Clinical trial results:
heiGHt: A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of lonapegsomatropin administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency (GHD)

Summary

EudraCT number	2016-001145-11
Trial protocol	DE IT BG PL GR
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	02 September 2020
First version publication date	02 September 2020

Trial information

Trial identification

Sponsor protocol code	TransCon hGH CT-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02781727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ascendis Pharma A/S
Sponsor organisation address	Tuborg Boulevard 12, Hellerup, Denmark, 2900
Public contact	Clinical Trial Information Desk, Ascendis Pharma A/S, +45 70 22 22 44, clinhelpdesk@ascendispharma.com
Scientific contact	Clinical Trial Information Desk, Ascendis Pharma A/S, +45 70 22 22 44, clinhelpdesk@ascendispharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002692-PIP01-19
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	17 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2019
Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the annualized height velocity of prepubertal children with growth failure due to GHD treated with weekly lonapegsomatropin to that of a commercially available daily hGH formulation at 52 weeks.

Protection of trial subjects:

Institutional review board and independent ethics committee approval as well as signed informed consent from subjects was obtained prior to any trial-specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Armenia: 10
Country: Number of subjects enrolled	Georgia: 11
Country: Number of subjects enrolled	Belarus: 5
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	162
EEA total number of subjects	20

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)	133
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

54 sites in 14 countries enrolled subjects (Armenia, Australia, Belarus, Bulgaria, Georgia, Greece, Italy, New Zealand, Poland, Romania, Russia, Turkey, Ukraine, and United States). Subject screening was initiated in November 2016 and the final subject visit was in January 2019.

Pre-assignment

Screening details:

Screening lasted up to 6 weeks, plus a recommended period of up to 2 weeks between randomization and Visit 1.

Pre-assignment period milestones

Number of subjects started	162
Number of subjects completed	161

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lonapegsomatropin, 0.24 mg hGH/kg/wk

Arm description:

Once weekly subcutaneous injection of lonapegsomatropin equivalent to 0.24 mg hGH/kg/wk for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Lonapegsomatropn
Investigational medicinal product code	ACP-011
Other name	TransCon hGH
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lonapegsomatropin was provided as a lyophilized powder, in single-use glass vials, reconstituted with 1 mL sterile water for injection, and administered via syringe and needle as a once-weekly subcutaneous injection of 0.24 mg hGH/kg/week.

Arm title	Genotropin, 0.24 mg hGH/kg/wk

Arm description:

Once daily subcutaneous injection of human Growth Hormone (Genotropin) equivalent to 0.24 mg hGH/kg/week for 52 weeks.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	Human growth hormone, somatropin
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

Genotropin was administered as a daily subcutaneous injection in a standard dose of 0.24 mg hGH/kg/week. The total weekly dose was equally split into 7 daily doses of 0.034 mg hGH/kg/day. A commercially-approved injection device was used for administration of the trial drug.

Number of subjects in period 1[1]	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk
Started	105	56
Completed	104	55
Not completed	1	1
Consent withdrawn by subject	1	-
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 162 subjects were randomized to the study drug in a 2:1 manner. Among randomized subjects, 161 were dosed with a study drug and 1 subject withdrew consent and did not receive a study drug. 105 subjects received lonapegsomatropin and 56 subjects received Genotropin. Nearly all randomized and dosed subjects completed the trial (159/161).

Baseline characteristics

Reporting groups	
Reporting group title	Lonapegsomatropin, 0.24 mg hGH/kg/wk
Reporting group description:	
Once weekly subcutaneous injection of lonapegsomatropin equivalent to 0.24 mg hGH/kg/wk for 52 weeks.	
Reporting group title	Genotropin, 0.24 mg hGH/kg/wk
Reporting group description:	
Once daily subcutaneous injection of human Growth Hormone (Genotropin) equivalent to 0.24 mg hGH/kg/week for 52 weeks.	

Reporting group values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk	Total
Number of subjects	105	56	161
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 8.5 ± 2.7	 8.5 ± 2.8	 -
Gender categorical Units: Subjects			
Female	19	10	29
Male	86	46	132
Height Units: cm arithmetic mean standard deviation	 112.93 ± 14.09	 112.15 ± 15.29	 -
Height SDS Units: Standard deviation score (SDS) arithmetic mean	 -2.89 ± 0.85	 -3.00	 -

End points

End points reporting groups

Reporting group title	Lonapegsomatropin, 0.24 mg hGH/kg/wk
Reporting group description:	
Once weekly subcutaneous injection of lonapegsomatropin equivalent to 0.24 mg hGH/kg/wk for 52 weeks.	
Reporting group title	Genotropin, 0.24 mg hGH/kg/wk
Reporting group description:	
Once daily subcutaneous injection of human Growth Hormone (Genotropin) equivalent to 0.24 mg hGH/kg/week for 52 weeks.	

Primary: AHV at 52 weeks for weekly lonapegsomatropin and daily hGH treatment groups

End point title	AHV at 52 weeks for weekly lonapegsomatropin and daily hGH treatment groups
End point description:	
Annualized height velocity (AHV) in cm/year at week 52.	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: cm/year				
least squares mean (standard error)	11.17 (± 0.23)	10.31 (± 0.30)		

Statistical analyses

Statistical analysis title	Analysis of Covariance (ANCOVA) Model
Statistical analysis description:	
ANCOVA model with multiple imputation. For each imputed data set, an ANCOVA model with by visit AHV as the dependent variable, treatment and gender as factors, baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS - average parental height SDS as covariates were fitted.	
Comparison groups	Lonapegsomatropin, 0.24 mg hGH/kg/wk v Genotropin, 0.24 mg hGH/kg/wk

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0088 [2]
Method	ANCOVA with multiple imputation

Notes:

[1] - Non-inferiority margin of 2 cm/year

[2] - two-sided

Secondary: AHV for the lonapegsomatropin and the daily hGH treatment groups over 52 weeks

End point title	AHV for the lonapegsomatropin and the daily hGH treatment groups over 52 weeks

End point description:

Annualized height velocity (AHV) in cm/year by visit over 52 weeks.

End point type	Secondary

End point timeframe:

At Week 5, Week 13, Week 26, Week 39, and Week 52.

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: cm/year				
least squares mean (standard error)				
Week 5	13.54 (± 1.07)	12.83 (± 1.37)		
Week 13	13.28 (± 0.49)	12.22 (± 0.63)		
Week 26	12.65 (± 0.32)	11.21 (± 0.42)		
Week 39	11.89 (± 0.26)	10.90 (± 0.33)		
Week 52	11.17 (± 0.23)	10.31 (± 0.30)		

Statistical analyses

Statistical analysis title	ANCOVA model

Statistical analysis description:

ANCOVA model with multiple imputation. For each imputed data set, an ANCOVA model with by visit AHV as the dependent variable, treatment and gender as factors, baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS - average parental height SDS as covariates were fitted.

Comparison groups	Lonapegsomatropin, 0.24 mg hGH/kg/wk v Genotropin, 0.24 mg hGH/kg/wk
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0088 [3]
Method	ANCOVA with multiple imputation

Notes:

[3] - Week 5, P = 0.6402
Week 13, P = 0.1286
Week 26, P = 0.0017
Week 39, P = 0.0061
Week 52, P =0.0088
(two-sided)

Secondary: Change from baseline in Height SDS over 52 weeks for the lonapegsomatropin and the daily hGH treatment groups

End point title	Change from baseline in Height SDS over 52 weeks for the lonapegsomatropin and the daily hGH treatment groups

End point description:

Change from baseline in height (HT) standard deviation score by visit over 52 weeks.

End point type	Secondary

End point timeframe:

At Week 5, Week 13, Week 26, Week 39, and Week 52.

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Standard deviation score (SDS)				
least squares mean (standard error)				
Week 5	0.13 (± 0.02)	0.12 (± 0.02)		
Week 13	0.38 (± 0.02)	0.33 (± 0.03)		
Week 26	0.68 (± 0.03)	0.58 (± 0.04)		
Week 39	0.92 (± 0.03)	0.80 (± 0.04)		
Week 52	1.10 (± 0.04)	0.96 (± 0.05)		

Statistical analyses

Statistical analysis title	ANCOVA model

Statistical analysis description:

ANCOVA model included baseline age, peak GH levels (log transformed) at stimulation test and baseline height SDS as covariates, as well as treatment and gender as factors.

Comparison groups	Genotropin, 0.24 mg hGH/kg/wk v Lonapegsomatropin, 0.24 mg hGH/kg/wk
Number of subjects included in analysis	161
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0149 [4]
Method	ANCOVA

Notes:

[4] - Week 5, P = 0.7795
Week 13, P = 0.1078
Week 26, P = 0.0085
Week 39, P = 0.0130
Week 52, P = 0.0149
(two-sided)

Secondary: Average IGF-1 SDS by visit

End point title	Average IGF-1 SDS by visit

End point description:

Average IGF-1 standard deviation score by visit over 52 weeks.

End point type	Secondary

End point timeframe:

At Week 13, Week 26, Week 39, and Week 52.

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Standard deviation score (SDS)				
least squares mean (standard error)				
Week 13	0.31 (± 0.09)	-0.60 (± 0.11)		
Week 26	0.46 (± 0.08)	-0.51 (± 0.10)		
Week 39	0.59 (± 0.09)	-0.30 (± 0.11)		
Week 52	0.72 (± 0.09)	-0.02 (± 0.12)		

Statistical analyses

Statistical analysis title	ANCOVA model

Statistical analysis description:

ANCOVA model included baseline age, peak GH levels (log transformed) at stimulation test, baseline IGF-1 SDS as covariates, treatment and gender as factors. Modeled values begin at Week 13 corresponding with achievement of IGF-1 steady state. Average IGF-1 SDS values by visit for the Lonapegsomatropin group were derived from a population PD model; the average IGF-1 SDS values for the Genotropin group are represented by observed values.

Comparison groups	Lonapegsomatropin, 0.24 mg hGH/kg/wk v Genotropin, 0.24 mg hGH/kg/wk
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA

Notes:

[5] - P <0.0001 at Weeks 13, 26, 39, and 52
(two-sided)

Secondary: IGFBP-3 SDS by visit

End point title	IGFBP-3 SDS by visit

End point description:

IGFBP-3 standard deviation score by visit over 52 weeks.

End point type	Secondary

End point timeframe:

At Week 5, Week, 13, Week 26, Week 39, and Week 52.

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Standard deviation score (SDS)				
least squares mean (standard error)				
Week 5	-0.62 (± 0.07)	-0.36 (± 0.09)		
Week 13	0.34 (± 0.08)	-0.38 (± 0.11)		
Week 26	0.28 (± 0.08)	-0.30 (± 0.10)		
Week 39	0.42 (± 0.07)	-0.18 (± 0.10)		
Week 52	-0.22 (± 0.07)	0.01 (± 0.10)		

Statistical analyses

Statistical analysis title	Mixed Model for Repeated Measurement (MMRM) model

Statistical analysis description:

MMRM model includes baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline IGFBP-3 SDS as covariates, treatment, visit, treatment by visit interaction, and gender as fixed factors, and subject as random effect.

Comparison groups	Lonapegsomatropin, 0.24 mg hGH/kg/wk v Genotropin, 0.24 mg hGH/kg/wk
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0454 [6]
Method	MMRM

Notes:

[6] - Week 5, P = 0.0134
Week 13, P < 0.0001
Week 26, P < 0.0001
Week 39, P < 0.0001
Week 52, P = 0.0454
(two-sided)

Secondary: Incidence of treatment emergent anti-hGH binding antibody formation

End point title	Incidence of treatment emergent anti-hGH binding antibody formation

End point description:

Incidence of treatment emergent anti-hGH binding antibody formation during the 52 week study. All samples were negative for anti-hGH neutralizing antibodies.

End point type	Secondary

End point timeframe:

Start of study treatment through Week 52.

End point values	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	56		
Units: Subjects	6	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial-related activity after the subject signed the informed consent until the end of the post-treatment follow-up period (up to week 52).

Adverse event reporting additional description:

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Lonapegsomatropin, 0.24 mg hGH/kg/wk

Reporting group description:

Once weekly subcutaneous injection of lonapegsomatropin equivalent to 0.24 mg hGH/kg/wk for 52 weeks.

Reporting group title	Genotropin, 0.24 mg hGH/kg/wk

Reporting group description:

Once daily subcutaneous injection of human Growth Hormone (Genotropin) equivalent to 0.24 mg hGH/kg/week for 52 weeks.

Serious adverse events	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 105 (0.95%)	1 / 56 (1.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 105 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 56 (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	Lonapegsomatropin, 0.24 mg hGH/kg/wk	Genotropin, 0.24 mg hGH/kg/wk	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 105 (77.14%)	39 / 56 (69.64%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 105 (12.38%)	7 / 56 (12.50%)	
occurrences (all)	13	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 105 (15.24%)	5 / 56 (8.93%)	
occurrences (all)	16	5	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 105 (8.57%)	3 / 56 (5.36%)	
occurrences (all)	9	3	
Diarrhea			
subjects affected / exposed	6 / 105 (5.71%)	3 / 56 (5.36%)	
occurrences (all)	6	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 105 (9.52%)	4 / 56 (7.14%)	
occurrences (all)	10	4	
Endocrine disorders			
Secondary hypothyroidism			
subjects affected / exposed	7 / 105 (6.67%)	3 / 56 (5.36%)	
occurrences (all)	7	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 105 (11.43%)	8 / 56 (14.29%)	
occurrences (all)	12	8	
Pharyngitis			
subjects affected / exposed	10 / 105 (9.52%)	10 / 56 (17.86%)	
occurrences (all)	10	10	
Upper respiratory tract infection			
subjects affected / exposed	6 / 105 (5.71%)	5 / 56 (8.93%)	
occurrences (all)	6	5	

Respiratory tract infection subjects affected / exposed occurrences (all)	7 / 105 (6.67%) 7	3 / 56 (5.36%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	The amendment to the original protocol was issued to incorporate feedback from international regulatory agencies and to add pertinent clarifications and administrative edits. The amendment maintained the original intent of the protocol and aligned where possible, with current standard medical practice across various regions globally.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported