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EMA/145025/2015
Committee for Medicinal Products for Human Use (CHMP)

Mimpara

(cinacalcet)

Procedure No. EMEA/H/C/000570/P46 028

Amgen Europe B.V.

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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1. Introduction

On 2 October 2014, the MAH submitted a completed paediatric study for Mimpara 20070208, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are now submitted as a post-authorisation measure. Study 20070208 is also a binding measure of the Mimpara PIP.

No changes to the product labelling are proposed at this time. No changes to the pharmaceutical form or route of administration are involved.

2. Scientific discussion

2.1. Clinical aspects

2.1.1. Introduction

The MAH submitted a final report for:

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Pediatric Subjects with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis (study No 20070208)

The planned study population was 100 subjects. Due to an early termination, a total of 43 subjects were randomized, all of whom received at least 1 dose of investigational product.

Dosing was suspended following a fatality and was subsequently terminated early. One subject in the cinacalcet group experienced a fatal adverse event (reported term: cardiopulmonary failure) during the study. Although the fatality was determined to be multifactorial, a causal role for hypocalcemia could not be excluded.

2.1.2. Clinical study

in Pediatric Subjects with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis

Methods

Objectives / endpoints

Primary

- to demonstrate the efficacy of cinacalcet for reducing the plasma intact parathyroid hormone (iPTH) by ≥ 30%

Secondary

- to demonstrate the efficacy of cinacalcet for lowering the plasma iPTH level to ≤ 300 pg/mL (31.8 pmol/L)
- to demonstrate the impact of cinacalcet on corrected total serum calcium level
- to demonstrate the impact of cinacalcet on serum phosphorus level

- to demonstrate the impact of cinacalcet on the calcium phosphorous product (Ca x P)
- to assess the impact of cinacalcet on growth
- to assess percent change in ionized calcium from baseline to the mean value during the efficacy assessment phase (EAP)

Safety

- to assess the safety and tolerability of cinacalcet (including evaluation of adverse events and incidence of hypocalcemia)

Exploratory

- assessment of plasma cinacalcet concentrations

Study 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.

In addition to standard of care, in the double-blind phase, subjects were randomized 1:1 to receive either cinacalcet or placebo. Randomization was stratified by age group (6 years to < 12 years and 12 years to < 18 years). The double-blind, placebo-controlled phase of the study consisted of a 24-week dose-titration period followed by a 6-week EAP. Subjects who completed the double-blind phase were eligible to enter the 30-week open-label phase of the study. 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.

Dose-titration visits and the dispensation of new investigational product occurred once every 4 weeks in the dose-titration period of each phase. During the EAP of the double-blind phase and open-label maintenance phase, investigational product was dispensed once every 2 weeks.

Blood samples were collected to measure iPTH, total serum calcium, phosphorous, and albumin 1 week prior to each visit at which the dose of investigational product was allowed to be uptitrated. Serum calcium was reported as a corrected value by the central laboratory based on calcium and albumin concentrations. Blood samples for pharmacokinetic (PK) analysis were collected pre-dose (all subjects [those receiving peritoneal dialysis or hemodialysis]) 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. Other study visits to measure iPTH, total serum calcium, phosphorous, and albumin were scheduled after any change in investigational product dose.

Sample size

The primary endpoint in this study is the achievement of a ≥ 30% reduction in mean iPTH from the baseline during the EAP. A completed phase 3 clinical trial in the adult dialysis population revealed that among subjects who have baseline iPTH ≥ 350 pg/mL (37.1 pmol/L), about 64% of cinacalcet subjects compared to 11% of placebo subjects achieved greater or equal to 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 is anticipated in the pediatric dialysis population. The proportions are 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) will provide 99% power to detect the proposed difference. In addition, the study is also sufficiently powered for a smaller treatment difference; the power would be 88% should the observed proportions to be 45% and 15% respectively.

The planned study population was 100 subjects. Dosing was suspended following a fatality and was subsequently terminated early. Due to the early termination, a total of 43 subjects were randomized, all of whom received at least 1 dose of investigational product.

Treatments

Dosing

Cinacalcet was dosed once daily with a starting dose of 0.2 mg/kg and titrated upwards according to plasma iPTH, serum calcium levels, and subject safety information. The maximum dose was set to 4.2 mg/kg, not to exceed a total dose of 180 mg for any subject, the labelled recommended adult maximum dose.

Subjects were eligible for a dose increase once every 4 weeks during the double-blind, placebo-controlled, dose titration phase (ie, Week 4, 8, 12, 16, 20, and 24 visits) and during the open-label dose titration phase (ie, Week 34, 38, 42, 46, 50, and 54 visits).

Table. Investigational Product Dosage Administration for Double-blind and Open-label

Dry weight (kg)	Starting Daily Dose[a] (mg)	Possible Dose Titration[b]					
		Titration Step					
		1	2	3	4	5	6
12.5 to 14	2.5	5	10	15	30	30	30
> 14 to 21	2.5	5	10	15	30	60	60
> 21 to 25	2.5	5	10	15	30	60	90
> 25 to 28	5	10	15	30	60	90	90
> 28 to 49	5	10	15	30	60	90	120
> 49 to < 75	10	15	30	60	90	120	180
≥ 75	15	30	60	90	120	180	180

[a] Starting dose is ≤ 0.2 mg/kg/day for the first dose during double-blind and for the first dose during open-label.

Statistical Methods

All efficacy endpoints were assessed during the double-blind phase of the study, and analyses were performed using the full analysis set, defined as all randomized subjects with at least 1 post-randomization assessment. For efficacy endpoints, a hierarchical testing procedure was used to test the primary and first 4 secondary endpoints. The primary endpoint was tested at a significance level of 0.05 (2 sided). The first 4 secondary endpoints were tested using Holm's method at an overall significance level of 0.05 if the primary efficacy endpoint was significant. The other secondary endpoints were tested at a significance level of 0.05 without any multiplicity adjustment. 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.

Safety data were reported for both the double-blind and open-label phases of the study. The safety analysis set consisted of all randomized subjects who received at least 1 dose of investigational

product. Safety analyses included adverse events, serum corrected calcium, clinical laboratory tests, vital signs, and electrocardiograms.

Results

Actual dosages

Weight-adjusted cinacalcet dose (mg/kg) by visit in the double blind phase

Subject	Nominal Time (Week)							
	Day 1	Week 3	Week 7	Week 11	Week 15	Week 19	Week 23	Week 27
6-<12 yrs								
N	6	6	5	6	6	3	3	2
Min	0.105	0.105	0.207	0.259	0.130	0.126	0.128	0.128
Max	0.175	0.175	0.337	0.535	1.00	1.93	2.88	3.87
12-<18 yrs								
N	15	15	12	10	6	5	4	2
Min	0.106	0.106	0.199	0.181	0.294	0.291	0.194	0.601
Max	0.197	0.197	0.373	0.743	0.809	1.31	1.98	0.800

Pharmacokinetics

Assessor's comment:

No PK is reported. According to the study report a population PK analysis will be performed based on the sparse samples in the current study combined with exposure data from other paediatric studies with cinacalcet. The population PK analysis will be reported separately.

The sponsor is requested to submitted population PK analysis of cinacalcet.

Baseline dermographics

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)
Min, max	7, 17	6, 18	6, 18
Sex (n [%])			
Male/Female	11 (52.4)/10 (47.6)	10 (45.5)/12 (54.5)	21 (48.8)/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/Not Hispanic	5 (23.8)/16 (76.2)	3 (13.6)/19 (86.4)	8 (18.6)/35 (81.4)

SD = standard deviation; max = maximum.
Source: *Table 14-2.1 and Table 14-2.5*

Subject Disposition:

A total of 43 subjects were randomized, of whom 43 received at least 1 dose of investigational product. Of the 43 subjects randomized, 22 subjects received cinacalcet, and 21 subjects received placebo. A total of 16 (37.2%) subjects (5 [22.7%] from the cinacalcet group and 11 [52.4%] from the placebo group) completed the double-blind phase. Eighteen subjects (81.8%) in the cinacalcet group and 13

subjects (61.9%) in the placebo group discontinued investigational product during the double-blind phase. The most common reason for investigational product discontinuation in 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).

A total of 12 subjects were enrolled in the open-label phase, and 10 received investigational product: 4 previously received cinacalcet, and 6 previously received placebo. Four subjects (33.3%) completed the open-label phase, and 8 subjects (66.7%) discontinued investigational product during the open-label phase. The most common reason for investigational product discontinuation was administrative decision due to the early termination of the study (58.3%).

Efficacy Results:

In the analysis of the primary endpoint including all data collected prior to the suspension of investigational product, the proportion of subjects achieving ≥ 30% reduction from cinacalcet group and 19.0% (4/21 subjects) in the placebo group (p = 0.017, stratified by age); the difference (cinacalcet - placebo) in the proportions was 35.50% (95% confidence interval [CI] 8.76%, 62.24%)

An analysis that included all iPTH data collected before and after investigational product suspension showed that 50.0% of subjects (11/22 subjects) in the cinacalcet group and 23.8% of subjects (5/21 subjects) in the placebo group achieved a ≥ 30% reduction in iPTH (p = 0.081)

The proportion of subjects in the cinacalcet group who achieved a ≥ 30% reduction from baseline in iPTH was greater in younger children between 6 and < 12 years of age (100%; 6/6 subjects) than in adolescent children between 12 and < 18 years of age (37.5%; 6/16 subjects).

The proportion of subjects achieving a mean iPTH value ≤ 300 pg/mL (31.8 pmol/L) during the EAP was 27.3% in the cinacalcet group and 23.8% in the placebo group; the difference (cinacalcet - placebo) in the proportions was 3.46% (95% CI -22.58%,29.51%).

Analyses of additional secondary endpoints showed the following:

- The least squares (LS) mean (95% CI) of the percent change in mean corrected total serum calcium during the EAP was -4.6% (-8.4%, -0.9%) in the cinacalcet group and -1.0% (-4.9%, 2.9%) in the placebo group.
- The LS mean (95% CI) of the percent change in mean phosphorus during the EAP was 4.9% (-5.5%, 15.3%) in the cinacalcet group and 10.2% (-0.8%, 21.2%) in the placebo group.
- The LS mean (95% CI) of the percent change in mean Ca x P during the EAP was -2.0% (-11.4%, 7.4%) in the cinacalcet group and 8.0% (-1.8%, 17.7%) in the placebo group.

Safety results

In the double-blind phase, 81.8% of subjects in the cinacalcet group and 85.7% of subjects in the placebo group had at least 1 adverse event. The most common events in the cinacalcet group were vomiting (31.8%, 7/22 subjects), hypocalcemia (22.7%, 5/22 subjects), and nausea (18.2%, 4/22 subjects).

Adverse events were reported for 9 (90.0%) subjects in the open-label phase. The adverse events reported for more than 1 subject were hypocalcemia (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)

During the double-blind phase, 2 subjects (9.5%) in the placebo group and no subjects in the cinacalcet group experienced an adverse event that led to withdrawal of the investigational product. No subjects experienced an adverse event that led to withdrawal of the investigational product in the open-label phase.

During the double-blind phase, 9 subjects (42.9%) in the placebo group and 9 subjects (40.9%) in the cinacalcet group had a serious adverse event. During the open-label phase, 4 subjects (40.0%) had serious adverse events. No serious adverse event was experienced by more than 1 subject.

One subject experienced a fatal adverse event (reported preferred term: cardiopulmonary failure) during the study. This subject was randomized to and received cinacalcet. Although the fatality was determined to be multifactorial, a causal role for hypocalcemia could not be excluded.

Overall, the adverse events of interest were similarly distributed between subjects in the placebo and cinacalcet groups in the double-blind phase. No notable changes were observed in clinical chemistry evaluations by visit, with the exception of median iPTH and corrected total calcium. Both iPTH and corrected calcium concentrations were reduced in children who received cinacalcet.

2.1.3. Discussion on clinical aspects

- This study was terminated early due to a fatality and after consultation with regulatory authorities.
- The proportion of subjects achieving a ≥ 30% reduction from baseline in mean plasma iPTH during the EAP in the cinacalcet group was 54.5% compared with 19.0% of subjects in the placebo group ($p = 0.017$). This analysis excluded iPTH values collected after investigational product suspension.
- The observed adverse event profile in this study was generally consistent with the known safety profile of cinacalcet in the treatment of adults with secondary hyperparathyroidism as listed in the prescribing information.
- Hypocalcemia was reported as an adverse event in similar proportions of pediatric subjects in the cinacalcet and placebo groups.
- A higher proportion of pediatric 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).
- One subject in the cinacalcet group experienced a fatal adverse event (reported term: cardiopulmonary failure) during the study. Although the fatality was determined to be multifactorial, a causal role for hypocalcemia could not be excluded.

Following this fatal case in a paediatric patient, dosing was suspended in January 2013 and subsequently a decision was taken to conduct an early termination of the study. The outcome of Amgen investigation into the fatal case was shared with the EMA and the PDCO through various interactions in 2013 and 2014:

- Type II variation EMEA/H/C/000570/II/0042 (positive opinion 19th September 2013) which included inclusion of safety information regarding the paediatric fatal case in in the product information.

- EMA Pre-submission consultation with the cinacalcet PIP PDCO Rapporteur and Peer Reviewer on 30th September 2013
- EMEA-000078-PIP01-07-M04, submitted in October 2013 and completed 17 January 2014 which included consent from PDCO to terminate study 20070208 early.
- EMEA-000078-PIP01-07-M05 withdrawn July 2014.

Rapporteur's overall conclusion and recommendation

Overall conclusion

Following a fatal event reported in the Mimpara paediatric Study 20070208, the study was terminated early. A Dear Healthcare Provider (DHCP) letter was distributed to all global nephrologists in accordance with local regulations with the intent to alert them to the recent paediatric event and to reinforce that Mimpara is not indicated for use in paediatric subjects. The Summary of Product Characteristics (SmPC) wording was revised with regard to use in paediatric patients in 2013. Amgen is currently working on a PIP modification request to be submitted to the PDCO in the near future.

Although the fatality in Study 20070208 was determined to be multifactorial, a causal role for hypocalcemia could not be excluded. The risk of hypocalcaemia is known with Mimpara and is associated with its PTH lowering effect. The EU SmPC contains warnings, including precautions in higher risk patients, the need to monitor for the development of hypocalcaemia and appropriate management measures.

Recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide population PK analysis as part of this procedure. (see section IV "Additional clarifications requested")

Additional clarifications requested

Based on the data submitted, the MAH should provide the pediatric population PK analysis study report of cinacalcet as part of this procedure. The MAH should discuss if the model can be adequately qualified for predictive purposes with respect for any dosing recommendations or modifications of the current SmPC.

Annex 1. The following table shows the information for the paediatric studies that are part of the Mimpara PIP.

Non clinical studies

Product Name: Mimpara Active substance: Cinacalcet

Study title	Study number	Date of completion	
A Single Dose Escalating and 2-Week Tolerability Study of AMG 073 in Juvenile Beagle Dogs	109584	11 Jun 2008	
6-month oral gavage toxicity study in juvenile dogs	110057	11 Nov 2008	

Clinical studies

Study title	Study number	Date of completion	
Study 20030227 A Phase 1, open-label, non-randomised, single dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of cinacalcet HCl in paediatric subjects with chronic kidney disease receiving dialysis	20030227	13 Jun 2006	
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	20070293	05 Aug 2008	
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	20090005	Planned: Oct 2015	

Study title	Study number	Date of completion	
PK/PD Modelling Study	PIP Study 5	Planned: Jan 2016	
Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Cinacalcet HCl in Pediatric Subjects with Chronic Kidney Disease and Secondary Hyperparathyroidism Receiving Dialysis	20070208 (PIP Study 6)	30 Apr 2014	
Retrospective Chart Review	20090198 (PIP Study 7)	24 Mar 2011	
PB/PK simulation ion paediatric subjects < 1 year of age	PIP Study 8	Planned: Jan 2016	