Clinical trial results:
A Phase 3, Prospective, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Pharmacokinetics, Safety and Efficacy of Paricalcitol Capsules in Decreasing Serum Intact Parathyroid Hormone Levels in Pediatric Subjects Ages 10 to 16 years with Moderate to Severe Chronic Kidney Disease

Summary

EudraCT number	2010-019439-37
Trial protocol	DE GB PT ES
Global end of trial date	22 December 2014

Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	05 July 2015

Trial information

Trial identification

Sponsor protocol code	M10-149

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01020487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co.KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4XE
Public contact	Global Medical Information , AbbVie, 001 800-633-9110,
Scientific contact	Ann Eldred, AbbVie, ann.eldred@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are as follows:
Part I: To determine the safety, tolerability, and pharmacokinetics of a single dose of 3 mcg paricalcitol capsules in pediatric subjects ages 10 to 16 years with moderate to severe chronic kidney disease (CKD Stages 3 and 4).

Part II: To determine the safety and efficacy of paricalcitol capsules as compared to placebo in decreasing serum intact parathyroid hormone (iPTH) in pediatric subjects ages 10 to 16 years with moderate to severe chronic kidney disease (Stages 3 and 4) with 12 weeks double-blinded study drug and a minimum of 12 weeks open-label active drug.

Protection of trial subjects:

The study was conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.
The investigator or his/her representative explained the nature of the study to the subject and/or the subject's parent or legal guardian and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent and/or assent statement will be reviewed and signed and dated by the subject and/or the subject's parent or legal guardian and the person who administered the informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2010
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	Portugal: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Singapore: 1
Worldwide total number of subjects	47
EEA total number of subjects	18

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)	0
Children (2-11 years)	7
Adolescents (12-17 years)	40
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part I was an open label, single-dose study evaluating the pharmacokinetics of paricalcitol capsules in pediatric subjects with moderate to severe CKD. Part II consisted of a randomized, double blind, placebo-controlled study to evaluate safety and efficacy of paricalcitol and a 12-week open-label phase wherein all subjects received paricalcitol.

Pre-assignment

Screening details:

Subjects aged 10 to 16 years, with CKD, Stage 3, (estimated glomerular filtration rate, [eGFR] 30 to 59 mL/min/1.73 m²) or CKD, Stage 4, (eGFR 15 to 29 mL/min/1.73 m², not requiring dialysis), who met the study selection criteria were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Part 1: Paricalcitol

Arm description:

Subjects received a single 3 mcg dose of paricalcitol capsules on Study Day 1.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	ABT-358
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single 3 mcg dose of paricalcitol capsules (three 1 mcg paricalcitol capsules) on Study Day 1 administered orally with approximately 100 mL of water.

Arm title	Part 2: Placebo

Arm description:

Subjects received placebo capsules three times a week (TIW) for 12 weeks during the double-blind treatment phase. From Weeks 12 to 24 subjects received open-label paricalcitol at an initial dose of 1 mcg three times a week. Doses could be adjusted based on chemistry evaluations to target Kidney Disease Outcomes Quality Initiatives (KDOQI) target levels.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules administered 3 times a week.

Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	ABT-358
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

The initial dose of paricalcitol was 1 mcg TIW (3 mcg per week). Decisions to maintain, increase or decrease the dose were based on the limited chemistry results generated from the most recent visit. Dose decreases could occur at any time, and dose increases could occur in 1 mcg increments from the previous dose every 4 weeks starting at Treatment Week 16. The maximum allowable dose was therefore 3 mcg TIW.

Arm title	Part 2: Paricalcitol

Arm description:

Subjects received paricalcitol three times a week for 12 weeks during the double-blind treatment period and during the open-label period (Weeks 12-24). The initial dose of paricalcitol was 1 mcg TIW. Doses could be adjusted based on chemistry evaluations to target KDOQI target levels.

Arm type	Experimental
Investigational medicinal product name	Paricalcitol
Investigational medicinal product code	ABT-358
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The initial dose of paricalcitol was 1 mcg TIW (3 mcg per week). Decisions to maintain, increase or decrease the dose were based on the limited chemistry results generated from the most recent visit. Dose decreases could occur at any time, and dose increases could occur in 1 mcg increments from the previous dose every 4 weeks starting at Treatment Week 4. The maximum allowable dose for the first 12 weeks of the study was therefore 3 mcg TIW and the maximum allowable dose for the second 12 weeks of the study was 6 mcg TIW.

Number of subjects in period 1	Part 1: Paricalcitol	Part 2: Placebo	Part 2: Paricalcitol
Started	12	17	18
Received Treatment	12	18	18
Completed	12	12	12
Not completed	0	6	7
Randomized in error	-	-	1
Consent withdrawn by subject	-	-	1
Adverse event	-	6	2
Required a dose reduction	-	-	3
Joined	0	1	1
Enrolled in Part 2 after completing Part 1	-	1	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Part 1: Paricalcitol
Reporting group description:	
Subjects received a single 3 mcg dose of paricalcitol capsules on Study Day 1.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Subjects received placebo capsules three times a week (TIW) for 12 weeks during the double-blind treatment phase. From Weeks 12 to 24 subjects received open-label paricalcitol at an initial dose of 1 mcg three times a week. Doses could be adjusted based on chemistry evaluations to target Kidney Disease Outcomes Quality Initiatives (KDOQI) target levels.	
Reporting group title	Part 2: Paricalcitol
Reporting group description:	
Subjects received paricalcitol three times a week for 12 weeks during the double-blind treatment period and during the open-label period (Weeks 12-24). The initial dose of paricalcitol was 1 mcg TIW. Doses could be adjusted based on chemistry evaluations to target KDOQI target levels.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two subjects completed Part 1 and also enrolled in Part 2. These subjects are included in both the Part 1 and part 2 treatment arm Baseline data, but only once in the Worldwide Number of Subjects Enrolled and only once in the Total column.

Reporting group values	Part 1: Paricalcitol	Part 2: Placebo	Part 2: Paricalcitol
Number of subjects	12	18	19
Age categorical Units: Subjects			
Age continuous			
Data are provided for all randomized subjects who received at least one dose of study drug.			
Units: years			
arithmetic mean	13.5	13.3	13.9
standard deviation	± 1.98	± 1.75	± 1.81
Gender categorical Units: Subjects			
Female	3	5	6
Male	9	13	13
Chronic Kidney Disease Stage			
Stage 3: estimated glomerular filtration rate, (eGFR) 30 to 59 mL/min/1.73 m²) Stage 4: eGFR 15 to 29 mL/min/1.73 m², not requiring dialysis			
Units: Subjects			
Stage 3	6	11	10
Stage 4	6	7	8
Missing	0	0	1

Reporting group values	Total		
Number of subjects	47		
Age categorical Units: Subjects			

Age continuous			
Data are provided for all randomized subjects who received at least one dose of study drug.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	14		
Male	33		
Chronic Kidney Disease Stage			
Stage 3: estimated glomerular filtration rate, (eGFR) 30 to 59 mL/min/1.73 m²) Stage 4: eGFR 15 to 29 mL/min/1.73 m², not requiring dialysis			
Units: Subjects			
Stage 3	27		
Stage 4	19		
Missing	1		

End points

End points reporting groups

Reporting group title	Part 1: Paricalcitol

Reporting group description:

Subjects received a single 3 mcg dose of paricalcitol capsules on Study Day 1.

Reporting group title	Part 2: Placebo

Reporting group description:

Subjects received placebo capsules three times a week (TIW) for 12 weeks during the double-blind treatment phase. From Weeks 12 to 24 subjects received open-label paricalcitol at an initial dose of 1 mcg three times a week. Doses could be adjusted based on chemistry evaluations to target Kidney Disease Outcomes Quality Initiatives (KDOQI) target levels.

