Clinical trial results:
An Open-label, Single-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Cinacalcet HCl in Pediatric Subjects Aged 28 Days to less than 6 Years With Chronic Kidney Disease Receiving Dialysis

Summary

EudraCT number	2009-017999-25
Trial protocol	GB BE DE Outside EU/EEA
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	20090005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01290029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000078-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the safety and tolerability of cinacalcet after a single oral dose in children aged 28 days to less than 6 years with chronic kidney disease receiving dialysis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and other local regulations/ guidelines. The study and all amendments were reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each center. Before any study-specific screening procedures were performed, written informed consent was obtained from the subject's parent or legally acceptable representative. The investigator was responsible for providing the subject's legally acceptable representative an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.
A conservative single, oral dosing strategy of 0.25 mg/kg cinacalcet in pediatric subjects aged 28 days to less than 6 years old was implemented. This dose is approximately half the adult starting dose on a mg/kg basis, and is lower than the mean dose of 0.39 mg/kg previously studied in 12 subjects age 6 to < 18 years in Study 20030227. To monitor subject safety, serum calcium and phosphorus were monitored throughout the study. To minimize blood loss due to the study, the blood volume required for safety laboratory and PK assessment were minimized and the number of collections reduced to the minimum requirement to enable the endpoints of this study to be analyzed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	14
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	3
Children (2-11 years)	11
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 7 study centers in Belgium (1 site), Germany (1 site), the United Kingdom (2 sites), and the United States (3 sites). The first participant was enrolled 25 January 2011.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to one of the following 2 pharmacodynamic (PD) sampling sequences: 2, 8, and 48 hours postdose; or 2, 12, and 48 hours postdose.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cinacalcet 0.25 mg/kg

Arm description:

Participants received a single oral dose of 0.25 mg/kg cinacalcet on day 1.

Arm type	Experimental
Investigational medicinal product name	Cinacalcet
Investigational medicinal product code	
Other name	Sensipar®, Mimpara®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received single oral doses of 0.25 mg/kg cinacalcet.

Number of subjects in period 1	Cinacalcet 0.25 mg/kg
Started	14
Received Study Treatment	12
Completed	12
Not completed	2
Other	2

Baseline characteristics

Reporting groups	
Reporting group title	Cinacalcet 0.25 mg/kg
Reporting group description:	
Participants received a single oral dose of 0.25 mg/kg cinacalcet on day 1.	

Reporting group values	Cinacalcet 0.25 mg/kg	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	39.5		
standard deviation	± 17.1	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	7	7	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	2	2	
Black (or African American)	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	9	9	
Other	3	3	
Ethnicity Units: Subjects			
Hispanic/Latino	5	5	
Not Hispanic/Latino	7	7	
Unknown	2	2	

End points

End points reporting groups

Reporting group title	Cinacalcet 0.25 mg/kg

Reporting group description:

Participants received a single oral dose of 0.25 mg/kg cinacalcet on day 1.

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:
• fatal
• life threatening
• requires in patient hospitalization or prolongation of existing hospitalization
• results in persistent or significant disability/incapacity
• congenital anomaly/birth defect
• other medically important serious event.
Treatment-related adverse events are those the investigator assessed as being possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, device(s) and/or procedure).
Events of interest included acute pancreatitis, convulsions, drug related hepatic disorders, fractures, hypersensitivity, hypocalcemia, ischaemic heart disease, ventricular tachyarrhythmias, cardiac failure, and hypotension.

End point type	Primary

End point timeframe:

Day 1 to day 30

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were not performed in this open-label single-arm study.

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: participants				
number (not applicable)				
Any adverse event (AE)	3			
Serious adverse events	0			
AE leading to discontinuation of study drug	0			
Fatal adverse events	0			
Treatment-related adverse events	1			
Adverse events of interest	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve from Time Zero to Time of Last Quantifiable Concentration (AUClast) for Cinacalcet

End point title	Area Under the Plasma Concentration Time Curve from Time Zero to Time of Last Quantifiable Concentration (AUClast) for Cinacalcet

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	11.8 (± 8.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Time Curve from Time Zero to Infinity (AUCinf) for Cinacalcet

End point title	Area Under the Plasma Concentration Time Curve from Time Zero to Infinity (AUCinf) for Cinacalcet

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	11[2]			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	11.3 (± 7.86)			

Notes:

[2] - AUCinf values for one subject were excluded based on the goodness-of-fit (R^2) value < 0.8.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Cinacalcet

End point title	Maximum Observed Plasma Concentration (Cmax) of Cinacalcet

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)	2.86 (± 1.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration of Cinacalcet (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration of Cinacalcet (Tmax)

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	1 (0.5 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life of Cinacalcet

End point title	Terminal Half-life of Cinacalcet

End point description:

The terminal half-life (T1/2) of cinacalcet associated with the slope of the terminal phase.

End point type	Secondary

End point timeframe:

Baseline (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours post-dose

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	11[3]			
Units: hours				
arithmetic mean (standard deviation)	3.7 (± 2.57)			

Notes:

[3] - T1/2 values for one subject were excluded based on the goodness-of-fit (R^2) value < 0.8.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Intact Parathyroid Hormone

End point title	Percent Change from Baseline in Intact Parathyroid Hormone

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and at 2, 8, 12 and 48 hours post-dose.

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
median (inter-quartile range (Q1-Q3))				
2 hours post-dose (n=9)	-10.8 (-18.5 to 23.1)			
8 hours post-dose (n=5)	-29.6 (-42.2 to -12.6)			
12 hours post-dose (n=5)	29.4 (27.7 to 31.2)			
48 hours post-dose (n=9)	-5.4 (-42.3 to 69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Total Calcium

End point title	Percent Change from Baseline in Total Calcium

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 2, 8, 12 and 48 hours post-dose.

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
arithmetic mean (standard deviation)				
2 hours post-dose (n=11)	-4.33 (± 6.82)			
8 hours post-dose (n=5)	-6.38 (± 5.12)			
12 hours post-dose (n=6)	-6.63 (± 5.05)			
48 hours post-dose (n=8)	-4.54 (± 5.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Albumin Corrected Calcium

End point title	Percent Change from Baseline in Albumin Corrected Calcium

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 2, 8, 12 and 48 hours post-dose.

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
arithmetic mean (standard deviation)				
2 hours post-dose (n=9)	-4.01 (± 7.11)			
8 hours post-dose (n=5)	-7.12 (± 6.71)			
12 hours post-dose (n=5)	-4.24 (± 1.7)			
48 hours post-dose (n=6)	-4.1 (± 5.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Ionized Calcium

End point title	Percent Change from Baseline in Ionized Calcium

End point description:

End point type	Secondary

End point timeframe:

Baseline (predose) and 2, 8, 12 and 48 hours post-dose.

End point values	Cinacalcet 0.25 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
arithmetic mean (standard deviation)				
2 hours post-dose (n=9)	-1.77 (± 3.55)			
8 hours post-dose (n=4)	-4.2 (± 3.83)			
12 hours post-dose (n=4)	-4.15 (± 10.12)			
48 hours post-dose (n=6)	-1.45 (± 4.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
30 Days	
Adverse event reporting additional description:	
Adverse Events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Cinacalcet 0.25 mg/kg
Reporting group description:	
Participants received a single oral dose of 0.25 mg/kg cinacalcet on day 1.	

Serious adverse events	Cinacalcet 0.25 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cinacalcet 0.25 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Device expulsion			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	- This protocol was amended in response to a request by the MHRA to provide detailed procedures for reporting and recording adverse events in accordance with the EU Clinical Trials Directive. Specifically, details on adverse event reporting procedures were added to Section 9.3.
20 August 2010	- This protocol was amended to include the European Medicines Agency (EMEA) Pediatric Committee (PDCO) requirement for ionized calcium, ie, total calcium, albumin corrected calcium, and ionized calcium; updated corresponding sections as appropriate. - Changes were made to the inclusion/exclusion criteria to address comments from the Medicines for Children Research Network (MCRN) in the United Kingdom. o Removed inclusion criterion requirement to be hemodynamically and neurologically stable for at least 4 weeks postpartum if < 6 months old o Changed inclusion criterion hemoglobin requirement to ≥ 8 g/dL at screening and at day -1. o Defined major surgery under exclusion criteria as any surgical procedure requiring general anesthesia or respiratory assistance.
04 January 2011	- This protocol was amended in response to comments by the FDA as follows: o Secondary hyperparathyroidism was added to the CKD diagnosis in the inclusion criteria. o The day 1, 4-hour postdose blood collection was changed to 2 hours postdose and a 12-hour, postdose blood collection was added for subjects weighing ≥ 7.5 kg. Blood sampling procedures and volumes for calcium and iPTH were updated accordingly. - Serum calcium laboratory results were clarified as ≥ 2.1 mmol/L or within normal ranges at screening and day -1. - Statistical analyses for the pharmacokinetics parameters AUC, t1/2, Cmax, and tmax were clarified. - The US was added as a location for new study centers and the IRB was added where appropriate. - Schedule of Assessments and footnotes were updated.
11 April 2011	- This protocol was amended in response to FDA comments and clarifications made by the study team. Since hemodialysis can change a subject's clinical chemistry test results, blood sample collections were modified to be concurrent with hemodialysis. Changes included the following: o The pharmacodynamics blood sample collection was changed to include randomization into 2 pharmacodynamic sampling sequences (a and b) within each age group. Six subjects were randomized in a 1:1 ratio into 1 of the following pharmacodynamics sampling sequences: a) approximately day 1: -2, 8 and 48 hours postdose; or b) approximately day 1: -2, 12 and 48 hours postdose. Blood collection volumes were updated as appropriate. o If the safety blood sample collection was concurrent with or within 4 hours after hemodialysis, only albumin, calcium, and iPTH levels were required to be tested for that time point. o The sample size consideration section was updated. - Serum calcium requirement in inclusion criteria was changed to within normal ranges at screening and day -1. - A description of cinacalcet investigational product was added. - Schedule of Assessments and footnotes were updated.

14 June 2011	- The protocol was amended to add randomization by IVRS to assign subjects to 1 of the 2 pharmacodynamic sampling sequences and revise the reporting period for adverse event collection to begin following initiation of investigational product. - Due to the addition of the IVRS, the time of enrollment was redefined as the time of randomization. - With reference to the ICF, the term "subject" was updated to "subject's parent or legally acceptable representative (SPoLAR)" and "assent" was removed throughout the protocol. Information regarding the treatment of hypocalcemia was moved to the Concomitant Therapy section. - Stopping rules were clarified to apply at the age group or study level. The use of CTCAE v4.0 was clarified. - Sites were required to report dialysis and dialysate information for subjects undergoing dialysis on study day -1 through day 4. - Wording changes and clarifications were made throughout the document as appropriate.
28 October 2013	- This protocol was amended to comply with DMC recommendations after review of the cinacalcet program following a fatality in the pediatric Study 20070208, which includes: o Revision of the inclusion/exclusion criteria to exclude subjects with prolonged QTc interval, corrected QTc (Bazett's) > 500 ms, or QTc (Bazett's) ≥ 450 ms and ≥ 500 ms during screening; exclusion of subjects who used drugs which may prolong QTc interval within 28 days prior to enrollment. o Addition of an updated safety summary from the cinacalcet pediatric program including a description of the fatality in Study 20070208. o Addition of a second follow-up phone call for all subjects at day 30 for assessment of serious adverse events. - Based on available study data showing no age-related differences in safety and pharmacokinetics profile, the Age Group 28 days to < 3 years and the Age Group ≥ 3 years to < 6 years were merged into a single age group comprising approximately 12 subjects. Appropriate changes were made throughout the document. - Updated inclusion criterion to "age-appropriate" serum calcium normal ranges at screening and day -1. - Section on overdosing effects of cinacalcet was added. - Specified the Safety Analysis Set for the analysis of all endpoints. - Updated statistical analysis of pharmacokinetics parameters.
20 May 2015	- To align with other, ongoing, pediatric clinical trials of cinacalcet, the following changes were made: o Modified the exclusion criterion from a history of seizures to new onset of seizure or worsening of a pre-existing seizure disorder within 2 months prior to investigational product administration. o Updated the Investigational Product Dosage and Administration to clarify the water preparation was only for administration through nasogastric or gastric tubes, while the syrup formulation could be used for either oral or nasogastric/gastric tube administration. - The pharmacokinetics and pharmacodynamics endpoints were updated to align with the Study 20090005 SAP and PIP Key Elements Form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 January 2013	Dosing and enrollment in study 20090005 were suspended to allow time for a full investigation into the circumstances surrounding the death in another cinacalcet study, 20070208, and to ensure the safety of participants in this study.	13 December 2013

Notes:

Limitations and caveats

None reported