Clinical trial results:
Evolution of Growth Rate in Children Suffering From a Disease Associated With Growth Retardation and Treated by Genotonorm. A Pilot Study

Summary

EudraCT number	2004-002991-40
Trial protocol	Outside EU/EEA
Global end of trial date	05 October 2011

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	A6281269

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00163215
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: 93-8122-001; CTN 93-8122-001

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Call Center, Pfizer Inc, 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer Call Center, Pfizer Inc, 001 800-718-1021, 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	06 March 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show an increase in annual growth rate (AGR) 3 years after Visit 2. Annual growth rate in standard deviation (SD) after 3 years will be compared to growth rate before the start of growth hormone (GH) treatment.

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	17 January 2005
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	France: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	25
Adolescents (12-17 years)	21
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 number of subjects screened were 64, out of which 46 were enrolled in the study. The study was conducted in France which started on 17 January 2005 and completed on 05 October 2011.

Period 1

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

Arms

Arm title	Genotonorm

Arm description:

Genotonorm (recombinant somatropin) up to maximum of 50 microgram/kilogram/day (mcg/kg/day) subcutaneously as decided by the investigator, divided in 7 daily doses for up to 3 years.

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

Dosage and administration details:

Genotonorm was administered up to maximum of 50 mcg/kg/day, divided in 7 daily doses for up to 3 years.

Number of subjects in period 1	Genotonorm
Started	46
Completed	31
Not completed	15
Withdrawal by Subject	5
Unspecified	7
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Subjects were administered with Genotonorm (recombinant somatropin) up to maximum of 50 mcg/kg/day subcutaneously as decided by the investigator, divided in 7 daily doses for up to 3 years.	

Reporting group values	Overall Study	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	10.3		
standard deviation	± 3.6	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	34	34	

End points

End points reporting groups

Reporting group title	Genotonorm

Reporting group description:

Genotonorm (recombinant somatropin) up to maximum of 50 microgram/kilogram/day (mcg/kg/day) subcutaneously as decided by the investigator, divided in 7 daily doses for up to 3 years.

Primary: Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36 in Intent-to-Treat (ITT) Population

End point title	Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36 in Intent-to-Treat (ITT) Population[1]

End point description:

Change in annual growth rate (AGR) standard deviation score (SDS) for chronological age (CA) derived by subtracting AGR SDS CA at baseline from each time point (Yx) value. AGR at Yx= (height Yx–height Y[x-1])/([date of Yx–date of Y{x-1}]/365.25). AGR as SDS calculated using Sempe reference means and standard deviations (SD) for growth rate. AGR SDS CA (for both baseline and Yx)= (AGR-reference mean for growth rate CA)/reference SD for growth rate CA. CA calculated as integer (Date of height measurement-Date of birth)/365.25*12. SDS indicates how similar subject was to reference population. Intent to Treat (ITT) set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Primary

End point timeframe:

Baseline, Month 36

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	42[2]			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n = 42)	-1.29 (± 1.79)			
Change at Month 36 (n = 26)	2.36 (± 1.98)			

Notes:

[2] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36 in Per-Protocol (PP) Population

End point title	Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 36 in Per-Protocol (PP) Population[3]

End point description:

Change in AGR, SDS for CA derived by subtracting AGR, SDS and CA at baseline from each time point

(Yx) value. AGR at Yx= (height Yx–height Y[x-1])/([date of Yx–date of Y{x-1}]/365.25). AGR as SDS calculated using Sempe reference means and SD for growth rate. AGR SDS CA (for both baseline and Yx)= (AGR-reference mean for growth rate CA)/reference SD for growth rate CA. CA calculated as integer (Date of height measurement-Date of birth)/365.25*12. SDS indicates how similar subject was to reference population. PP analysis set included all subjects in the ITT set without a major protocol violation. Here "n" signifies subjects evaluated at that time point.

End point type	Primary

End point timeframe:

Baseline, Month 36

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	14[4]			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n = 14)	-1.98 (± 1.06)			
Change at Month 36 (n = 12)	2.7 (± 2.02)			

Notes:

[4] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate at Month 12, Month 24 and Month 36 in ITT Population

End point title	Change From Baseline in Annual Growth Rate at Month 12, Month 24 and Month 36 in ITT Population

End point description:

Change in AGR at Yx was derived by subtracting AGR at baseline from Yx value. AGR was calculated each year and rescaled to 1 year if the interval between Yx and Y[x-1] was not 365 days, as long as a subject remained in the study. AGR at Yx was calculated using the previous height measurements (Y[x-1]) and height recorded at Yx (AGR Yx = [height Yx–height Y{x-1}] / ([date of Yx – date of Y{x-1}] /365.25). ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	42[5]			
Units: centimeter per year (cm/year)				
arithmetic mean (standard deviation)				
Baseline (n = 42)	4.5 (± 1.8)			
Change at Month 12 (n = 36)	3.3 (± 2.9)			
Change at Month 24 (n = 35)	2.5 (± 2.7)			

Change at Month 36 (n = 26)	2 (± 2)			

Notes:

[5] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate at Month 12, Month 24, Month 36 in PP Population

End point title	Change From Baseline in Annual Growth Rate at Month 12, Month 24, Month 36 in PP Population

End point description:

Change in AGR at Yx was derived by subtracting AGR at baseline from Yx value. AGR was calculated each year and rescaled to 1 year if the interval between Yx and Y[x-1] was not 365 days, as long as a subject remained in the study. AGR at Yx was calculated using the previous height measurements (Y[x-1]) and height recorded at Yx (AGR Yx = [height Yx–height Y{x-1}] / ([date of Yx – date of Y{x-1}] /365.25). PP analysis set included all subjects in the ITT set without a major protocol violation. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	14[6]			
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (n = 14)	4 (± 1)			
Change at Month 12 (n = 14)	4 (± 1)			
Change at Month 24 (n = 14)	2.5 (± 1.3)			
Change at Month 36 (n = 12)	1.8 (± 1.1)			

Notes:

[6] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Height

End point title	Height

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). The standing height of the subjects was measured two times and the mean of these measurements was recorded. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: cm				
arithmetic mean (standard deviation)				
Baseline (n = 44)	123.9 (± 17.3)			
Month 12 (n = 39)	130.3 (± 17.5)			
Month 24 (n = 39)	137.8 (± 16.9)			
Month 36 (n = 27)	143.5 (± 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height at Month 12, Month 24 and Month 36

End point title	Change From Baseline in Height at Month 12, Month 24 and Month 36

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). The standing height of the subjects was measured two times and the mean of these measurements was recorded. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	39[7]			
Units: cm				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 39)	7.7 (± 2.1)			
Change at Month 24 (n = 39)	14.9 (± 3.4)			
Change at Month 36 (n = 27)	22.3 (± 3.7)			

Notes:

[7] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Height Standard Deviation Score (SDS) for Chronological Age (CA)

End point title	Mean Height Standard Deviation Score (SDS) for Chronological Age (CA)

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). The standing height of the subject was measured two times and the mean of these measurements was recorded. Height SDS CA Yx = (height Yx – reference mean for CA Yx) / reference SD for CA Yx. Height in SDS was calculated using Sempe reference means and SD for height. CA calculated as integer (Date of height measurement–Date of birth)/365.25*12. SDS indicates how similar the subject was to the reference population. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here"n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n = 44)	-2.84 (± 0.91)			
Month 12 (n = 39)	-2.42 (± 0.98)			
Month 24 (n = 39)	-2.09 (± 1.08)			
Month 36 (n = 27)	-1.72 (± 0.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12, Month 24 and Month 36

End point title	Change From Baseline in Height Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12, Month 24 and Month 36

End point description:

Change in height SDS CA was derived by subtracting height SDS CA at baseline from Yx value. Height SDS CA (for both baseline and Yx) = (height – reference mean for CA)/reference SD for CA. Height in SDS was calculated using Sempe reference means and SD for height. CA calculated as integer (Date of height measurement – Date of birth)/365.25*12. SDS indicates how similar the subject was to the reference population. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	39[8]			
Units: SDS				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 39)	0.41 (± 0.42)			
Change at Month 24 (n = 39)	0.81 (± 0.6)			
Change at Month 36 (n = 27)	1.03 (± 0.62)			

Notes:

[8] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Height Standard Deviation Score (SDS) for Bone Age (BA)

End point title	Mean Height Standard Deviation Score (SDS) for Bone Age (BA)