Reporting group title	Part 2: Paricalcitol

Reporting group description:

Subjects received paricalcitol three times a week for 12 weeks during the double-blind treatment period and during the open-label period (Weeks 12-24). The initial dose of paricalcitol was 1 mcg TIW. Doses could be adjusted based on chemistry evaluations to target KDOQI target levels.

Primary: Part 1: Paricalcitol Maximum Observed Plasma Concentration (Cmax)

End point title	Part 1: Paricalcitol Maximum Observed Plasma Concentration (Cmax)[1][2]

End point description:

End point type	Primary

End point timeframe:

Blood samples were collected at hour 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours after dosing.

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 for PK paramters

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were assessed in Part 1 of the study only

End point values	Part 1: Paricalcitol			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic mean (standard deviation)	0.13 (± 0.052)			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC0-∞)

End point title	Part 1: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC0-∞)[3][4]

End point description:

End point type	Primary

End point timeframe:

Blood samples were collected at hour 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours after dosing.

Notes:

[3] - 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 for PK parameters

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were assessed in Part 1 of the study only

End point values	Part 1: Paricalcitol			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng*h/mL				
arithmetic mean (standard deviation)	2.87 (± 0.84)			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Percentage of Subjects Achieving Two Consecutive Reductions at Least 30% from Baseline in iPTH

End point title	Part 2: Percentage of Subjects Achieving Two Consecutive Reductions at Least 30% from Baseline in iPTH[5]

End point description:

The primary efficacy endpoint was the percentage of subjects who achieved two consecutive ≥ 30% reductions from Baseline in intact parathyroid hormone (iPTH) levels during the 12 week double-blind portion of the study regardless of CKD stage.

End point type	Primary

End point timeframe:

12-week double-blind treatment period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[6]	18[7]		
Units: percentage of subjects				
number (not applicable)	0	27.8		

Notes:

[6] - Intent-to-treat dataset

[7] - Intent-to-treat dataset

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Fisher exact
Parameter estimate	Difference
Point estimate	27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	52.8

Secondary: Part 2: Percentage of Subjects Achieving a Final iPTH Within KDOQI Target Ranges

End point title	Part 2: Percentage of Subjects Achieving a Final iPTH Within KDOQI Target Ranges[8]

End point description:

The Kidney Disease Outcomes Quality Initiatives (KDOQI) Pediatric Subcommittee on Practice Guidelines for Bone Metabolism and Disease in Children with CKD target range for intact parathyroid hormone (iPTH):
CKD Stage 3: 35 – 69 pg/mL;
CKD Stage 4: 70 – 110 pg/mL.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage of subjects				
number (not applicable)	11.1	33.3		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - Cochran-Mantel-Haenszel (CHM) test, adjusting for CKD Stage.

Secondary: Part 2: Change from Baseline in iPTH to each Post-baseline Visit

End point title	Part 2: Change from Baseline in iPTH to each Post-baseline Visit[10]

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 4, 8 and 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: pg/mL				
least squares mean (standard error)				
Week 2 (n=15, 16)	50.39 (± 15.186)	-12.16 (± 14.695)		
Week 4 (n=18, 16)	57.16 (± 20.813)	-11.27 (± 22.117)		
Week 8 (n=18, 13)	57.31 (± 22.099)	-12.79 (± 24.814)		
Week 12 (n=15, 12)	71.47 (± 17.661)	-17.05 (± 19.186)		

Statistical analyses

Statistical analysis title	Overall Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-72.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.05
upper limit	-36.75

Notes:

[11] - Mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement.

Statistical analysis title	Week 2 Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [12]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-62.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-105.6
upper limit	-19.49

Notes:

[12] - Mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement.

Statistical analysis title	Week 4 Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [13]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-68.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-130.39
upper limit	-6.47

Notes:

[13] - Mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement.

Statistical analysis title	Week 8 Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [14]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-70.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-137.82
upper limit	-2.37

Notes:

[14] - Mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement.

Statistical analysis title	Week 12 Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [15]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-88.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-142.04
upper limit	-35.01

Notes:

[15] - Mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement.

Secondary: Part 2: Percentage of Subjects Achieving a Final Calcium Within KDOQI Target Ranges

End point title	Part 2: Percentage of Subjects Achieving a Final Calcium Within KDOQI Target Ranges[16]

End point description:

The KDOQI target ranges for calcium are: to maintain within the normal range for age (years):
Age 6 – 12: 9.4 – 10.2 mg/dL (2.35 – 2.55 mmol/L);
Age 13 – 20: 8.8 – 10.2 mg/dL (2.20 – 2.55 mmol/L).

End point type	Secondary

End point timeframe:

Week 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage of subjects				
number (not applicable)	94.4	83.3		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327 [17]
Method	Cochran-Mantel-Haenszel

Notes:

[17] - Cochran-Mantel-Haenszel (CHM) test, adjusting for CKD Stage.

Secondary: Part 2: Percentage of Subjects Achieving a Final Phosphorus Within KDOQI Target Ranges

End point title	Part 2: Percentage of Subjects Achieving a Final Phosphorus Within KDOQI Target Ranges[18]

End point description:

The KDOQI target ranges of serum phosphorus are to maintain at or above age appropriate lower limits and no higher than the age-appropriate upper limits:
Age 6 – 12: 3.6 – 5.8 mg/dL (1.16 – 1.87 mmol/L);
Age 13 – 20: 2.3 – 4.5 mg/dL (0.74 – 1.45 mmol/L).

End point type	Secondary

End point timeframe:

Week 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percentage of subjects				
number (not applicable)	72.2	50		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Part 2: Paricalcitol v Part 2: Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194 [19]
Method	Cochran-Mantel-Haenszel

Notes:

[19] - Cochran-Mantel-Haenszel (CHM) test, adjusting for CKD Stage.

Secondary: Part 2: Change From Baseline in First Morning Void (FMV) Urinary Albumin to Creatinine Ratio (UACR)

End point title	Part 2: Change From Baseline in First Morning Void (FMV) Urinary Albumin to Creatinine Ratio (UACR)[20]

End point description:

The mean change from Baseline in FMV UACR on a log scale to each post baseline visit.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8 and 12

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy was assessed in Part 2 of the study only

End point values	Part 2: Placebo	Part 2: Paricalcitol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[21]	16[22]		
Units: mg/g				
least squares mean (standard error)				
Week 4 (n=15, 13)	-0.12 (± 0.126)	-0.13 (± 0.132)		
Week 8 (n=14, 11)	-0.13 (± 0.141)	-0.01 (± 0.155)		
Week 12 (n=12, 10)	-0.08 (± 0.259)	0.22 (± 0.292)		

Notes:

[21] - Intent-to-treat dataset with available Baseline data

[22] - Intent-to-treat dataset with available Baseline data

Statistical analyses

Statistical analysis title	Overall Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.469 [23]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.53

Notes:

[23] - A mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement

Statistical analysis title	Week 4 Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.975 [24]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.37

Notes:

[24] - A mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement

Statistical analysis title	Week 8 Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.567 [25]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.56

Notes:

[25] - A mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement

Statistical analysis title	Week 12 Comparison
Comparison groups	Part 2: Placebo v Part 2: Paricalcitol

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.462 [26]
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	1.12

Notes:

[26] - A mixed effects repeated measures analysis using all the longitudinal observations across the visits including the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous covariate of baseline measurement

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events reported from the time of study drug administration through 30 days following discontinuation of study drug administration were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Part 1: Paricalcitol

Reporting group description:

Subjects received a single 3 mcg dose of paricalcitol capsules on Study Day 1.

Reporting group title	Part 2: Placebo

Reporting group description:

Subjects received placebo capsules three times a week for 12 weeks during the double-blind treatment phase.

Reporting group title	Part 2: Paricalcitol

Reporting group description:

Subjects received paricalcitol three times a week (TIW) for 12 weeks during the double-blind treatment period. The initial dose of paricalcitol was 1 mcg TIW. Doses could be adjusted based on chemistry evaluations to target Kidney Disease Outcomes Quality Initiatives (KDOQI) levels.

Reporting group title	Part 2: Placebo/Paricalcitol

Reporting group description:

Subjects who received placebo in the double-blind treatment phase received open-label paricalcitol at an initial dose of 1 mcg three times a week in the open-label treatment phase (Weeks 12-24). Doses could be adjusted based on chemistry evaluations to target KDOQI levels.

Reporting group title	Part 2: Paricalcitol/Paricalcitol

Reporting group description:

Subjects who received paricalcitol during the double-blind treatment period continued to receive paricalcitol three times a week during the open-label period (Weeks 12-24).

Serious adverse events	Part 1: Paricalcitol	Part 2: Placebo	Part 2: Paricalcitol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive Crisis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Homicidal Ideation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Failure Chronic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral Infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Placebo/Paricalcitol	Part 2: Paricalcitol/Paricalcitol	
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Homicidal Ideation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure Chronic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Viral Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: Paricalcitol	Part 2: Placebo	Part 2: Paricalcitol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	15 / 18 (83.33%)	7 / 18 (38.89%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Feeling Hot			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Oedema Peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nasal Congestion			

subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Thinking Abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood Potassium Increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Vitamin D Decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cold Sweat			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ingrowing Nail			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Micturition Urgency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal Failure Chronic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Muscle Spasms			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute Sinusitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Herpes Simplex			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Otitis Media			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Tooth Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Viral Infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Metabolic Acidosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 2: Placebo/Paricalcitol	Part 2: Paricalcitol/Paricalcitol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	7 / 13 (53.85%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Feeling Hot			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oedema Peripheral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	2	2	
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Nasal Congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal Pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Psychiatric disorders			
Thinking Abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood Potassium Increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vitamin D Decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 16 (6.25%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Lymphadenopathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			

subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Gastritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cold Sweat			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ingrowing Nail			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Micturition Urgency			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal Failure Chronic			

subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Muscle Spasms			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Herpes Simplex			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Otitis Media			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Pharyngitis Streptococcal			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tooth Infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	4	0	
Viral Infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	4 / 16 (25.00%)	1 / 13 (7.69%)	
occurrences (all)	4	1	
Hyperkalaemia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Hyperphosphataemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Metabolic Acidosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2009	Amendment 1 revised the 6 month treatment phase to a 12 week, double-blind treatment period followed by a 12 week, open-label treatment period. Revision of the treatment periods was made to address the concerns of both physicians and parents with continuation in the placebo arm of subjects with secondary hyperparathyroidism, while treatment for this disease state was already established and is part of current clinical practice.
01 October 2009	Amendment 2 clarified throughout the document that the initial dose for the Safety and Efficacy Portion, Part 2 of the study was to be based on the PK data from the first 6 subjects that completed the PK Portion, Part 1.
08 April 2010	Amendment 3 added EudraCT number (2010-019439-37) as this clinical trial was submitted to the European regulatory authorities and conducted in the U.S. Europe, Latin America, and Singapore.
25 May 2010	With Amendment 4 the primary and secondary efficacy endpoints involving assessments based on two consecutive iPTH measurements were changed to assessments based on the final iPTH measurement since scheduling of study visits was changed to be less frequent than scheduled biweekly visits. In previous communication with Food and Drug Agency (FDA), it was clear that either two consecutive time points or the last time point as the primary endpoint was acceptable to the FDA. Since the original sample size calculation was based on parameter estimates obtained from simulations run on the achievement of two consecutive iPTH values within KDOQI iPTH limits, these were conservative estimates for a final response rate. Therefore, the sample size was not changed in this amendment.
20 August 2012	Amendment 5 changed the enrollment target from 72 to 36 subjects, with a maximum of 12 transplant subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported