Clinical trial results:
A Two Years Multicentre Study of Genotropin Treatment of Short Prepubertal Children With Intra-Uterine Growth Retardation

Summary

EudraCT number	2014-004160-38
Trial protocol	Outside EU/EEA
Global end of trial date	07 May 2009

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	27 June 2015

Trial information

Trial identification

Sponsor protocol code	93-8122-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01073605
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: A6281186

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	18 January 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of continuous and intermittent administration of Genotropin 16 international unit (IU) on stature in prepubertal short children with intra-uterine growth retardation (IUGR).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 1993
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	France: 206
Worldwide total number of subjects	206
EEA total number of subjects	206

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)	205
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 208 subjects were enrolled from 32 sites in France. Study started on 01 July 1993 and completed on 07 May 2009. Out of 208 enrolled subjects, only 206 subjects were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Genotonorm 0.7 (Continuous Treatment)

Arm description:

Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Arm type	Active comparator
Investigational medicinal product name	Genotonorm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 0.7 IU/kg/week at a dose of 0.03 milligram (mg)/kg/day of Genotonorm growth hormone (GH) as a continuous treatment.

Arm title	Genotonorm 1.4 (Continuous Treatment)

Arm description:

Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Arm type	Active comparator
Investigational medicinal product name	Genotonorm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 1.4 IU/kg/week at a dose of 0.06 mg/kg/day of growth hormone Genotonorm as a continuous treatment.

Arm title	Genotonorm 1.4 (Intermittent Treatment)

Arm description:

Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Arm type	Active comparator

Investigational medicinal product name	Genotonorm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 1.4 IU/kg/week at a dose of 0.06 mg/kg/day of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Number of subjects in period 1	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)
Started	68	70	68
Received Treatment	68	70	68
Completed	6	4	8
Not completed	62	66	60
Consent withdrawn by subject	31	39	22
Unknown	25	21	29
Ongoing at Cutoff Date	1	1	-
Adverse event	2	1	-
Lost to follow-up	3	4	9

Baseline characteristics

Reporting groups	
Reporting group title	Genotonorm 0.7 (Continuous Treatment)
Reporting group description:	
Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.	
Reporting group title	Genotonorm 1.4 (Continuous Treatment)
Reporting group description:	
Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.	
Reporting group title	Genotonorm 1.4 (Intermittent Treatment)
Reporting group description:	
Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.	

Reporting group values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)
Number of subjects	68	70	68
Age, Customized Units: subjects			
Less than (<) 4 years	15	8	6
4 - 8 years	29	32	29
8 - 12 years	23	30	33
Greater than or equal to (>=) 12 years	1	0	0
Gender, Male/Female Units: subjects			
Female	25	31	39
Male	43	39	29

Reporting group values	Total		
Number of subjects	206		
Age, Customized Units: subjects			
Less than (<) 4 years	29		
4 - 8 years	90		
8 - 12 years	86		
Greater than or equal to (>=) 12 years	1		
Gender, Male/Female Units: subjects			
Female	95		
Male	111		

End points

End points reporting groups

Reporting group title	Genotonorm 0.7 (Continuous Treatment)
Reporting group description:	
Subjects received 0.7 IU/kilogram (kg)/week of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.	
Reporting group title	Genotonorm 1.4 (Continuous Treatment)
Reporting group description:	
Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.	
Reporting group title	Genotonorm 1.4 (Intermittent Treatment)
Reporting group description:	
Subjects received 1.4 IU/kg/week of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.	

Primary: Change from Baseline in Annual Growth Rate Measured at 2 Years Following Treatment With Genotonorm

End point title	Change from Baseline in Annual Growth Rate Measured at 2 Years Following Treatment With Genotonorm
End point description:	
Annual growth rate was expressed as height velocity (centimeter [cm]/year). This was derived by substracting annual growth rate at Baseline from 2-year value. (Annual growth rate was calculated each year and rescaled to 1 year if the interval between x and x-1 was not 365 days, as long as a subject remains in the study): ANGRYx = (Height Yx – Height Y[x-1]) / ([Date of Yx – Date of Y{x-1}] /365.25). All subjects who received at least 1 study dose of Genotonorm were included in the Full Analysis Set (FAS).	
End point type	Primary
End point timeframe:	
Baseline, 2 years	

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[1]	37[2]	40[3]	
Units: cm/year				
arithmetic mean (standard deviation)	3.07 (± 2.21)	3.97 (± 1.72)	2.84 (± 1.71)	

Notes:

[1] - N signifies number of subjects with change in annual growth rate at 2 years.

[2] - N signifies number of subjects with change in annual growth rate at 2 years.

[3] - N signifies number of subjects with change in annual growth rate at 2 years.

Statistical analyses

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)
Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02922 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs 1.4 (Intermittent)
Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74299 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent)
Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00467 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Annual Growth Rate Standard Deviation Score (SDS)

End point title	Annual Growth Rate Standard Deviation Score (SDS)

End point description:

Calculated using Sempe reference means and standard deviations for growth rate according to age and sex. Standardization was performed for chronological age. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50[7]	42[8]	43[9]	
Units: SDS				

arithmetic mean (standard deviation)				
Baseline (n=50, 42, 43)	-2.72 (± 1.83)	-2.58 (± 1.39)	-2.75 (± 1.73)	
1 year (n=57, 55, 59)	2.14 (± 1.52)	3.97 (± 2.26)	1.71 (± 1.51)	
2 years (n=53, 49, 56)	0.77 (± 1.57)	2 (± 1.73)	0.67 (± 1.22)	
3 years (n=39, 34, 41)	0.36 (± 1.14)	1.35 (± 1.78)	0.31 (± 1.12)	
4 years (n=21, 18, 27)	0.13 (± 1.55)	0.61 (± 1.2)	0.34 (± 1.2)	
5 years (n=12, 10, 20)	0.18 (± 1.24)	0.09 (± 0.88)	-0.02 (± 1.46)	
6 years (n=11, 7, 19)	0.9 (± 1.92)	0.59 (± 1.61)	0.05 (± 1.2)	

Notes:

[7] - N signifies number of subjects with evaluable data at Baseline.

[8] - N signifies number of subjects with evaluable data at Baseline.

[9] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate SDS

End point title	Change From Baseline in Annual Growth Rate SDS

End point description:

Calculated corresponding to the gender and chronological age by substracting annual growth rate SDS at baseline from annual growth rate SDS at each year. FAS. Here, n = number of subjects with evaluable data at each time point.

End point type	Secondary

End point timeframe:

Baseline, 1 to 3 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49[10]	42[11]	42[12]	
Units: SDS				
arithmetic mean (standard deviation)				
1 year (n=49, 42, 42)	4.81 (± 2.27)	6.56 (± 2.55)	4.37 (± 2.16)	
2 years (n=47, 37, 40)	3.51 (± 2.5)	4.53 (± 1.89)	3.37 (± 2.33)	
3 years (n=34, 25, 32)	3.31 (± 2.06)	3.8 (± 2.2)	3.17 (± 1.86)	

Notes:

[10] - N signifies number of subjects with evaluable data at 1 year.

[11] - N signifies number of subjects with evaluable data at 1 year.

[12] - N signifies number of subjects with evaluable data at 1 year.

Statistical analyses

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)

Statistical analysis description:

Statistical analysis for 1 year.

Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment)

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00125 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent)

Statistical analysis description:

Statistical analysis for 1 year.

Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25995 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent) Groups

Statistical analysis description:

Statistical analysis for 1 year.

Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00008 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)

Statistical analysis description:

Statistical analysis for 2 years.

Comparison groups	Genotonorm 0.7 (Continuous Treatment) v Genotonorm 1.4 (Continuous Treatment)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03273 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent)

Statistical analysis description:

Statistical analysis for 2 years.

Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68581 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent) Groups

Statistical analysis description:

Statistical analysis for 2 years.

Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0053 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)

Statistical analysis description:

Statistical analysis for 3 years.

Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57556 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent)

Statistical analysis description:

Statistical analysis for 3 years.

Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63956 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent) Groups

Statistical analysis description:	
Statistical analysis for 3 years.	
Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16421 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Height (cm)

End point title	Height (cm)

End point description:

Performed by use of a wallmounted device (eg, Harpenden Stadiometer). Each subject was measured 3 times and the mean of these measurements was recorded as the present height. Final Height: Childrens were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years, final height

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[22]	56[23]	60[24]	
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n=58, 56, 60)	105.22 (± 15.04)	107.06 (± 12.29)	106.44 (± 12.04)	
1 year (n=57, 55, 59)	113.38 (± 15.09)	116.31 (± 12.24)	113.71 (± 12.01)	
2 years (n=53, 49, 56)	119.67 (± 15.18)	124.11 (± 13.02)	120.64 (± 12.34)	
3 years (n=39, 34, 41)	123.92 (± 15.08)	131.75 (± 13.76)	125.39 (± 12.52)	
4 years (n=21, 18, 27)	124.67 (± 13.14)	132.3 (± 13.23)	127.59 (± 11.51)	
5 years (n=12, 10, 21)	126.73 (± 10.01)	131.01 (± 9.26)	129.98 (± 9.93)	
6 years (n=11, 7, 20)	133.29 (± 10.46)	138.84 (± 8.69)	135.45 (± 10.1)	
Final height (n=17, 12, 22)	146.86 (± 11.26)	151.98 (± 6.52)	149.13 (± 9.07)	

Notes:

[22] - N signifies number of subjects with evaluable data at Baseline.

[23] - N signifies number of subjects with evaluable data at Baseline.

[24] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height (cm)

End point title	Change From Baseline in Height (cm)

End point description:

Calculated by substracting height at Baseline from height at each year. Final Height: Children were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at Baseline and each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years, final height

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[25]	56[26]	60[27]	
Units: cm				
arithmetic mean (standard deviation)				
1 year (n=57, 55, 59)	8.21 (± 1.38)	9.21 (± 1.45)	7.33 (± 1.32)	
2 years (n=53, 49, 56)	14.77 (± 2.45)	17.01 (± 2.21)	13.92 (± 2.03)	
3 years (n=39, 34, 41)	20.62 (± 3)	24.49 (± 3.04)	20.14 (± 2.78)	
4 years (n=21, 18, 27)	26.36 (± 4.37)	30.77 (± 3.43)	25.83 (± 3.26)	
5 years (n=12, 10, 21)	32.23 (± 5.92)	35.7 (± 4.27)	32.16 (± 3.81)	
6 years (n=11, 7, 20)	38.2 (± 6.66)	44.03 (± 3.09)	38.01 (± 4.82)	
Final height (n=17, 12, 22)	45.39 (± 13.08)	45.3 (± 13.72)	40.93 (± 9.22)	

Notes:

[25] - N signifies number of subjects with evaluable data at Baseline.

[26] - N signifies number of subjects with evaluable data at Baseline.

[27] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Height (SDS)

End point title	Height (SDS)

End point description:

Calculated using Sempe reference means and standard deviations for height. Final Height: Children were

defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years, final height

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[28]	56[29]	60[30]	
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=58, 56, 60)	-3.16 (± 0.52)	-3.07 (± 0.46)	-3.21 (± 0.65)	
1 year (n=57, 55, 59)	-2.49 (± 0.54)	-2.17 (± 0.5)	-2.68 (± 0.69)	
2 years (n=53, 49, 56)	-2.21 (± 0.66)	-1.68 (± 0.52)	-2.38 (± 0.75)	
3 years (n=39, 34, 41)	-2.17 (± 0.7)	-1.38 (± 0.57)	-2.24 (± 0.9)	
4 years (n=21, 18, 27)	-2.16 (± 1.03)	-1.16 (± 0.73)	-2.09 (± 0.96)	
5 years (n=12, 10, 21)	-1.95 (± 1.26)	-1.15 (± 0.83)	-1.96 (± 1.1)	
6 years (n=11, 7, 19)	-1.8 (± 1.28)	-0.67 (± 0.66)	-1.93 (± 1.18)	
Final height (n=14, 9, 18)	-2.06 (± 0.76)	-1.97 (± 0.95)	-2.29 (± 1.35)	

Notes:

[28] - N signifies number of subjects with evaluable data at Baseline.

[29] - N signifies number of subjects with evaluable data at Baseline.

[30] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height (SDS)

End point title	Change From Baseline in Height (SDS)

End point description:

Calculated by substracting height SDS at Baseline from height SDS at each year. Final Height: Children were defined as reaching their final height when annual Growth Rate was less than 2 cm in the previous year and bone age was equal to or greater than 17 years in boys and equal to or greater than 15 years in girls. FAS. Here, n = number of subjects with evaluable data at Baseline and each time point. Data beyond 6 years were not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years, final height

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[31]	56[32]	60[33]	
Units: SDS				
arithmetic mean (standard deviation)				
1 year (n=57, 55, 59)	0.67 (± 0.28)	0.88 (± 0.3)	0.53 (± 0.28)	
2 years (n=53, 49, 56)	0.94 (± 0.45)	1.4 (± 0.43)	0.84 (± 0.37)	
3 years (n=39, 34, 41)	1.06 (± 0.54)	1.7 (± 0.54)	0.99 (± 0.51)	
4 years (n=21, 18, 27)	1.2 (± 0.81)	1.98 (± 0.69)	1.21 (± 0.54)	
5 years (n=12, 10, 21)	1.37 (± 1.12)	2.03 (± 0.87)	1.46 (± 0.69)	
6 years (n=11, 7, 19)	1.54 (± 1.12)	2.6 (± 0.66)	1.54 (± 0.86)	
Final height (n=14, 9, 18)	1 (± 0.53)	0.97 (± 0.95)	0.86 (± 1.16)	

Notes:

[31] - N signifies number of subjects with evaluable data at Baseline.

[32] - N signifies number of subjects with evaluable data at Baseline.

[33] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)
Comparison groups	Genotonorm 0.7 (Continuous Treatment) v Genotonorm 1.4 (Continuous Treatment)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent)
Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58324 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent) Groups
Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment)

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - P-values for the 3 treatment comparisons should be interpreted in line with the Bonferroni stepwise (Holm) testing procedure, to maintain the Type 1 error at p=0.05.

Secondary: Body Mass Index (BMI)

End point title	Body Mass Index (BMI)

End point description:

BMI was calculated by weight divided by height squared. FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[37]	56[38]	60[39]	
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline (n=58, 56, 60)	14.74 (± 1.48)	15.14 (± 1.76)	14.59 (± 1.51)	
1 year (n=56, 55, 59)	14.82 (± 1.52)	15.44 (± 1.94)	14.87 (± 1.76)	
2 years (n=53, 49, 56)	15.33 (± 1.78)	15.92 (± 2.15)	15.29 (± 2)	
3 years (n=39, 34, 41)	15.59 (± 2.02)	16.65 (± 2.92)	15.58 (± 2.11)	
4 years (n=21, 18, 27)	15.32 (± 1.56)	17.03 (± 3.7)	15.8 (± 2.37)	
5 years (n=12, 10, 21)	15.8 (± 1.57)	16.25 (± 1.7)	16.69 (± 3.92)	
6 years (n=11, 7, 20)	16.21 (± 1.46)	16.34 (± 1.8)	17.28 (± 4.21)	

Notes:

[37] - N signifies number of subjects with evaluable data at Baseline.

[38] - N signifies number of subjects with evaluable data at Baseline.

[39] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Weight

End point title	Weight

End point description:

FAS. Here, n = number of subjects with evaluable data at each time point. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58[40]	56	60	
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=58, 56, 60)	16.77 (± 5.43)	17.7 (± 5.12)	16.79 (± 4.35)	
1 year (n=56, 55, 59)	19.71 (± 6.28)	21.29 (± 6.04)	19.56 (± 5.17)	
2 years (n=53, 49, 56)	22.66 (± 7.62)	25.08 (± 7.43)	22.64 (± 6.05)	
3 years (n=39, 34, 41)	24.77 (± 8.8)	29.61 (± 9.62)	24.98 (± 7.05)	
4 years (n=21, 18, 27)	24.3 (± 7.01)	30.56 (± 10.42)	26.28 (± 7.94)	
5 years (n=12, 10, 21)	25.74 (± 6.22)	28.07 (± 5.22)	28.52 (± 8.96)	
6 years (n=11, 7, 21)	29.13 (± 6.42)	31.94 (± 7.28)	32.3 (± 10.32)	

Notes:

[40] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age

End point title	Change From Baseline in Bone Age

End point description:

Bone age was determined by the Greulich-Pyle method. Calculated by substracting bone age at baseline from bone age at each year. Safety population = all subjects who received at least 1 study dose of GH. Here, n = number of subjects with evaluable data at baseline and each time point.

