Clinical trial results:
A 12-month, open-labelled, randomised, parallel-group, multi-centre, interventional trial to evaluate the efficacy and safety of recombinant human growth hormone (hGH) (Norditropin® Nordilet®) therapy on height velocity (Ht-V) in patients with idiopathic short stature in Korea.

Summary

EudraCT number	2015-002613-30
Trial protocol	Outside EU/EEA
Global end of trial date	18 December 2014

Results information

Result version number	v1 (current)
This version publication date	02 July 2017
First version publication date	02 July 2017

Trial information

Trial identification

Sponsor protocol code	GH-3899

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01778023
WHO universal trial number (UTN)	U1111-1125-4790

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsværd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2014
Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of recombinant human growth hormone (hGH) (Norditropin® Nordilet®) therapy compared with untreated group assessed by height velocity after 6 months of treatment in patients with idiopathic short stature (ISS) in Korea.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 January 2013
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	Korea, Republic of: 51
Worldwide total number of subjects	51
EEA total number of subjects	0

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)	51
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 10 sites in South Korea.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A: 12-month Growth Hormone Treatment

Arm description:

For 12 months, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	Norditropin® Nordilet®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Somatropin (recombinant deoxyribonucleic acid [rDNA] origin) 0.469 mg per kg of body weight was injected subcutaneously (s.c.; under the skin) in the evening in 7 days per week using the Norditropin® Nordilet® pen.

Arm title	Group B: 6-month Untreated + 6-month Growth Hormone Treatment

Arm description:

Subjects participated in the trial for 12 months. For the first six months of the trial period, subjects were untreated. For the last six months of the trial period, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	Norditropin® Nordilet®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Somatropin (rDNA origin) 0.469 mg per kg of body weight was injected s.c. in the evening in 7 days per week using the Norditropin® Nordilet® pen.

Number of subjects in period 1	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment
Started	36	15
Completed	36	15

Baseline characteristics

Reporting groups	
Reporting group title	Group A: 12-month Growth Hormone Treatment
Reporting group description:	
For 12 months, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.	
Reporting group title	Group B: 6-month Untreated + 6-month Growth Hormone Treatment
Reporting group description:	
Subjects participated in the trial for 12 months. For the first six months of the trial period, subjects were untreated. For the last six months of the trial period, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.	

Reporting group values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment	Total
Number of subjects	36	15	51
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	36	15	51
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	6.3	5.9	
standard deviation	± 1.5	± 1.2	-
Gender Categorical Units: Subjects			
Female	17	6	23
Male	19	9	28
Height Units: cm			
arithmetic mean	107.7	105.8	
standard deviation	± 8.7	± 7.5	-

End points

End points reporting groups

Reporting group title	Group A: 12-month Growth Hormone Treatment

Reporting group description:

For 12 months, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Reporting group title	Group B: 6-month Untreated + 6-month Growth Hormone Treatment

Reporting group description:

Subjects participated in the trial for 12 months. For the first six months of the trial period, subjects were untreated. For the last six months of the trial period, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Primary: Height velocity (Ht-V)

End point title	Height velocity (Ht-V)

End point description:

Height velocity (Ht-V) (cm/year) is the change in height per year (after 6 months of treatment). Three sort of Ht-V was calculated from height data at Visit 2 (day 0), Visit 4 (6 months ± 7 days) and Visit 6 (12 months ± 7 days), as follows: Between Visits 2 and 4, between Visit 4 and 6 and between Visit 2 and 6. Ht-V was calculated by Novo Nordisk. The analysis was performed on the full analysis set (FAS), which included all randomised subjects in Group A, who received at least one dose of the trial product and all randomised subjects in Group B.

End point type	Primary

End point timeframe:

After 6-month of treatment

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[1]	15		
Units: cm/year				
least squares mean (standard error)	12.02 (± 0.29)	6.87 (± 0.43)		

Notes:

[1] - Out of 36 exposed subjects, 4 subjects had missing values for height at baseline visit.

Statistical analyses

Statistical analysis title	Group A: 12-month GH Treatment, Group

Statistical analysis description:

"D" represents a mean difference of the primary endpoint between group A and group B. Null hypothesis H0: D = 0 vs. alternative H1: D ≠ 0 will be statistically tested by an ANOVA model.

Comparison groups	Group A: 12-month Growth Hormone Treatment v Group B: 6-month Untreated + 6-month Growth Hormone Treatment

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [2]
Method	ANOVA
Parameter estimate	Treatment-Contrast
Point estimate	5.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.09
upper limit	6.21

Notes:

[2] - The Ht-V after 6 months of treatment was analysed using an analysis of variance (ANOVA) method with group and sex as fixed effects, and age as a covariate.

Secondary: Change in Ht-SDS (Height Standard Deviation Score)

End point title	Change in Ht-SDS (Height Standard Deviation Score)

End point description:

HSDS were calculated using Korean growth data (reported by the Korea Centre for Disease Control and Prevention). The mean normal range for HSDS is from - 2 to +2. Negative scores below -2 indicate a height below normal range, whereas positive scores above +2 indicate a height above normal. The analysis was performed on the FAS, which included all randomised subjects in Group A, who received at least one dose of the trial product and all randomised subjects in Group B.

End point type	Secondary

End point timeframe:

From the baseline to 6-month of treatment.

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[3]	15		
Units: Standard Deviation Score (SDS)				
least squares mean (standard error)	0.76 (± 0.04)	0.19 (± 0.06)		

Notes:

[3] - Out of 36 exposed subjects, 4 subjects had missing values for height at baseline visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGF Related Factors: IGF-I (Insulin-like Growth Factor-I)

End point title	Change in IGF Related Factors: IGF-I (Insulin-like Growth Factor-I)

End point description:

IGF-I was measured at Visit 1 (screening), Visit 3 (3 months ± 7 days), Visit 4 (6 months ± 7 days), Visit 5 (9 months ± 7 days) and Visit 6 (12 months ± 7 days). Change of IGF-I from baseline to 6-month of treatment was calculated. The analysis was performed on the FAS, which included all

randomised subjects in Group A, who received at least one dose of the trial product and all randomised subjects in Group B.

End point type	Secondary

End point timeframe:

From the baseline to 6-month of treatment.

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	15		
Units: ng/mL				
least squares mean (standard error)	192.58 (± 14)	28.03 (± 21.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IGF Related Factors: IGFBP-3 (Insulin-like Growth Factor Binding Protein-3)

End point title	Change in IGF Related Factors: IGFBP-3 (Insulin-like Growth Factor Binding Protein-3)

End point description:

IGFBP-3 was measured at visit 1(screening), visit 3 (3 months ± 7 days), visit 4 (6 months ± 7 days), visit 5 (9 months ± 7 days) and visit 6 (12 months ± 7 days). Change of IGFBP-3 from baseline to 6-month of treatment were calculated. The analysis was performed on the FAS, which included all randomised subjects in Group A, who received at least one dose of the trial product and all randomised subjects in Group B.

End point type	Secondary

End point timeframe:

From the baseline to 6-month of treatment.

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	15		
Units: µg/mL				
least squares mean (standard error)	0.89 (± 0.19)	0.22 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ht-V (Height Velocity)

End point title	Ht-V (Height Velocity)[4]

End point description:

Height velocity (Ht-V) (cm/year) is the change in height per year (after 6 months of treatment). Three sort of Ht-V was calculated from height data at visit 2 (day 0), visit 4 (6 months ± 7 days) and visit 6 (12 months ± 7 days), as follows: Between visits 2 and 4, between visits 4 and 6 and between visit 2 and 6. Ht-V was calculated by Novo Nordisk. It is the difference between Ht-V for the last 6 months and Ht-V for the first 6 months of treatment in group A. The analysis was performed on the FAS, which included all randomised subjects in Group A, who received at least one dose of the trial product and all randomised subjects in Group B.

End point type	Secondary

End point timeframe:

At the first 6 months and the last 6 months in group A

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was evaluated only for the treatment arm, 'Group A: 12-month Growth Hormone Treatment' as per the trial protocol.

End point values	Group A: 12-month Growth Hormone Treatment			
Subject group type	Reporting group			
Number of subjects analysed	32[5]			
Units: cm/year				
least squares mean (confidence interval 95%)	2.8 (1.55 to 4.04)			

Notes:

[5] - Out of 36 exposed subjects, 4 subjects had missing values for height at baseline visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Adverse Events (AEs)

End point title	Occurrence of Adverse Events (AEs)

End point description:

An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All AEs mentioned here are treatment emergent. For Group A, a treatment emergent adverse event (TEAE) was defined as an event that has onset date on or after the first day of exposure to GH treatment (day 0) and no later than the last day of randomised treatment (month 12). For Group B, a TEAE was defined as an event that has onset date on or after Visit 2 (day 0) and no later than the last visit date (Visit 6 [month 12] for completers and withdrawal date for withdrawals). The analysis was performed on the safety analysis set (SAS), which included all

subjects in Group A receiving at least one dose of the trial product and all subjects in Group B who had any available data after visit 2 (day 0).

End point type	Secondary

End point timeframe:

Throughout the trial (12 months).

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	15		
Units: events	70	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Bone Age

End point title	Change in Bone Age

End point description:

Plain X-rays of the left hand and wrist ex-posed for bone age appraisal were obtained at Visit 1 (screening), visit 4 (month 6) and 6 (month 12). For both group A and group B, change in bone age was evaluated from baseline to 6-month of treatment and from baseline to 12-month of treatment. The analysis was performed on the SAS, which included all subjects in Group A receiving at least one dose of the trial product and all subjects in Group B who had any available data after visit 2 (day 0).

End point type	Secondary

End point timeframe:

From baseline to 6-month of treatment and 12-month of treatment, respectively.

End point values	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	15		
Units: years				
arithmetic mean (standard deviation)				
Change from baseline to 6-month of treatment	0.5 (± 0.2)	0.5 (± 0.2)		
Change from baseline to 12-month of treatment	1 (± 0.3)	1 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Bone Age; for Group B only

End point title	Change in Bone Age; for Group B only[6]

End point description:

Plain X-rays of the left hand and wrist ex-posed for bone age appraisal were obtained at Visit 1 (screening), visit 4 (month 6) and 6 (month 12). For group B, change in bone age was evaluated from 6 months to 12 months (i.e., last 6-month of treatment period). The analysis was performed on the SAS, which included all subjects in Group A receiving at least one dose of the trial product and all subjects in Group B who had any available data after visit 2 (day 0).

End point type	Secondary

End point timeframe:

For group B: From 6 months to 12 months.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated only for the treatment arm, 'Group B: 6-month Untreated + 6-month Growth Hormone Treatment' as per the trial protocol.

End point values	Group B: 6-month Untreated + 6-month Growth Hormone Treatment			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Years				
arithmetic mean (standard deviation)	0.5 (± 0.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the trial (12 months).

Adverse event reporting additional description:

Safety analysis set included all subjects in Group A receiving at least one dose of the trial product and all subjects in Group B who had any available data after visit 2 (day 0). All AEs mentioned here are treatment emergent, i.e., TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Group A: 12-month Growth Hormone Treatment

Reporting group description:

For 12 months, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Reporting group title	Group B: 6-month Untreated + 6-month Growth Hormone Treatment

Reporting group description:

Subjects participated in the trial for 12 months. For the first six months of the trial period, subjects were untreated. For the last six months of the trial period, a weekly dosage of 0.469 mg of somatropin (hGH) per kg body weight was injected subcutaneously in the evening in seven (7) days per week using the Norditropin® Nordilet®.

Serious adverse events	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 36 (11.11%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	1 / 36 (2.78%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pharyngotonsillitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A: 12-month Growth Hormone Treatment	Group B: 6-month Untreated + 6-month Growth Hormone Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 36 (55.56%)	10 / 15 (66.67%)	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Rhinitis allergic			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	3 / 36 (8.33%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	3 / 36 (8.33%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	15 / 36 (41.67%)	7 / 15 (46.67%)	
occurrences (all)	43	14	
Rhinitis			
subjects affected / exposed	0 / 36 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 36 (8.33%)	1 / 15 (6.67%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2012	The change was the revision of height measurement method, statistical method (per protocol (PP) analysis to be conducted, 1st, 2nd exploratory purpose to be included in the secondary purpose.), In/Exclusion criteria ('Bone age ≤ 12 years' was added in the inclusion criteria and 'Bone age is advanced over chronological age more than 3 years (inclusive)' was added in the exclusion criteria).
31 October 2012	The change was the revision of IGF-I/ IGFBP-3, addition of withdrawal criterion, sample size adjustment, exclusion criteria, change of dose regimen, change of screening period, paper CRF, data management, central laboratory assessment, monitoring procedures and trial sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported