, co-medication, cinacalcet doses) in pediatric patients treated with cinacalcet (Category 3)	To describe characteristics of pediatric patients receiving dialysis who initiate cinacalcet and assess laboratory values longitudinally, and the risk of hypocalcaemia and subsequent changes in treatment following cinacalcet initiation.	Hypocalcaemia	Planned	To be determined

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hypocalcemia	Relevant text is provided in the following sections of the SmPC: • Section 4.1, Therapeutic indications • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 4.8, Undesirable effects • Section 4.9, Overdose • Section 5.1, Pharmacodynamic properties • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the PIL: • What Mimpara is and what it is used for • What you need to know before you take	*None*

	Mimpara • Possible side effects	
Convulsions/seizure	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects • How to take Mimpara	None
Hypersensitivity reactions (including rash, urticaria, and angioedema	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects	None
Hypotension and/or worsening heart failure	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects	None
QT Prolongation and ventricular arrhythmias secondary to hypocalcemia	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL:	None

	• What you need to know before you take Mimpara • Possible side effects	
Important Potential Risks		
Fracture	Relevant text is provided in the following sections of the SmPC: • Section 5.1, Pharmacodynamic properties Relevant text is provided in the following sections of the PIL: • What Mimpara is and what it is used for	None
Acute pancreatitis	None	None
Possible drug-related hepatic disorders	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 Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara	None
Nervous system disorders (excluding seizure)	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Possible side effects	None
Neoplastic events	None	None
Medication errors with cinacalcet granules in capsules for pediatric use	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.9, Overdose Relevant text is provided in the following sections of the PIL: • How to take Mimpara	None
Missing Information		
Pregnant or	Relevant text is provided in the following	None

breastfeeding women	sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.3 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Secondary hyperparathyroidism (HPT) develops in children and adults with chronic kidney disease (CKD). The disorder is characterized by persistently elevated levels of parathyroid hormone (PTH) in serum or plasma, and it represents an adaptive response that serves primarily to maintain calcium homeostasis systemically as kidney function declines.

The development of CKD-mineral bone disease (CKD-MBD) is manifested by either 1 or a combination of the following: 1) abnormalities in calcium, phosphorus, PTH, or vitamin D metabolism; 2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and 3) vascular or other soft tissue calcification (KDIGO, 2009). In children, CKD-MBD develops early in the course of CKD, such that a significant portion of children on dialysis have manifestations of CKD-MBD.

The clinical outcome most frequently associated with secondary HPT is the development of high-turnover bone disease, which results in reduced bone mass and increases the risk of bone deformities and fractures in adults and children with advanced CKD. Secondary HPT is also thought to play a role in growth retardation in children, potentially through alterations in bone architecture (including lesions in the epiphyseal growth plate), which interfere with bone formation and lead to impaired bone growth.

3.1.2. Available therapies and unmet medical need

Children with ESRD and secondary HPT are prioritized for kidney transplant and often undergo definitive treatment with renal transplant within the first year after starting dialysis. In addition, to adequately treat paediatric patients with cinacalcet, an age appropriate formulation is needed since the starting dose of 0.2 mg/kg cannot be reached with the 30 mg tablets, the dose will always be too high.

Currently, there are no approved medical therapies for the management of secondary HPT in paediatric patients with CKD receiving dialysis in the European Union (EU) or the US. A number of drugs have been approved in adult patients including Cinacalcet. Current treatment consists of vitamin D sterols, such as calcitriol or synthetic vitamin D analogues and phosphate binding. In some circumstances, their use may be limited due to aggravation of hypercalcemia and hyperphosphatemia, conditions associated with increased long-term cardiovascular morbidity and mortality.

The pathophysiology of secondary HPT is thought to be similar in adults and children. Since secondary hyperparathyroidism is relatively common in children with CKD receiving dialysis, this may lead to off-label use of Cinacalcet without information about age- and weight-based dosing and titration.

3.1.3. Main clinical studies

The primary biochemical end-point in main paediatric studies (achievement of a ≥ 30% reduction from baseline in mean plasma iPTH) is considered to be a relevant surrogate marker for efficacy in treatment of

sHPT in CKD). Plasma iPTH is used in clinical routine today to balance currently available therapy for this condition.

The safety and efficacy of cinacalcet in paediatrics is primarily studied in two phase 3, controlled studies (20070208 and 20130356), conducted in subjects aged 6 to < 18 years with CKD and secondary HPT receiving dialysis. Study 20070208 was conducted in 43 subjects and included a 30-week double-blind, placebo-controlled phase followed by a 30-week open-label phase. Study 20130356 was a randomized, multicentre, open-label, controlled study. Cinacalcet was evaluated in paediatric subjects between the ages of 6 and < 18 years, with secondary hyperparathyroidism (HPT) and chronic kidney disease (CKD) who were receiving either haemodialysis or peritoneal dialysis. Subjects were randomized into 1 of 2 treatment groups; administration of cinacalcet daily in addition to standard of care (SOC) treatment group, or a SOC treatment group. Subjects in both treatment groups who completed the 20-week treatment period were eligible to enrol in an open-label extension study (Study 20140159) for further safety follow-up.

All subjects in these studies received standard of care with vitamin D sterols (calcitriol and its analogues), calcium supplements, and phosphate binders at the discretion of the investigator.

A phase 2 single arm study in children <6 years has also recently been completed. A retrospective chart review has also been performed in children <6 years.

In addition, the submission included paediatric data from a Bayesian extrapolation study, two single dose phase 1 studies and description of an ongoing extension study.

PK data are available in a single dose setting in paediatric patients from 8 month up to 16 years (study 20030227, study 20090005) and in a multiple dose setting from children 12 month -18 years (study 20070208 and study 20110100). In addition, PK data in children 28 days-18 years were modelled in POP PK and PD study 122055 and PBPK study 122086.

3.2. Favourable effects

Two controlled phase 3 studies were performed in paediatric subjects 6 to 18 years. Both were terminated early, study 20070208 due to a fatality in the study and study 20130356 due to difficulties in recruitment.

Study 20070208 showed trend to positive efficacy results. A total of 5 out of 21 (24%) of the placebo patients and 11 out of 22 (50%) of Cinacalcet treated patients reached the primary endpoint (p= 0.08), which was the number of patients achieving ≥ 30% reduction in mean iPTH from baseline to the efficacy assessment phase. When iPTH values collected after investigational product suspension were excluded, the corresponding numbers presented were 4 out of 21 (19%) in placebo and 12 out of 22 (55%) in Cinacalcet treated patients, p=0.017.

Cinacalcet + SOC were compared with SOC only in the second pivotal study for the paediatric application, open-label study 20130356. The results of study 21030356 showed that the proportion of subjects achieving ≥ 30% reduction from baseline in mean plasma iPTH during weeks 17 to 20 was lower (22.2% [6 of 27 subjects]) in the cinacalcet + SOC group than in the SOC group (32.1% [9 of 28 subjects]) (p =0.42, stratified by age). The difference ([cinacalcet + SOC] – [SOC]) in the proportions was -9.9% (95% confidence interval [CI] -33.3%, 13.4%).

In summary, no trend towards cinacalcet efficacy in reducing iPTH compared to SOC was seen in this study. However, the mean dose of cinacalcet during the EAP in Study 20130356 was approximately 80% lower than

the mean dose during the EAP in Study 20070208. The drug exposure in this open-label study might have been a direct consequence of additional safety measures and a conservative management of investigational product dosing focused on further minimizing the risk of hypocalcemia. Cinacalcet dose was reduced or withheld even in situations when the subject's corrected serum calcium level was still in the normal range.

Comparison with adult data: A total of 1136 adult subjects with secondary HPT and ESRD were enrolled in 3 key phase 3 studies. When the results were pooled, the iPTH concentration was reduced by 42% during the efficacy-assessment phase in the cinacalcet group (n=665) compared with an increase of 8% in the placebo group (n=471). Serum calcium was reduced by 7% during the efficacy-assessment phase in the cinacalcet group compared with an increase of 0.6% in the placebo group.

3.3. Uncertainties and limitations about favourable effects

In the pivotal study 20070208, a larger proportion of patients discontinued IP in the Cinacalcet group (17 vs 10 subjects in the placebo group). Although a numeric imbalance in IP discontinuation was observed between treatment groups, the primary reasons for discontinuation (study termination and kidney transplant) were unrelated to treatment received or treatment outcomes.

Because of the early termination of this study due to fatality, less data were collected than originally planned. As a large proportion of the patients did not complete the planned treatment period, LOCF has a large impact on the results. Consequently, the results for the primary efficacy endpoint in study 20070208 are not robust. The observed effect in reduction of iPTH levels in study 20070208 is considered rather small. The mean differences are directionally consistent with the primary analysis for the study, which was based on the dichotomized response endpoint of PTH reduction of > 30% from baseline. However the individual patients' data show that there is no substantial difference between the two treatment groups over the time. Consequently, it is not possible to make a clear statement that the iPTH reduction is in favour for cinacalcet arm.

Secondary endpoints that could have helped interpreting the clinical effect outside the surrogate endpoint (such as e.g. bone mineral density) could not be thoroughly assessed due to the relatively short duration of drug exposure and the low number of evaluable subjects in both groups.

The summary of results of study 20130356 showed that dose titration seems not to have been performed according to the anticipated protocol or the recommendations in the SmPC and that drug exposure might in general have been too low to achieve therapeutic benefit. This might also be an issue later in clinical practice where the chronic "sub therapeutic" treatment might not provide any benefit to the patient. The study results did not demonstrate a statistically significant difference between treatment groups in the primary endpoint (proportion of subjects who achieved a $\geq$ 30% reduction in iPTH during the EAP). The effect was even smaller than could be anticipated from interim data.

The results of the Bayesian extrapolation study show a tendency to higher response rate in the adult population compared to the paediatric population.

Since the final results from study 20130356 became available, the applicant proposes to restrict the paediatric indication for Mimpara capsules as a second line treatment option in paediatric patients where treatment with vitamin D is not sufficient.

The sought indication was from children > 28 days. However, the youngest subject recruited and evaluated in any trials was 7 months old (Study 20090198, a retrospective chart review). Extrapolation on the basis of

modelling- and simulation was performed using popPK, PKPD and PBPK analyses. The PK/PD analysis was deemed too uncertain. The PBPK was suggested to be used to predict pK in young children as the clinical pk data is very limited in this age group. Even if the PBPK simulations provide a conservative estimate of expected exposures in children the use of PBPK in this context for cinacalcet is too uncertain as the PBPK model is children do not show adequate performance as well as the Qualification aspects in young children (below 3 years) is too limited to use PBPK for extrapolation.

The simulations from the popPK model can be used to guide the start dose in children down to 3 years of age and while the popPK model can be further improved, it appears passable for this purpose. There remain significant uncertainties that reliable and reasonable dosing recommendations can be derived, especially for younger age cohorts. As the extrapolation exercises do not provide reliable results for all age groups, the target population has been adapted accordingly and restricted to age 3 and older.

3.4. Unfavourable effects

The important identified risks in the Cinacalcet RMP include hypocalcaemia, convulsion/seizures, hypersensitivity reactions, hypotension and/or worsening of heart failure and QT prolongation and ventricular arrhythmias secondary to hypocalcemia. In adult studies, the most commonly reported undesirable effects were nausea (31% cinacalcet vs. 19% placebo) and vomiting (27% cinacalcet vs. 15% placebo)

In the controlled paediatric study 20070208, the most common events were vomiting (7 subjects [32%] cinacalcet vs 5 subjects [24%] in placebo group), hypocalcemia (5 subjects [23%] cinacalcet) vs 4 subjects [19%] in placebo group, and nausea (4 subjects [18%] vs 3 subjects [14%]).

A higher proportion of paediatric subjects in the cinacalcet group compared to the placebo group had corrected total calcium concentrations < 8.4 mg/dL (32% in the cinacalcet group and 14% in the placebo group) and < 7.5 mg/dL (14% in the cinacalcet group and 0% in the placebo group).

The study 20070208 was terminated early due to a fatality in the cinacalcet group. At the time of event onset, the 14-year old patient was on 90 mg of cinacalcet. A causal role for hypocalcaemia could not be excluded.

In the final study report from studies 20130356 and 20110100, no subjects were withdrawn from the study due to an adverse event and no events were fatal. No new signals or unexpected safety concerns were observed.

3.5. Uncertainties and limitations about unfavourable effects

The important potential risks in the cinacalcet RMP include possible drug-related hepatic disorders, nervous system disorders, acute pancreatitis, fracture, myocardial ischemia and neoplastic events.

Across the entire cinacalcet paediatric development program, 103 subjects were exposed to cinacalcet in phase 1, 2, and 3 interventional clinical studies (cut-off date for Study 20140159: 29 April 2016; all other studies complete). This includes 5 subjects between 28 days and < 2 years, 24 subjects between 2 and < 6 years, 24 subjects between 6 and < 12 years, and 48 subjects between 12 and < 18 years; 2 subjects were 18 years old at enrolment and are classified into "18 to < 65 years" category. This limited number of paediatric subjects allows only the detection of common and very common adverse events.

Due to the fatality in a hypocalcaemic patient in Study 20070208, the maximum dose was lower in recently completed study 20130356 compared to study 20070208. However, the recorded level of frequency of hypocalcaemia was not lower in Study 20130356 (7/28 subjects in the cinacalcet group) than in study 20070208 (5/23 in the double-blind phase), Due to preclinical findings, growth retardation in children secondary to hypocalcaemia has been proposed to be added as an important potential risk. However, it is considered that this risk is already covered by the general important identified risk of hypocalcaemia.

No formal drug-drug interaction studies were conducted in paediatric patients with CKD and secondary HPT receiving dialysis. The activity of CYP3A4 and 2D6 reaches levels similar to those of adults by approximately 2-3 year of age. The main differences with regards to the treatment of hyperparathyroidism between both treatment groups therefore lies in the treatment of possible growth retardation and the underlying comorbidities. Treatment regimens directed at secondary hyperparathyroidism and associated comorbidities can be considered comparable between adults and paediatric patients and are already covered with appropriate statements in section 4.4 and 4.5 of the SmPC.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The favorable effects of Cinacalcet were measured mainly in terms of surrogate endpoint, iPTH, both in adult and paediatric studies. Maintenance of PTH levels within a target range and of serum calcium in the normal range as well as avoidance of hyperphosphatemia are the main goals of treatment. Reaching these goals is challenging, however. The clinical relevance of reaching target levels of PTH is supported by relevant treatment guidelines and publications, but the clinical benefit of lowering PTH over a limited period of time is unknown. As in the paediatric population patients will be prioritized for kidney transplant, treatment durations will be shorter for most patients when compared to adults. An impact on harder clinical outcome measures such as growth or skeletal development seems not established in the respective population and associations between reductions in PTH and reductions of bone metabolism markers were not statistically significant.

The presentations of patients with hypocalcaemia (main safety concern) vary widely, from asymptomatic to life-threatening situations. Most hypocalcaemic emergencies are mild and require only supportive treatment and further laboratory evaluation. Severe hypocalcaemia may result in seizures, tetany, refractory hypotension, arrhythmias and death. This is of concern since one fatality, possibly due to hypocalcaemia, has been reported in one of the paediatric studies.

A new formulation (granules filled in gelatine capsules that are intended to be sprinkled out on food or liquid or administered through gastric or gastro-nasal tubes) could be favourable in paediatric population and also in adult patients with difficulties in swallowing. However, the handling of the capsules (to open the capsules to administer just the granules) may not be optimal way of administration.

3.6.2. Balance of benefits and risks

Based on the pharmacological mechanism, PK extrapolation for a safe starting dose in children above 3 years as well as results from the 20070208 study, it is likely that Mimpara is effective in lowering PTH in paediatric

patients if the dose can be titrated without endangering hypocalcaemia- such as in cases where the use of SOC is limited by hypercalcaemia. Mimpara failed to meet its primary objective in study 20130356 and other treatment options should be considered before initiating cinacalcet. Nevertheless, individual subject profiles from the phase 3 studies show a trend toward iPTH reduction with increased dose of cinacalcet and an increase in iPTH is seen when cinacalcet treatment is stopped or interrupted. An unmet medical need to treat patients who still have elevated PTH levels in spite of optimally titrated standard of care therapy is recognized. Further data is expected to be obtained in a proposed registry study, agreed as a category 3 study.

A restricted indication in the paediatric population in whom sHPT is not "adequately controlled with standard of care therapy" was considered adequate by CHMP, in particular in the context of elevated S-Ca levels. Due to the risk of severe hypocalcaemia in children, the treatment should not be initiated at S-Ca levels at the lower limit of normal. Corrected serum calcium should be monitored, and be above or in the upper range of the reference interval prior to initiation of Mimpara in the paediatric population. Mimpara should not be used in hypocalcaemia in both adults and children and hypocalcaemia is therefore a contraindication in the SmPC.

For children under 3 years, the data is not sufficient to recommend a starting dose with acceptable safety.

Although the new formulation may represent an improvement compared to crushing tablets and are in line with the PDCO requirement to develop an age adequate formulation, the capsules used have proven to be very difficult to open without damaging them and avoiding spillage. The potential risk of spillage may jeopardize dose accuracy, especially since several capsules may need to be opened. The applicant has commited to evaluate alternative capsule designs and identify a more suitable primary container/capsule for the granules. Also, to reduce the number of capsules for the patients requiring a higher dose, the Applicant commits to considering the need for any additional strength of 10 or 15 mg. In addition, a commitment to improve the uniformity of content method has been made.

3.7. Conclusions

The benefit/risk for Mimpara for the proposed new indication in children above 3 years not adequately controlled with standard of care therapy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Mimpara 1 mg, 2.5 mg and 5 mg granules in capsules for opening, is favourable in the following indications:

Secondary hyperparathyroidism

Adults
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Paediatric population
Treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy (see section 4.4).

Mimpara may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section 5.1).

Parathyroid carcinoma and primary hyperparathyroidism in adults

Reduction of hypercalcaemia in adult patients with:
- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

The CHMP therefore recommends the extension of the marketing authorisation for Mimpara 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.

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.

In addition, CHMP recommends the variations to the terms of the marketing authorisation concerning the following changes:

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end stage renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.

A divergent position to the majority recommendation is appended to this report.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0008/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

APPENDIX 1

DIVERGENT POSITION DATED 22 June 2017

Although the tablets and the capsule formulations provide acceptable dosing flexibility for the starting dose and for those who can swallow and take 30 mg tablets, the available formulations are not considered adequate for the older children and those at a higher maintenance dose who are not able to swallow. The capsules have proven very difficult to open without damage by trained pharmaceutical assessors and performance in a real life setting may be even worse. Opening the capsule and mixing the granules with food or liquid may be found difficult by the patient or the responsible person such that inaccurate dosing may result. For children and patients with difficulties in swallowing, a large number of capsules (up to 12) may be needed on a daily basis. This would imply substantial discomfort for the patient, parent or care giver. The dose accuracy is also considered questionable, with content uniformity being tested on the entire capsule rather than the contents, essentially the delivered dose. Therefore, for patient's comfort and safety, this kind of administration seems to be questionable and should be reconsidered. A better single-dose container should be developed.

New instructions in the SmPC, the labelling, and the commitments by the applicant are acknowledged. Nonetheless, the current product is still poorly designed and not patient friendly. Replacing the off-label use of crushed tablets with a poorly designed alternative is not considered an improvement. Therefore, the benefit/risk remains negative.

London, 22 June 2017

DIVERGENT POSITION DATED 22 June 2017

Mimpara EMEA/H/C/000570/X/0055/G

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Jean-Louis Robert