End point type	Secondary

End point timeframe:

Baseline, 1 to 3 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[41]	62[42]	61[43]	
Units: Years				
arithmetic mean (standard deviation)				
1 year (n=53, 60, 56)	1.17 (± 0.51)	1.27 (± 0.72)	1.25 (± 0.54)	
2 years (n=52, 51, 49)	2.4 (± 0.9)	2.5 (± 1.08)	2.58 (± 0.97)	
3 years (n=41, 39, 35)	3.53 (± 1.22)	4.06 (± 1.05)	3.67 (± 0.97)	

Notes:

[41] - N signifies number of subjects with evaluable data at Baseline.

[42] - N signifies number of subjects with evaluable data at Baseline.

[43] - N signifies number of subjects with evaluable data at Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age/Change from Baseline in Chronological Age Ratio

End point title	Change From Baseline in Bone Age/Change from Baseline in Chronological Age Ratio

End point description:

Bone age was determined by the Greulich-Pyle method. Chronological Age (years) was calculated as: (Date minus Date of Birth) divided by 365.25. Chronological Age used was the age at the date that the corresponding Bone Age X-ray was performed. Ratio was calculated by change from Baseline in bone age divided by change from Baseline in chronological age. Safety population. Here, n = number of subjects with evaluable data at each time point.

End point type	Secondary

End point timeframe:

1 to 3 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53[44]	60[45]	56[46]	
Units: ratio				
arithmetic mean (standard deviation)				
1 year (n=53, 60, 56)	0.96 (± 0.41)	1.07 (± 0.62)	1.06 (± 0.45)	
2 years (n=51, 51, 49)	1.06 (± 0.41)	1.14 (± 0.5)	1.18 (± 0.44)	
3 years (n=35, 37, 35)	1.09 (± 0.39)	1.26 (± 0.32)	1.14 (± 0.29)	

Notes:

[44] - N signifies number of subjects with evaluable data at 1 year.

[45] - N signifies number of subjects with evaluable data at 1 year.

[46] - N signifies number of subjects with evaluable data at 1 year.

Statistical analyses

No statistical analyses for this end point

Secondary: Chronological Age at Onset of Puberty

End point title	Chronological Age at Onset of Puberty

End point description:

Chronological age (years) at first study visit with onset of puberty = (Date of study visit minus Date of Birth) divided by 365.25. Safety population.

End point type	Secondary

End point timeframe:
Onset of puberty

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[47]	35[48]	45[49]	
Units: Years				
arithmetic mean (standard deviation)	11.88 (± 2.22)	11.12 (± 1.74)	11.58 (± 1.42)	

Notes:

[47] - N signifies number of subjects who started puberty by the end of the study.

[48] - N signifies number of subjects who started puberty by the end of the study.

[49] - N signifies number of subjects who started puberty by the end of the study.

Statistical analyses

Statistical analysis title	Genotonorm 0.7 vs. 1.4 (Continuous Treatment)
Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 0.7 (Continuous Treatment)
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0681 [50]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	1.39

Notes:

[50] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

Statistical analysis title	Genotonorm 0.7 (Continuous) vs. 1.4 (Intermittent)
Comparison groups	Genotonorm 1.4 (Intermittent Treatment) v Genotonorm 1.4 (Continuous Treatment)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8971 [51]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.74

Notes:

[51] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

Statistical analysis title	Genotonorm 1.4 (Continuous vs.Intermittent) Groups
Comparison groups	Genotonorm 1.4 (Continuous Treatment) v Genotonorm 1.4 (Intermittent Treatment)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0583 [52]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.02

Notes:

[52] - There is no adjustment for multiplicity of treatment comparisons. The Analysis of Covariance took into account the patient covariates age and gender.

Secondary: Number of Subjects Reaching Puberty

End point title	Number of Subjects Reaching Puberty

End point description:

The defined criteria for reaching puberty were: boy=if right or left testes volume >=4 ml; girl=if breast development >=2. Tanner Adolescent Pubertal Staging Questionnaire documents the stage of development of secondary sexual characteristics rated in 5 stages: stage 1 (no development) to 5 (adult-like development in quantity and size). Onset of puberty was defined as the visit where the data recorded first met the above criteria for starting puberty. Safety population. Data beyond 6 years are not reported due to the low proportion of subjects followed up beyond 6 years. Started = started puberty; Not Started = not started puberty yet as per Tanner scale.

End point type	Secondary

End point timeframe:

Baseline, 1 to 6 years

End point values	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	70	68	
Units: subjects				
number (not applicable)				
Baseline (Female, Not Started)	25	31	39	
Baseline (Male, Not Started)	43	39	29	

1 year (Female, Not Started)	24	27	37	
1 year (Female, Started)	1	3	2	
1 year (Male, Not Started)	36	35	27	
1 year (Male, Started)	4	3	1	
2 years (Female, Not Started)	20	20	31	
2 years (Female, Started)	3	7	6	
2 years (Male, Not Started)	31	28	20	
2 years (Male, Started)	9	7	6	
3 years (Female, Not Started)	16	10	16	
3 years (Female, Started)	3	9	11	
3 years (Male, Not Started)	19	15	9	
3 years (Male, Started)	6	7	4	
4 years (Female, Not Started)	10	7	10	
4 years (Female, Started)	2	5	7	
4 years (Male, Not Started)	10	5	7	
4 years (Male, Started)	1	2	3	
5 years (Female, Not Started)	5	4	5	
5 years (Female, Started)	2	3	10	
5 years (Male, Not Started)	6	6	4	
5 years (Male, Started)	2	1	1	
6 years (Female, Not Started)	3	3	3	
6 years (Female, Started)	3	2	12	
6 years (Male, Not Started)	5	4	1	
6 years (Male, Started)	3	1	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were reported from time of first dose of study treatment up to 7 days after last dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Genotonorm 0.7 (Continuous Treatment)

Reporting group description:

Subjects received 0.7 IU/kg/week (0.03 milligram [mg]/kg/day) of Genotonorm growth hormone (GH) as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Reporting group title	Genotonorm 1.4 (Continuous Treatment)

Reporting group description:

Subjects received 1.4 IU/kg/week (0.06 mg/kg/day) of the growth hormone Genotonorm as a continuous treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Reporting group title	Genotonorm 1.4 (Intermittent Treatment)

Reporting group description:

Subjects received 1.4 IU/kg/week (0.06 mg/kg/day) of the growth hormone Genotonorm as an intermittent treatment. Treatment was allowed to be taken until final height of the subject had been reached.

Serious adverse events	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 68 (8.82%)	19 / 70 (27.14%)	9 / 68 (13.24%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Appendicectomy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hospitalisation			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoidectomy			

subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchidopexy			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthopaedic procedure			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal reconstruction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgery			
subjects affected / exposed	0 / 68 (0.00%)	3 / 70 (4.29%)	4 / 68 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenotomy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue tie operation			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			

subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour excision			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric repair			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 68 (0.00%)	2 / 70 (2.86%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular disorder			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular torsion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ligament sprain			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
DiGeorge's syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 68 (1.47%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			

subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal prolapse			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Precocious puberty			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nuchal rigidity			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 70 (1.43%)	3 / 68 (4.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Genotonorm 0.7 (Continuous Treatment)	Genotonorm 1.4 (Continuous Treatment)	Genotonorm 1.4 (Intermittent Treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 68 (58.82%)	42 / 70 (60.00%)	35 / 68 (51.47%)
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 68 (0.00%)	4 / 70 (5.71%)	0 / 68 (0.00%)
occurrences (all)	0	5	0
Headache			
subjects affected / exposed	2 / 68 (2.94%)	5 / 70 (7.14%)	3 / 68 (4.41%)
occurrences (all)	5	8	6
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 68 (5.88%)	3 / 70 (4.29%)	3 / 68 (4.41%)
occurrences (all)	4	4	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 68 (5.88%)	3 / 70 (4.29%)	4 / 68 (5.88%)
occurrences (all)	6	3	4
Diarrhoea			
subjects affected / exposed	5 / 68 (7.35%)	0 / 70 (0.00%)	4 / 68 (5.88%)
occurrences (all)	6	0	4
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	5 / 68 (7.35%)	3 / 70 (4.29%)	3 / 68 (4.41%)
occurrences (all)	8	3	3
Cough			
subjects affected / exposed	1 / 68 (1.47%)	3 / 70 (4.29%)	5 / 68 (7.35%)
occurrences (all)	1	3	6
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	4 / 68 (5.88%)	1 / 70 (1.43%)	1 / 68 (1.47%)
occurrences (all)	9	1	1
Urticaria			

subjects affected / exposed	4 / 68 (5.88%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences (all)	6	0	1
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	2 / 68 (2.94%)	4 / 70 (5.71%)	0 / 68 (0.00%)
occurrences (all)	3	5	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 68 (19.12%)	9 / 70 (12.86%)	17 / 68 (25.00%)
occurrences (all)	20	18	32
Ear infection			
subjects affected / exposed	15 / 68 (22.06%)	15 / 70 (21.43%)	9 / 68 (13.24%)
occurrences (all)	25	39	21
Fungal infection			
subjects affected / exposed	4 / 68 (5.88%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences (all)	4	1	0
Gastroenteritis			
subjects affected / exposed	4 / 68 (5.88%)	8 / 70 (11.43%)	11 / 68 (16.18%)
occurrences (all)	4	11	21
Influenza			
subjects affected / exposed	6 / 68 (8.82%)	9 / 70 (12.86%)	7 / 68 (10.29%)
occurrences (all)	7	15	8
Nasopharyngitis			
subjects affected / exposed	16 / 68 (23.53%)	16 / 70 (22.86%)	11 / 68 (16.18%)
occurrences (all)	27	28	21
Pharyngitis			
subjects affected / exposed	2 / 68 (2.94%)	6 / 70 (8.57%)	7 / 68 (10.29%)
occurrences (all)	4	8	8
Rhinitis			
subjects affected / exposed	4 / 68 (5.88%)	2 / 70 (2.86%)	6 / 68 (8.82%)
occurrences (all)	5	2	8
Tracheitis			
subjects affected / exposed	3 / 68 (4.41%)	5 / 70 (7.14%)	2 / 68 (2.94%)
occurrences (all)	3	6	2
Upper respiratory tract infection			

subjects affected / exposed	19 / 68 (27.94%)	19 / 70 (27.14%)	12 / 68 (17.65%)
occurrences (all)	31	39	20
Varicella			
subjects affected / exposed	8 / 68 (11.76%)	6 / 70 (8.57%)	1 / 68 (1.47%)
occurrences (all)	8	6	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 1995	Treatment with Genotonorm was stopped in prepubescent children with short stature due to IUGR who, after 2 years on the initial protocol or during their third year of treatment, had begun puberty at least 6 months before. The aim of this change was to study the spontaneous progress of their growth until reaching final height.
15 June 1998	Treatment of children with Genotonorm ® for one additional year was continued , in order to obtain long-term data on the safety and efficacy of the product, that subjects who started puberty would continue to be treated according to the same therapeutic regimen, for the possibility of using the Genotonorm ® Pen 16 or 36, depending on the weight of the subject and subjects who had discontinued their treatment were to be followed in the context of the protocol so as to obtain data on their final height.
17 September 2001	A modification of the treatment period was done, allowing the administration of Genotonorm to children until they attain their final height in order to obtain long-term data on the safety and efficacy of the product. Changes in dosage units of 5.3 mg instead of 16 IU and 12 mg instead of 36 IU.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported