Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism

Summary

EudraCT number	2020-003380-26
Trial protocol	DK NO FR DE HU IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	27 April 2023
First version publication date	27 April 2023

Trial information

Trial identification

Sponsor protocol code	TCP-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04701203
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ascendis Pharma Bone Diseases A/S
Sponsor organisation address	Tuborg Boulevard 12, Hellerup, Denmark, DK 2900
Public contact	Clinical Trial Information Desk , Ascendis Pharma Bone Diseases A/S, 45 70222244, clinhelpdesk@ascendispharma.com
Scientific contact	Clinical Trial Information Desk , Ascendis Pharma Bone Diseases A/S, 45 70222244, clinhelpdesk@ascendispharma.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	Interim
Date of interim/final analysis	15 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the treatment effect of daily TransCon PTH on serum calcium levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment.

Protection of trial subjects:

Written informed consent was obtained from all subjects prior to enrollment into the trial, as dictated by the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 December 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	82
EEA total number of subjects	31

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)	72
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 82 subjects were enrolled and dosed. Enrollment of subjects occurred in seven countries: Canada, Denmark, Germany, Italy, Hungary, Norway, and the United States.

Pre-assignment

Screening details:

A total of 106 subjects were screened and 84 of these met eligibility criteria and were enrolled into the study. Two subjects randomized to TransCon PTH were not treated. A total of 82 subjects were therefore included in the ITT and the Safety analysis populations.

Pre-assignment period milestones

Number of subjects started	84[1]
Number of subjects completed	82

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 84 subjects met eligibility criteria and were enrolled into the study. However, 2 subjects randomized to TransCon PTH were not treated.

Period 1

Period 1 title	26 Week Blinded Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	TransCon PTH

Arm description:

Once daily subcutaneous administration of TransCon PTH at a starting dose of 18 mcg/day

Arm type	Experimental
Investigational medicinal product name	TransCon PTH
Investigational medicinal product code	ACP-014
Other name	Palopegteriparatide
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TransCon PTH drug product was supplied as a clear solution containing palopegteriparatide with a nominal PTH(1-34) content of 0.3 mg/mL in a pre-filled pen intended for subcutaneous injection. All subjects were initially prescribed TransCon PTH 18 µg PTH(1-34)/d and were individually and progressively titrated to an optimal dose (allowable range 6–60 µg/d) in increments of 3 µg/d. Titration of study drug and conventional therapy was performed according to a protocol-specified algorithm guided by serum calcium values.

Arm title	Placebo

Arm description:

Once daily subcutaneous administration of placebo for TransCon PTH to mimick the dose of investigational product

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 for TransCon PTH drug product was supplied as a clear solution containing placebo liquid to match the investigational product in a pre-filled pen intended for subcutaneous injection.

Number of subjects in period 1	TransCon PTH	Placebo
Started	61	21
Completed	60	19
Not completed	1	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TransCon PTH
Reporting group description:	
Once daily subcutaneous administration of TransCon PTH at a starting dose of 18 mcg/day	
Reporting group title	Placebo
Reporting group description:	
Once daily subcutaneous administration of placebo for TransCon PTH to mimick the dose of investigational product	

Reporting group values	TransCon PTH	Placebo	Total
Number of subjects	61	21	82
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	49.0	47.3	
standard deviation	± 13.13	± 11.43	-
Gender categorical			
Units: Subjects			
Female	46	18	64
Male	15	3	18
Race			
Units: Subjects			
Asian	3	2	5
White	57	19	76
Other	1	0	1
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	57	18	75
Not Reported	3	1	4
Unknown	1	2	3
Height			
Units: cm			
arithmetic mean	168.22	166.67	
standard deviation	± 8.353	± 8.831	-
Weight			
Units: kg			
arithmetic mean	77.18	81.61	
standard deviation	± 17.335	± 15.631	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	27.27	29.47	
standard deviation	± 5.813	± 5.691	-

End points

End points reporting groups

Reporting group title	TransCon PTH
Reporting group description:	
Once daily subcutaneous administration of TransCon PTH at a starting dose of 18 mcg/day	
Reporting group title	Placebo
Reporting group description:	
Once daily subcutaneous administration of placebo for TransCon PTH to mimick the dose of investigational product	

Primary: Efficacy - Primary Endpoint

End point title	Efficacy - Primary Endpoint
End point description:	
The proportion of subjects with albumin-adjusted serum calcium measured within 4 weeks prior to and on Week 26 visit within the normal range (8.3 to 10.6 mg/dL), and independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN ≤7 days during the 4 weeks), and independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤7 days during the 4 weeks) and, no increase in prescribed study drug within 4 weeks prior to Week 26 visit.	
End point type	Primary
End point timeframe:	
26 weeks	

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	21		
Units: Percent				
number (confidence interval 95%)	78.7 (66.3 to 88.1)	4.8 (0.1 to 23.8)		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint
Statistical analysis description:	
For the primary efficacy endpoint, the Cochran–Mantel Haenszel test stratified by etiology of hypoparathyroidism (postsurgical or other) was used to compare the proportion of participants meeting the composite primary endpoint in the TransCon PTH versus placebo groups. Participants without week 26 albumin-adjusted serum calcium or with >25% (ie, >7 days) missing diary data of active vitamin D or elemental calcium during the 4 weeks before week 26 were considered non-responders.	
Comparison groups	TransCon PTH v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: HPES - Symptom - Physical Domain Score

End point title	HPES - Symptom - Physical Domain Score

End point description:

Hypoparathyroidism Patient Experience Scale (HPES) - Symptom - Physical Domain score change from baseline. A decrease in HPES score denotes an improvement in hypoparathyroidism related physical symptoms.

End point type	Secondary

End point timeframe:

Week 26

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	19		
Units: LS Mean Change from Baseline				
least squares mean (confidence interval 95%)	-21.01 (-25.41 to -16.60)	-4.81 (-15.22 to 5.59)		

Statistical analyses

Statistical analysis title	HPES - Symptom - Physical Domain Score

Statistical analysis description:

ANCOVA model with unequal variance was used to analyze the key secondary Endpoints. The change from baseline is variable of interest at week 26 and was included in the model as response variables. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate.

Comparison groups	TransCon PTH v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0038
Method	t-test, 2-sided

Secondary: HPES - Symptom - Cognitive Domain Score

End point title	HPES - Symptom - Cognitive Domain Score

End point description:

Hypoparathyroidism Patient Experience Scale (HPES) - Symptom - Cognitive Domain score change from baseline. A decrease in HPES score denotes an improvement in hypoparathyroidism related cognitive

symptoms.

End point type	Secondary

End point timeframe:

Week 26

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	19		
Units: LS Mean Change from Baseline				
least squares mean (confidence interval 95%)	-20.49 (-25.67 to -15.31)	-6.16 (-15.92 to 3.60)		

Statistical analyses

Statistical analysis title	HPES - Symptom - Cognitive Domain Score

Statistical analysis description:

ANCOVA model with unequal variance was used to analyze the key secondary Endpoints. The change from baseline is variable of interest at week 26 and was included in the model as response variables. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate.

Comparison groups	Placebo v TransCon PTH
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0055
Method	t-test, 2-sided

Secondary: HPES - Impact - Physical Functioning Domain Score

End point title	HPES - Impact - Physical Functioning Domain Score

End point description:

Hypoparathyroidism Patient Experience Scale (HPES) - Impact - Physical Functioning Domain score change from baseline. A decrease in HPES score denotes an improvement in health-related quality of life.

End point type	Secondary

End point timeframe:

Week 26

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	19		
Units: LS Mean Change from Baseline				
least squares mean (confidence interval 95%)	-18.29 (-23.59 to -12.99)	-1.01 (-12.40 to 10.38)		

Statistical analyses

Statistical analysis title	HPES - Impact - Physical Functioning Domain Score

Statistical analysis description:

ANCOVA model with unequal variance was used to analyze the key secondary Endpoints. The change from baseline is variable of interest at week 26 and was included in the model as response variables. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate.

Comparison groups	TransCon PTH v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0046
Method	t-test, 2-sided

Secondary: HPES - Impact - Daily Life Domain Score

End point title	HPES - Impact - Daily Life Domain Score

End point description:

Hypoparathyroidism Patient Experience Scale (HPES) - Impact - Daily Life Domain score change from baseline. A decrease in HPES score denotes an improvement in health-related quality of life.

End point type	Secondary

End point timeframe:

Week 26

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	19		
Units: LS Mean Change from Baseline				
least squares mean (confidence interval 95%)	-17.65 (-22.39 to -12.91)	-0.36 (-12.19 to 11.46)		

Statistical analyses

Statistical analysis title	HPES - Impact - Daily Life Domain Score

Statistical analysis description:

ANCOVA model with unequal variance was used to analyze the key secondary Endpoints. The change

from baseline is variable of interest at week 26 and was included in the model as response variables. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate.

Comparison groups	TransCon PTH v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0061
Method	t-test, 2-sided

Secondary: SF-36 – Physical Functioning Subscale Score

End point title	SF-36 – Physical Functioning Subscale Score

End point description:

36-item Short Form Survey (SF-36) – Physical Functioning Subscale Score change from baseline. An increase in SF-36 score denotes an improvement in health-related quality of life.

End point type	Secondary

End point timeframe:

Week 26

End point values	TransCon PTH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	19		
Units: LS Mean Change from Baseline				
least squares mean (confidence interval 95%)	5.29 (3.47 to 7.10)	0.12 (-4.64 to 4.89)		

Statistical analyses

Statistical analysis title	SF-36 – Physical Functioning Subscale Score

Statistical analysis description:

ANCOVA model with unequal variance was used to analyze the key secondary Endpoints. The change from baseline is variable of interest at week 26 and was included in the model as response variables. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate.

Comparison groups	TransCon PTH v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0347
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
26 Week Blinded Period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	TransCon PTH
Reporting group description:	
Once daily subcutaneous administration of TransCon PTH at a starting dose of 18 mcg/day	
Reporting group title	Placebo
Reporting group description:	
Once daily subcutaneous administration of placebo for TransCon PTH to mimick the dose of investigational product	

Serious adverse events	TransCon PTH	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 61 (8.20%)	3 / 21 (14.29%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive breast carcinoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 61 (1.64%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 61 (1.64%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	TransCon PTH	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 61 (81.97%)	20 / 21 (95.24%)	
Investigations			
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 61 (3.28%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 61 (4.92%)	3 / 21 (14.29%)	
occurrences (all)	3	3	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 61 (21.31%)	2 / 21 (9.52%)	
occurrences (all)	20	2	
Paraesthesia			
subjects affected / exposed	11 / 61 (18.03%)	3 / 21 (14.29%)	
occurrences (all)	22	10	
Dizziness			
subjects affected / exposed	4 / 61 (6.56%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	19 / 61 (31.15%)	0 / 21 (0.00%)	
occurrences (all)	19	0	
Fatigue			
subjects affected / exposed	9 / 61 (14.75%)	5 / 21 (23.81%)	
occurrences (all)	10	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 61 (11.48%)	2 / 21 (9.52%)	
occurrences (all)	11	3	
Diarrhoea			
subjects affected / exposed	6 / 61 (9.84%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Constipation			
subjects affected / exposed	4 / 61 (6.56%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 61 (6.56%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	4 / 61 (6.56%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 61 (11.48%)	3 / 21 (14.29%)	
occurrences (all)	9	3	
Arthralgia			
subjects affected / exposed	6 / 61 (9.84%)	3 / 21 (14.29%)	
occurrences (all)	7	3	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	5 / 61 (8.20%)	9 / 21 (42.86%)	
occurrences (all)	7	14	
Hypercalcaemia			
subjects affected / exposed	5 / 61 (8.20%)	0 / 21 (0.00%)	
occurrences (all)	8	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2021	The protocol amendment was to address comments and recommendations from Health Authorities and provide clarification on the trial.
10 June 2021	The protocol amendment provided clarification on the trial and addressed a Health Authority comment.
03 August 2021	The protocol amendment updated the primary and secondary efficacy endpoints based on FDA recommendation.
20 December 2021	The protocol amendment updated the primary and secondary efficacy endpoints based on FDA recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36271471