End point description:

Height SDS BA Yx = (height Yx – reference mean for BA Yx) / reference SD for BA Yx. Height in SDS was calculated using Sempe reference means and SD for height. BA was estimated locally using an X-ray from the left wrist and hand. SDS indicates how similar the subject was to the reference population. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	35[9]			
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n = 35)	-0.71 (± 1.52)			
Month 12 (n = 32)	-0.55 (± 1.68)			
Month 24 (n = 32)	-0.49 (± 1.77)			
Month 36 (n = 20)	-0.3 (± 1.46)			

Notes:

[9] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Standard Deviation Score (SDS) for Bone Age (BA) at Month 12, Month 24 and Month 36

End point title	Change From Baseline in Height Standard Deviation Score (SDS) for Bone Age (BA) at Month 12, Month 24 and Month 36

End point description:

Change in height SDS BA was derived by subtracting height SDS BA at baseline from Yx value. Height SDS BA (for both baseline and Yx) = (height–reference mean for BA)/reference SD for BA. Height in SDS was calculated using Sempe reference means and SD for height. BA was estimated locally using an X-ray from the left wrist and hand. SDS indicates how similar the subjects was to the reference population. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	28[10]			
Units: SDS				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 28)	-0.05 (± 1.04)			
Change at Month 24 (n = 27)	0.06 (± 1.36)			
Change at Month 36 (n = 17)	0.05 (± 1.32)			

Notes:

[10] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12 and Month 24 in ITT Population

End point title	Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12 and Month 24 in ITT Population

End point description:

Change in AGR SDS for CA derived by subtracting AGR SDS CA at baseline from Yx value. AGR at Yx= (height Yx–height Y[x-1])/([date of Yx–date of Y{x-1}]/365.25). AGR as SDS calculated using Sempe reference means and standard deviations (SD) for growth rate. AGR SDS CA (for both baseline and Yx)= (AGR-reference mean for growth rate CA)/reference SD for growth rate CA. CA calculated as integer (Date of height measurement-Date of birth)/365.25*12. SDS indicates how similar subject was to reference population. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	36[11]			
Units: SDS				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 36)	3.23 (± 2.66)			

Change at Month 24 (n = 35)	2.62 (± 2.05)			

Notes:

[11] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12 and Month 24 in PP Population

End point title	Change From Baseline in Annual Growth Rate Standard Deviation Score (SDS) for Chronological Age (CA) at Month 12 and Month 24 in PP Population

End point description:

Change in AGR, SDS for CA derived by subtracting AGR SDS CA at baseline from each time point (Yx) value. AGR at Yx= (height Yx–height Y[x-1])/([date of Yx–date of Y{x-1}]/365.25). AGR as SDS calculated using Sempe reference means and standard deviations (SD) for growth rate. AGR SDS CA (for both baseline and Yx)= (AGR-reference mean for growth rate CA)/reference SD for growth rate CA. CA calculated as integer (Date of height measurement-Date of birth)/365.25*12. SDS indicates how similar subject was to reference population. PP analysis set included all subjects in the ITT set without a major protocol violation.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	14[12]			
Units: SDS				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 14)	4.4 (± 2.12)			
Change at Month 24 (n = 14)	2.97 (± 1.68)			

Notes:

[12] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Growth Rate Standard Deviation Score (SDS) for Bone Age (BA)

End point title	Mean Growth Rate Standard Deviation Score (SDS) for Bone Age (BA)

End point description:

AGR at Yx was derived by subtracting AGR at baseline from Yx value. AGR was calculated each year and rescaled to 1 year if the interval between Yx and Y[x-1] was not 365 days, as long as a subject remained in the study. AGR at Yx = [height Yx–height Y{x-1}] / ([date of Yx – date of Y{x-1}] /365.25). GR in SDS was calculated using Sempe reference means and SD for growth. BA was estimated locally using an X-ray from the left wrist and hand. SDS indicates how similar the subject was to the reference population. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated

at that time point.

End point type	Secondary

End point timeframe:

Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	28[13]			
Units: SDS				
arithmetic mean (standard deviation)				
Month 12 (n = 28)	1.06 (± 1.57)			
Month 24 (n = 25)	0.46 (± 1.15)			
Month 36 (n = 19)	-0.01 (± 1.19)			

Notes:

[13] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Body Mass Index (BMI)

End point title	Body Mass Index (BMI)

End point description:

BMI was used to measure body fat based on height and weight. It was calculated as body weight (kilogram) divided by the height (meter) squared. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies those subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: kilogram per square meter (kg/m^2)				
arithmetic mean (standard deviation)				
Baseline (n = 44)	16.57 (± 2.37)			
Month 12 (n = 39)	16.96 (± 2.64)			
Month 24 (n = 39)	17.59 (± 2.69)			
Month 36 (n = 27)	17.67 (± 2.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI) at Month 12, Month 24 and Month 36

End point title	Change From Baseline in Body Mass Index (BMI) at Month 12, Month 24 and Month 36

End point description:

BMI was used to measure body fat based on height and weight. It was calculated as body weight (kilogram) divided by the height (meter) squared. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	39[14]			
Units: kg/m^2				
arithmetic mean (standard deviation)				
Change at Month 12 (n = 39)	0.52 (± 1.01)			
Change at Month 24 (n = 39)	1.3 (± 1.35)			
Change at Month 36 (n = 27)	1.89 (± 1.61)			

Notes:

[14] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Age (BA) at Month 12, Month 24 and Month 36

End point title	Change From Baseline in Bone Age (BA) at Month 12, Month 24 and Month 36

End point description:

BA was estimated locally using an X-ray from the left wrist and hand. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	40[15]			
Units: years				
arithmetic mean (standard deviation)				
Baseline (n = 40)	8.7 (± 3.28)			
Change at Month 12 (n = 28)	1.69 (± 0.9)			
Change at Month 24 (n = 28)	2.6 (± 0.97)			
Change at Month 36 (n = 21)	4.04 (± 1.09)			

Notes:

[15] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Bone Age (BA) to Chronological Age (CA)

End point title	Ratio of Bone Age (BA) to Chronological Age (CA)

End point description:

BA was estimated locally using an X-ray from the left wrist and hand. CA at the date of corresponding X-ray (Date of X-ray – Date of birth)/365.25. Ratio of BA/CA at each annual study visit was calculated. ITT set included all subjects who received at least 1 dose of study medication and had at least 1 evaluation of height after start of study medication. Here "n" signifies subjects evaluated at that time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24, Month 36

End point values	Genotonorm			
Subject group type	Reporting group			
Number of subjects analysed	40[16]			
Units: ratio				
arithmetic mean (standard deviation)				
Baseline (n = 40)	0.79 (± 0.15)			
Month 12 (n = 30)	0.83 (± 0.15)			
Month 24 (n = 32)	0.85 (± 0.12)			
Month 36 (n = 23)	0.89 (± 0.14)			

Notes:

[16] - N= (Number of subjects analyzed) signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from Baseline up to the end of treatment (month 36). SAEs were reported any time during the study through and including 28 days after the last dose of the study drug.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another, or 1 subject may have experienced both serious, nonserious event during study. EU BR specific AE tables were generatedseparately as per EU format using latest coding.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Genotonorm

Reporting group description:

Genotonorm (recombinant somatropin) up to maximum of 50 microgram/kilogram/day (mcg/kg/day) subcutaneously as decided by the investigator, divided in 7 daily doses for up to 3 years.

Serious adverse events	Genotonorm		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cryptorchism			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Laryngitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Genotonorm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 46 (45.65%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Surgical and medical procedures			
Ear tube insertion			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Encopresis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Investigations			
Ammonia increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Ligament sprain			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Loss of consciousness			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Nail disorder			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Back pain			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Knee deformity			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Rickets			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Scoliosis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Tracheitis			

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 3		
Metabolism and nutrition disorders Glucose tolerance impaired subjects affected / exposed occurrences (all) Insulin resistance subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 1 1 / 46 (2.17%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2011	Following review of growth hormone (GH) data conducted by the European Medicines Agency (EMA) and the Committee for Medicinal Products for Human use (CHMP), the agencies had requested that the highest approved dose in Europe of 50 mcg/kg/day of recombinant human GH not be exceeded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Certain GCP compliance issues noted at one site for this study. Impact on the study results from noted GCP compliance issues could not be fully assessed; however, it was considered that the results were compromised for the interpretation of efficacy

Notes: