Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]

Summary

EudraCT number	2017-000284-32
Trial protocol	GB NL SE DK ES NO PT BE IT
Global end of trial date	19 May 2022

Results information

Result version number	v1 (current)
This version publication date	28 May 2023
First version publication date	28 May 2023

Trial information

Trial identification

Sponsor protocol code	SHP634-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03324880
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, +1 877-825-3327, TrialDisclosures@takeda.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	19 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to test the hypothesis that rhPTH(1-84) treatment resulted in superior improvements in the symptoms of hypoparathyroidism (HypoPT) as assessed by the HypoPT symptom diary (HypoPT-SD) symptom subscale compared with standard therapy.

Protection of trial subjects:

Study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2018
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	Canada: 5
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	93
EEA total number of subjects	70

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 35 investigative sites in Belgium, Canada, Denmark, Spain, France, United Kingdom, Italy, Netherlands, Norway, Portugal, Sweden and the United States (US) from 24 January 2018 to 19 May 2022.

Pre-assignment

Screening details:

Participants with a diagnosis of symptomatic hypoparathyroidism were enrolled in 1:1 ratio to receive placebo matching rhPTH (1-84) with active vitamin D and/or calcium supplements or rhPTH (1-84) with active vitamin D and/or calcium supplements.

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	Assessor, Carer, Data analyst, Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to rhPTH (1-84) as subcutaneous (SC) injection once daily (QD) with active vitamin D and calcium supplements up to 31.3 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo QD SC injection.

Arm title	rhPTH (1-84)

Arm description:

Participants received rhPTH (1-84) 50 microgram (mcg) SC injection QD, titrated within the dose range of 25-100 mcg QD as an adjunctive treatment with active vitamin D and calcium supplements based on metabolic response up to 32 weeks.

Arm type	Experimental
Investigational medicinal product name	rhPTH (1-84)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

rhPTH (1-84) SC injection.

Number of subjects in period 1	Placebo	rhPTH (1-84)
Started	48	45
Completed	46	39
Not completed	2	6
Consent withdrawn by subject	2	2
Product Recall	-	1
Adverse event, non-fatal	-	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to rhPTH (1-84) as subcutaneous (SC) injection once daily (QD) with active vitamin D and calcium supplements up to 31.3 weeks.	
Reporting group title	rhPTH (1-84)
Reporting group description:	
Participants received rhPTH (1-84) 50 microgram (mcg) SC injection QD, titrated within the dose range of 25-100 mcg QD as an adjunctive treatment with active vitamin D and calcium supplements based on metabolic response up to 32 weeks.	

Reporting group values	Placebo	rhPTH (1-84)	Total
Number of subjects	48	45	93
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.2	47.8	
standard deviation	± 12.16	± 10.41	-
Gender categorical Units: Subjects			
Female	40	42	82
Male	8	3	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	39	31	70
Unknown or Not Reported	5	11	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	47	43	90
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Hypoparathyroidism Symptom Diary (HPT-SD/HypoPT-SD) Symptom Subscale Score at Baseline			
HypoPT-SD: 13-item patient-reported outcomes instrument incl. symptom subscale(items 1-7), anxiety(item 8), sadness/depression(item 9), impact subscale(items 10-13).Items 1-9 score: None=0 to Very severe=4; Items 10-13: Not at all=0 to Very much=2. Item score=average of daily item response over 14-day period before visit. If data were unavailable for at least 4 out of 7 days during both 7-day periods within the 14-days, score set to missing.Symptom subscale score=average of symptom items 1-7 scores.Symptom subscale score:0 to 4 points with higher scores=more severe symptoms. Placebo group n=47			
Units: score on a scale			

arithmetic mean	2.23	2.56	
standard deviation	± 0.541	± 0.728	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to rhPTH (1-84) as subcutaneous (SC) injection once daily (QD) with active vitamin D and calcium supplements up to 31.3 weeks.	
Reporting group title	rhPTH (1-84)
Reporting group description:	
Participants received rhPTH (1-84) 50 microgram (mcg) SC injection QD, titrated within the dose range of 25-100 mcg QD as an adjunctive treatment with active vitamin D and calcium supplements based on metabolic response up to 32 weeks.	

Primary: Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Subscale Score at Week 26

End point title	Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Subscale Score at Week 26
End point description:	
The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. The symptom subscale score was computed as the average of symptom items 1-7 scores with more than 3 of the 7 symptom item scores were non-missing. Negative change in scores indicates improvement. A mixed model for repeated measures (MMRM) was used for analysis.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)	-0.93 (± 0.130)	-1.46 (± 0.137)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [1]
Method	MMRM
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.189

Notes:

[1] - 1-sided p-value was reported.

Secondary: Change From Baseline in Physical Component Summary (PCS) Derived From 36-Item Short Form Health Survey Version 2 (SF-36v2) Scores at Week 26

End point title	Change From Baseline in Physical Component Summary (PCS) Derived From 36-Item Short Form Health Survey Version 2 (SF-36v2) Scores at Week 26

End point description:

The SF-36 is a validated instrument that questions participants about perceived physical and mental health and function. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. Change in PCS derived from SF-36v2 at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: score on a scale				
least squares mean (standard error)	4.404 (± 1.3514)	8.646 (± 1.3406)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [2]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	4.242
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.413
upper limit	8.072
Variability estimate	Standard error of the mean
Dispersion value	1.9219

Notes:

[2] - 1-sided p-value was reported.

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score at Week 26

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score at Week 26

End point description:

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire contains 13 fatigue-related questions. The responses to the 13 items on the FACIT-Fatigue questionnaire are each measured on a 5-point Likert scale, where 0=Not at all, 1=A little bit, 2=Somewhat, 3=Quite a bit and 4=Very much. Thus, the total score ranges from 0 to 52. High scores represent less fatigue. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: score on a scale				
least squares mean (standard error)	4.4 (± 1.87)	15.0 (± 1.93)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	15.9
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[3] - 1-sided p-value was reported.

Secondary: Change From Baseline in Individual Hypoparathyroidism Symptom Diary (HypoPT-SD) Impact Items Score at Week 26

End point title	Change From Baseline in Individual Hypoparathyroidism Symptom Diary (HypoPT-SD) Impact Items Score at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. The change in individual symptom item scores was reported. Negative change in scores indicates improvement. MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)				
Impact on Sleep	-0.39 (± 0.086)	-0.68 (± 0.090)		
Ability to Exercise	-0.35 (± 0.088)	-0.71 (± 0.093)		
Ability to Complete Work	-0.39 (± 0.084)	-0.76 (± 0.089)		
Impact Family Relationships	-0.29 (± 0.083)	-0.66 (± 0.088)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Impact on Sleep	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [4]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.125

Notes:

[4] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Impact Family Relationships	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [5]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.121

Notes:

[5] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Ability to Complete Work	
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [6]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.123

Notes:

[6] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Ability to Exercise

Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [7]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.128

Notes:

[7] - 1-sided p-value was reported.

Secondary: Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Impact Subscale Score at Week 26

End point title	Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Impact Subscale Score at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. The impact subscale score was computed as the average of impact items 10-13 scores with no impact item score was non-missing. Negative change in scores indicates improvement. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)	-0.36 (± 0.076)	-0.69 (± 0.081)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [8]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.112

Notes:

[8] - 1-sided p-value was reported.

Secondary: Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Sadness or Depression (Item 9) Score at Week 26

End point title	Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Sadness or Depression (Item 9) Score at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. The sadness or depression item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the item score was set to missing. Negative change in scores indicates improvement. MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)	-0.76 (± 0.137)	-1.30 (± 0.145)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [9]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[9] - 1-sided p-value was reported.

Secondary: Change From Baseline in Individual Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Scores at Week 26

End point title	Change From Baseline in Individual Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Scores at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. Negative change in scores indicates improvement. MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)				
Muscle Cramps	-0.91 (± 0.150)	-1.47 (± 0.158)		
Tingling	-1.04 (± 0.146)	-1.58 (± 0.154)		
Numbness	-0.89 (± 0.158)	-1.37 (± 0.167)		
Muscle Spasms	-0.87 (± 0.149)	-1.49 (± 0.159)		
Feelings of Heaviness	-0.96 (± 0.157)	-1.34 (± 0.166)		
Physical Fatigue	-0.89 (± 0.155)	-1.45 (± 0.165)		
Brain Fog	-0.90 (± 0.127)	-1.40 (± 0.134)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Tingling	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [10]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.213

Notes:
[10] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Muscle Cramps	
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [11]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.218

Notes:

[11] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Feelings of Heaviness	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [12]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.229

Notes:

[12] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Physical Fatigue	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [13]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.227

Notes:

[13] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Brain Fog	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [14]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.186

Notes:

[14] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [15]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.231

Notes:

[15] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Muscle Spasms	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [16]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.219

Notes:

[16] - 1-sided p-value was reported.

Secondary: Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Anxiety (item 8) Score at Week 26

End point title	Change From Baseline in Hypoparathyroidism Symptom Diary (HypoPT-SD) Symptom Item Anxiety (item 8) Score at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; for items 10-13, it ranges from Not at all=0 to Very much=2. The anxiety item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the anxiety item score was set to missing. Negative change in scores indicates improvement. MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	30		
Units: score on a scale				
least squares mean (standard error)	-0.79 (± 0.139)	-1.35 (± 0.147)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [17]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.203

Notes:

[17] - 1-sided p-value was reported.

Secondary: Number of Participants With Response at Week 26 [Early Termination (ET)]

End point title	Number of Participants With Response at Week 26 [Early Termination (ET)]

End point description:

Response was defined as a 30% reduction in HypoPT-SD symptom subscale score from baseline. The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4; and for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. The symptom subscale score was computed as the average of symptom items 1-7 scores with more than 3 of the 7 symptom item scores were non-missing. Data reported also includes results for early terminated participants.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: participants	24	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-

Cognitive Function (FACT-Cog) Perceived Cognitive Impairments (PCI) Score at Week 26

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) Perceived Cognitive Impairments (PCI) Score at Week 26

End point description:

The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) assessment is a 37-item instrument. The perceived cognitive impairment and the impact on quality of life domains were assessed in this study. These 2 domains include 22 items rated on a 5-point scale. The perceived cognitive impairments subscale contains 18 items and each item has a 5-point ordinal response scale (0=Never, 1= About once a week, 2 = Two to three times a week, 3= Nearly every day, 4 = Several times a day). Each item score is calculated as (4 minus item response), and the subscale score is [sum of (4 minus item response)]*18/(number of items answered)]. The perceived cognitive impairment subscale score ranges from 0 to 72, with higher scores indicate better cognitive function. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: score on a scale				
least squares mean (standard error)	2.7 (± 0.74)	4.8 (± 0.76)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [18]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	1.07

Notes:

[18] - 1-sided p-value was reported.

Secondary: Change From Baseline in the Most Bothersome Symptom Score at Week 26

End point title	Change From Baseline in the Most Bothersome Symptom Score at Week 26

End point description:

The HypoPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: symptom subscale (items 1-7), anxiety (item 8), sadness or depression (item 9) and impact subscale (items 10-13). For items 1-9, the individual score ranges from None=0 to Very severe=4 and for items 10-13, it ranges from Not at all=0 to Very much=2. An item score was computed by taking the average of the daily item response over the 14-day period immediately before the visit. If data were not available for at least 4 out of 7 days during both 7-day periods within the 14-day period, the individual item score was set to missing. The Most Bothersome Symptom Score was analyzed. Negative change in scores indicates improvement. MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	26		
Units: score on a scale				
least squares mean (standard error)	-0.87 (± 0.156)	-1.77 (± 0.174)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.235

Notes:

[19] - 1-sided p-value was reported.

Secondary: Change From Baseline in Individual Domains of 36-Item Short Form Health Survey Version 2 (SF-36v2) at Week 26

End point title	Change From Baseline in Individual Domains of 36-Item Short Form Health Survey Version 2 (SF-36v2) at Week 26

End point description:

The SF-36 is a validated instruments that question participants about perceived physical and mental

health and function. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. Change in the score of individual domains of SF-36v2 at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary
End point timeframe: Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: score on a scale				
least squares mean (standard error)				
Standard-Bodily Pain	4.194 (± 1.4987)	11.404 (± 1.4919)		
Standard-General Health	3.515 (± 1.4509)	9.061 (± 1.4463)		
Standard-Mental Health	3.719 (± 1.6098)	11.576 (± 1.6043)		
Standard-Physical Functioning	4.833 (± 1.4850)	9.387 (± 1.4669)		
Standard-Role-Emotional	5.228 (± 1.6322)	13.648 (± 1.6254)		
Standard-Role-Physical	5.964 (± 1.5799)	10.194 (± 1.5670)		
Standard-Social Functioning	6.005 (± 1.8636)	9.814 (± 1.8661)		
Standard-Vitality	4.205 (± 1.6539)	12.147 (± 1.6547)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Standard-Bodily Pain	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [20]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	7.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.951
upper limit	11.469

Variability estimate	Standard error of the mean
Dispersion value	2.1376

Notes:
[20] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Standard-General Health	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [21]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	5.545
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.452
upper limit	9.638
Variability estimate	Standard error of the mean
Dispersion value	2.0542

Notes:
[21] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Standard-Mental Health	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	7.857
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.292
upper limit	12.423
Variability estimate	Standard error of the mean
Dispersion value	2.2913

Notes:
[22] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Standard-Vitality	

Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [23]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	7.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.253
upper limit	12.63
Variability estimate	Standard error of the mean
Dispersion value	2.353

Notes:

[23] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Standard-Role-Emotional	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	8.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	13.04
Variability estimate	Standard error of the mean
Dispersion value	2.3186

Notes:

[24] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Standard-Role-Physical	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [25]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	4.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.251
upper limit	8.711
Variability estimate	Standard error of the mean
Dispersion value	2.2489

Notes:
[25] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Standard-Social Functioning	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079 [26]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	3.809
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.502
upper limit	9.121
Variability estimate	Standard error of the mean
Dispersion value	2.6658

Notes:
[26] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Standard-Physical Functioning	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [27]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	4.554
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.345
upper limit	8.763
Variability estimate	Standard error of the mean
Dispersion value	2.1123

Notes:

[27] - 1-sided p-value was reported.

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) Impact on Quality of Life (QoL) Score at Week 26

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) Impact on Quality of Life (QoL) Score at Week 26

End point description:

The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) assessment is a 37-item instrument. The perceived cognitive impairment and the impact on quality of life domains were assessed in this study. These 2 domains include 22 items rated on a 5-point scale. The impact on quality of life domain contains 4 items and each item has a 5-point ordinal response scale (0=Never, 1= About once a week, 2 = Two to three times a week, 3= Nearly every day, 4 = Several times a day). Each item score is calculated as (4 minus item response), and the subscale score is [sum of (4 minus item response)]*4/(number of items answered)]. The impact on quality of life subscale score ranges from 0 to 16 with higher score indicates better cognitive function. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: score on a scale				
least squares mean (standard error)	2.7 (± 0.74)	4.8 (± 0.76)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [28]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	1.07

Notes:

[28] - 1-sided p-value was reported.

Secondary: Change From Baseline in Mental Component Summary (MCS) Score of 36-Item Short Form Health Survey Version 2 (SF-36v2) at Week 26

End point title	Change From Baseline in Mental Component Summary (MCS) Score of 36-Item Short Form Health Survey Version 2 (SF-36v2) at Week 26

End point description:

The SF-36 is a validated instruments that question participants about perceived physical and mental health and function. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. Change in the MCS of SF-36v2 at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: score on a scale				
least squares mean (standard error)	4.297 (± 1.5898)	12.597 (± 1.5904)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.788
upper limit	12.811
Variability estimate	Standard error of the mean
Dispersion value	2.2642

Notes:

[29] - 1-sided p-value

Secondary: Change From Baseline in Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI: Hypoparathyroidism) Score at Week 26

End point title	Change From Baseline in Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI: Hypoparathyroidism) Score at Week 26

End point description:

WPAI assessed impact of HypoPT on work productivity and daily activities. Concepts that WPAI: Hypoparathyroidism measures include time missed from work and impairment of work and other regular activities due to specific health problem (HypoPT). WPI was calculated based on 4 items including Q2: hours of work missed due to HPT; Q4: actual hours worked; Q5: HPT effect on productivity at work; Q6: HPT effect on daily activities. Scores for 4 subscales were calculated as Percent work time missed due to problem: Q2/(Q2+Q4)*100; Percent impairment while working due to problem: Q5/10*100; Percent overall work impairment due to problem: Q2/(Q2+Q4)+[(1(Q2/(Q2+Q4)))x(Q5/10)]*100; Percent activity impairment due to problem: Q6/10*100. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. Change from baseline in questionnaire response was reported. A MMRM was used for analysis. Percent Impairment=PI.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	27		
Units: score on a scale				
least squares mean (standard error)				
Percent Work Time Missed Due to Problem(n=15,11)	2.30 (± 6.279)	5.43 (± 7.155)		
PI While Working Due to Problem(n=14,9)	-11.7 (± 4.79)	-26.3 (± 5.76)		
PI Overall Work, Due to Problem(n=14,9)	-11.17 (± 3.854)	-26.08 (± 4.774)		
PI, Activity Due to Problem(n=29,27)	-10.2 (± 3.97)	-23.3 (± 4.17)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Percent Work Time Missed Due to Problem

Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627 [30]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	3.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.33
upper limit	22.6
Variability estimate	Standard error of the mean
Dispersion value	9.578

Notes:

[30] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Percent Activity Impairment Due to Problem	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 [31]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.5
upper limit	-1.5
Variability estimate	Standard error of the mean
Dispersion value	5.78

Notes:

[31] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Percent Overall Work Impairment Due to Problem	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [32]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.42
upper limit	-2.39
Variability estimate	Standard error of the mean
Dispersion value	6.146

Notes:
[32] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Percent Impairment While Working Due to Problem	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031 [33]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.9
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	7.52

Notes:
[33] - 1-sided p-value was reported.

Secondary: Change From Baseline in Scores of Patient's Assessment of Overall Health Status Using Patient Global Impression of Change (PGI-C) at Week 26

End point title	Change From Baseline in Scores of Patient's Assessment of Overall Health Status Using Patient Global Impression of Change (PGI-C) at Week 26

End point description:

The PGI-C is verbal rating scale asks the respondent to best describe change in symptoms compared to the beginning of study. Response options are assessed using a 7-point scale: very much improved (0), much improved (1), minimally improved (2), no change (3), minimally worse (4), much worse (5), and very much worse (6). Negative change indicates improvement. Mean change in scores of PGI-C at Week 26 was be reported.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.6 (± 1.04)	-1.7 (± 1.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in In-Clinic Neurocognitive Assessment Scores at Week 24

End point title	Change From Baseline in In-Clinic Neurocognitive Assessment Scores at Week 24

End point description:

Neurocognitive test battery included tests evaluating frontal-executive domain, which encompasses functions attributable to prefrontal cortex and its connections to basal ganglia (mostly striatum). Tests included the CogState (CS) Brief Battery (including the Detection: speed [range from 2.001 to 6; lower scores (LS) indicate improvement (IMP)], Identification: speed [range from 2.001 to 6; LS indicate IMP], One Card Learning: accuracy [range from 0 to 1.5708; higher scores (HS) indicate IMP], One Back: speed [range from 2.001 to 6; LS indicate IMP]), CS Groton Maze Learning Test: total errors (range from 0 to infinity; LS indicate IMP), CS International Shopping List Task (ISLT): number of correct responses (range from 0 to infinity; HS indicate IMP), and CS ISLT -Delayed Recall: number of correct responses (range from 0 to infinity; HS indicate IMP). Change in in-clinic neurocognitive assessment scores at Week 24 was reported. Analysis of Covariance (ANCOVA) was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	30		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Detection(n=34,30)	0.03 (0.01 to 0.06)	0.05 (0.02 to 0.08)		
Identification(n=33,30)	0.02 (-0.01 to 0.05)	0.04 (0.01 to 0.07)		
One Card Learning(n=33,30)	0.12 (0.07 to 0.16)	0.13 (0.08 to 0.17)		
One Back (ONB)(n=33,30)	-2.43 (-9.89 to 5.02)	7.49 (-0.46 to 15.45)		
Groton Maze Learning(n=33,30)	1.98 (0.73 to 3.24)	1.42 (0.08 to 2.76)		
International Shopping List(n=34,30)	1.31 (0.62 to 1.99)	1.86 (1.13 to 2.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Detection

Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.516
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.05

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Identification	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.06

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: One Card Learning	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.07

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: One Back (ONB)	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.831
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.05

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Groton Maze Learning (GML)	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	9.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	20.85

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: International Shopping List (ISL)	
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.545
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	1.27

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
International Shopping List Test Delayed Recall (ISRL)	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	1.56

Secondary: Change From Baseline in 24-hour Urine Calcium Excretion at Week 26

End point title	Change From Baseline in 24-hour Urine Calcium Excretion at Week 26
End point description:	
Change in 24-hour urine calcium excretion at Week 26 was reported. A MMRM was used for analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	33		
Units: millimoles per day (mmol/day)				
least squares mean (standard error)	-1.99 (± 0.574)	0.11 (± 0.651)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.991 [34]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	3.83
Variability estimate	Standard error of the mean
Dispersion value	0.871

Notes:

[34] - 1-sided p-value was reported.

Secondary: Change From Baseline in At-Home Neurocognitive Assessment Scores at Week 26

End point title	Change From Baseline in At-Home Neurocognitive Assessment Scores at Week 26

End point description:

Neurocognitive test battery included tests evaluating frontal-executive domain, which encompasses functions attributable to prefrontal cortex and its connections to basal ganglia (mostly striatum). Tests included the CogState (CS) Brief Battery (including the Detection: speed [range from 2.001 to 6; lower scores (LS) indicate improvement (IMP)], Identification: speed [range from 2.001 to 6; LS indicate IMP], One Card Learning: accuracy [range from 0 to 1.5708; higher scores (HS) indicate IMP], One Back: speed [range from 2.001 to 6; LS indicate IMP]). Changes in at-home neurocognitive assessment scores (CS Brief Battery) at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	38		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Detection (DET)(n=45,37)	-0.01 (-0.03 to 0.00)	-0.01 (-0.03 to 0.01)		
Identification (IDN)(n=45,38)	-0.01 (-0.03 to 0.01)	0.00 (-0.02 to 0.02)		
One Card Learning (OCL)(n=45,37)	0.08 (0.05 to 0.11)	0.09 (0.06 to 0.12)		
One Back (ONB)(n=45,38)	0.02 (0.00 to 0.04)	0.03 (0.01 to 0.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582 [35]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04

Notes:

[35] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: One Back Test	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.438 [36]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04

Notes:
[36] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: One Card Learning (OCL)	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506 [37]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06

Notes:
[37] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Identification (IDN)	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.492 [38]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.04

Notes:
[38] - 1-sided p-value was reported.

Secondary: Change From Baseline in Scores of Patient's Assessment of Overall Health Status Using Patient Global Impression of Severity (PGI-S) at Week 26

End point title	Change From Baseline in Scores of Patient's Assessment of Overall Health Status Using Patient Global Impression of Severity (PGI-S) at Week 26

End point description:

The PGI-S is a global index that can be used to rate the severity of a specific condition. The PGI-S is a rating scale that asks the respondent to best describe how their symptoms severity. Response options are assessed as per 5-point scale: no symptoms (0), mild (1), moderate (2), severe (3), and very severe (4). Mean change in scores of PGI-S at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	29		
Units: score on a scale				
least squares mean (standard error)	-0.8 (± 0.15)	-1.4 (± 0.16)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [39]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:
[39] - 1-sided p-value

Secondary: Change From Baseline in Serum Phosphate Level at Week 26	
End point title	Change From Baseline in Serum Phosphate Level at Week 26
End point description:	
Change in serum phosphate level at Week 26 was reported. A MMRM was used for analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)	0.030 (± 0.0270)	-0.145 (± 0.0289)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [40]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.254
upper limit	-0.097
Variability estimate	Standard error of the mean
Dispersion value	0.0395

Notes:

[40] - 1-sided p-value was reported.

Secondary: Change From Baseline in Doses of Active Vitamin D at Week 26

End point title	Change From Baseline in Doses of Active Vitamin D at Week 26
End point description:	
Changes in doses of active vitamin D at Week 26 was reported. A MMRM was used for analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	38		
Units: micrograms per day (µg/day)				
least squares mean (standard error)	-5.65 (± 3.155)	-1.57 (± 3.418)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [41]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	4.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	13.22
Variability estimate	Standard error of the mean
Dispersion value	4.654

Notes:

[41] - 1-sided p-value was reported.

Secondary: Change From Baseline in Doses of Calcium Supplements at Week 26

End point title	Change From Baseline in Doses of Calcium Supplements at Week 26

End point description:

Changes in doses of calcium supplements at Week 26 was reported. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: milligrams per day (mg/day)				
least squares mean (standard error)	-44.3 (± 91.13)	-375.6 (± 96.20)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [42]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-331.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-594.6
upper limit	-67.9
Variability estimate	Standard error of the mean
Dispersion value	132.56

Notes:

[42] - 1-sided p-value was reported.

Secondary: Number of Participants who Achieve Composite Criteria for Albumin-corrected Serum Calcium Concentration, Active Vitamin D Dose and Oral Elemental Calcium Supplement Dose at Week 26

End point title	Number of Participants who Achieve Composite Criteria for Albumin-corrected Serum Calcium Concentration, Active Vitamin D Dose and Oral Elemental Calcium Supplement Dose at Week 26

End point description:

Number of participants achieving composite criteria of the following: albumin-corrected serum calcium between 1.875 mmol/L (7.5 mg/dL) and the ULN for the central laboratory normal range, dose of active vitamin D decreased by 50% and at least a 50% reduction from the baseline oral elemental calcium supplement dose at Week 26 was reported.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: participants	6	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Albumin-corrected Serum Calcium Control at Week 26

End point title	Change From Baseline in Albumin-corrected Serum Calcium Control at Week 26

End point description:

Change From Baseline in albumin-corrected serum calcium between 1.875 millimoles per liter (mmol/L)

(7.5 milligram per deciliter [mg/dL]) and upper limit of normal (ULN) for the central laboratory normal range at Week 26 was reported.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.033 (± 0.2072)	0.090 (± 0.2254)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Turnover Marker Bone Specific Alkaline Phosphatase at Week 26

End point title	Change From Baseline in Bone Turnover Marker Bone Specific Alkaline Phosphatase at Week 26

End point description:

Bone turnover markers included serum bone-specific alkaline phosphatase, procollagen amino-terminal peptide, C-terminal telopeptide of type 1 collagen, and osteocalcin. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	37		
Units: units per liter (U/L)				
least squares mean (standard error)	0.69 (± 2.256)	23.03 (± 2.365)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [43]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	22.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.83
upper limit	28.84
Variability estimate	Standard error of the mean
Dispersion value	3.271

Notes:

[43] - 1-sided p-value was reported.

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs are defined as AEs that started or worsened on or after the date and time of the first dose of investigational product.

End point type	Secondary

End point timeframe:

From start of study drug administration to 4 weeks post follow-up (up to Week 36)

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	45		
Units: participants	46	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Turnover Marker Osteocalcin and Procollagen 1 N-Terminal Propeptide at Week 26

End point title	Change From Baseline in Bone Turnover Marker Osteocalcin and Procollagen 1 N-Terminal Propeptide at Week 26

End point description:

Bone turnover markers included serum bone-specific alkaline phosphatase, procollagen amino-terminal peptide, C-terminal telopeptide of type 1 collagen, and osteocalcin. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:
Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	36		
Units: micrograms per liter (µg/L)				
least squares mean (standard error)				
Osteocalcin(n=45,36)	-0.88 (± 4.109)	55.55 (± 4.476)		
Procollagen 1 N-Terminal Propeptide(n=45,34)	1.95 (± 22.744)	228.52 (± 24.475)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Procollagen 1 N-Terminal Propeptide	
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [44]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	226.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	160.17
upper limit	292.98
Variability estimate	Standard error of the mean
Dispersion value	33.425

Notes:
[44] - 1-sided p-value was reported.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Osteocalcin	
Comparison groups	Placebo v rhPTH (1-84)

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [45]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	56.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.33
upper limit	68.53
Variability estimate	Standard error of the mean
Dispersion value	6.091

Notes:

[45] - 1-sided p-value was reported.

Secondary: Change From Baseline in Bone Turnover Marker Type I Collagen C-Telopeptides at Week 26

End point title	Change From Baseline in Bone Turnover Marker Type I Collagen C-Telopeptides at Week 26

End point description:

Bone turnover markers included serum bone-specific alkaline phosphatase, procollagen amino-terminal peptide, C-terminal telopeptide of type 1 collagen, and osteocalcin. A MMRM was used for analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Placebo	rhPTH (1-84)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	36		
Units: nanograms per liter (ng/L)				
least squares mean (standard error)	-5.0 (± 76.52)	780.5 (± 84.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v rhPTH (1-84)
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [46]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	785.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	559.6
upper limit	1011.3
Variability estimate	Standard error of the mean
Dispersion value	113.65

Notes:

[46] - 1-sided p-value was reported.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration to 4 weeks post follow-up (up to Week 36)	
Adverse event reporting additional description:	
Safety Analysis Set included all participants in the ITT Set who took at least 1 dose of investigational product (study drug or placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	rhPTH (1-84)
Reporting group description:	
Participants received rhPTH (1-84) 50 mcg SC injection QD, titrated within the dose range of 25-100 mcg QD as an adjunctive treatment with active vitamin D and calcium supplements based on metabolic response up to 32 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to rhPTH (1-84) as SC injection QD with active vitamin D and calcium supplements up to 31.3 weeks.	

Serious adverse events	rhPTH (1-84)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 45 (13.33%)	6 / 48 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ganglioneuroma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 45 (2.22%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bradyphrenia			

subjects affected / exposed	1 / 45 (2.22%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 45 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 45 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 45 (6.67%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	1 / 3	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetany			
subjects affected / exposed	0 / 45 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	rhPTH (1-84)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 45 (84.44%)	41 / 48 (85.42%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 45 (2.22%)	5 / 48 (10.42%)	
occurrences (all)	1	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 45 (11.11%)	6 / 48 (12.50%)	
occurrences (all)	5	10	
Headache			
subjects affected / exposed	14 / 45 (31.11%)	11 / 48 (22.92%)	
occurrences (all)	26	12	
Paraesthesia			
subjects affected / exposed	6 / 45 (13.33%)	5 / 48 (10.42%)	
occurrences (all)	8	7	
Hypoaesthesia			
subjects affected / exposed	4 / 45 (8.89%)	1 / 48 (2.08%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Feeling abnormal			
subjects affected / exposed	5 / 45 (11.11%)	1 / 48 (2.08%)	
occurrences (all)	5	1	
Fatigue			
subjects affected / exposed	5 / 45 (11.11%)	4 / 48 (8.33%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 45 (24.44%)	9 / 48 (18.75%)	
occurrences (all)	15	9	
Diarrhoea			

subjects affected / exposed	5 / 45 (11.11%)	8 / 48 (16.67%)	
occurrences (all)	13	8	
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 45 (4.44%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Cough			
subjects affected / exposed	4 / 45 (8.89%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 45 (8.89%)	3 / 48 (6.25%)	
occurrences (all)	5	3	
Depression			
subjects affected / exposed	4 / 45 (8.89%)	1 / 48 (2.08%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 45 (11.11%)	2 / 48 (4.17%)	
occurrences (all)	5	2	
Myalgia			
subjects affected / exposed	3 / 45 (6.67%)	4 / 48 (8.33%)	
occurrences (all)	3	4	
Muscular weakness			
subjects affected / exposed	1 / 45 (2.22%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Muscle spasms			
subjects affected / exposed	5 / 45 (11.11%)	4 / 48 (8.33%)	
occurrences (all)	7	4	
Bone pain			
subjects affected / exposed	3 / 45 (6.67%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Back pain			

subjects affected / exposed	4 / 45 (8.89%)	2 / 48 (4.17%)	
occurrences (all)	5	2	
Arthralgia			
subjects affected / exposed	8 / 45 (17.78%)	6 / 48 (12.50%)	
occurrences (all)	12	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 45 (8.89%)	7 / 48 (14.58%)	
occurrences (all)	5	9	
Influenza			
subjects affected / exposed	4 / 45 (8.89%)	3 / 48 (6.25%)	
occurrences (all)	4	3	
Gastroenteritis			
subjects affected / exposed	3 / 45 (6.67%)	2 / 48 (4.17%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)	3 / 48 (6.25%)	
occurrences (all)	3	3	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	5 / 45 (11.11%)	9 / 48 (18.75%)	
occurrences (all)	5	11	
Hypercalcaemia			
subjects affected / exposed	4 / 45 (8.89%)	0 / 48 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	0 / 45 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2017	Following changes were implemented with Protocol Amendment 1: -Reviewed the study title to reflect the double-blind, adaptive, study design, and new primary objective evaluating symptom improvement. -Deleted references to Phase 4 in the title. -Updated to the emergency contact information. -Extended the planned study period. -Updated the number of participants to be enrolled. -Modified primary objective of the study. -Added key secondary objectives. -Reviewed all endpoints. -Modified the statistical analyses, sample size calculation and study visit schedule. -Clarified that administration of the investigational product was to take place in the morning. -Removed renal ultrasounds and bone mineral density assessments. -Reviewed eligibility criteria. -Added the EQ-5D-5L as a second HRQoL assessment and as exploratory endpoint. -Deleted the Hospital Anxiety and Depression Scale from PROs assessments to be performed in the study. -Clarified the definition of severe hypocalcemia. -Allowed participants who failed to meet all inclusion/exclusion criteria to be rescreened. -Added dose of native vitamin D supplements and effect of rhPTH(1-84) on change in the item score of the most burdensome symptom from baseline as exploratory endpoints. -Revised dosing guidelines for active vitamin D supplements, calcium supplements, and investigational product.
03 May 2018	Following changes were implemented with Protocol Amendment 2: -Removed first blinded interim analysis. -Clarified that active vitamin D and/or calcium could be increased, decreased, and/or stopped during titration and that the investigational product was given with active vitamin D and/or calcium supplements. -Clarified language in the primary and key secondary objectives. -Added descriptive analyses and secondary objective based on for HypoPT-SD symptom subscale score. -Revised secondary endpoint about metabolic control (and criteria). -Added secondary objectives. -Revised number of participants anticipated to be enrolled at each site. -Clarified follow-up procedures. - Revised several inclusion criteria for clarity and accuracy with current clinical guidances. -Added serum TSH level was as an assessment to be performed at the Week 26 visit (EOT visit). -Added between visit predose nadir and postdose peak levels. -Added urine pregnancy test to assessments to be performed at Week 30 visit. -Clarified that protocol allows local laboratories to be used for evaluation. -Added phone call day before the baseline (Week 0) visit and EOT (Week 26). -Added denosumab to the list of common excluded treatments. -Clarified if active vitamin D and/or calcium supplements need to be taken. -Removed qualitative cystine from the urine chemistry parameters.
10 November 2020	Following changes were implemented with Protocol Amendment 3: -Revised sample size and power estimates for the interim and final analyses. -Updated time of the call to remind participants to complete PRO instruments to 2 days prior the applicable visits. -Defined type of follow-up EOS contact; on-site visit for participants who discontinue treatment with rhPTH(1-84) or phone call for participants on commercial rhPTH(1-84). -Removed restriction to maintain daily dietary intake of calcium, phosphate and sodium prior to blood draws and during the 24-hour urine collections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported