Clinical trial results:
Prevention of Retarded Growth by Early Treatment with Recombinant Human Growth Factor Genotonorm (Registered) in Children with Systemic Forms of Chronic Juvenile Arthritis Receiving Long-term Corticosteroid Therapy. Extension of the Study Beyond Three Years

Summary

EudraCT number	2014-004105-32
Trial protocol	Outside EU/EEA
Global end of trial date	28 October 2011

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	09 July 2015

Trial information

Trial identification

Sponsor protocol code	307-MET-9002-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00174291
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: A6281024

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., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov 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 November 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the effect of increasing the Human growth hormone (hGH) dose (0.6 versus 0.46 milligram per kilogram per week [mg/kg/week] or 1.8 versus 1.4 international unit per kilogram per week [IU/kg/week]) on the statural response:
1) in subjects initially in the treated group of Study CTN 97-8129-016, by comparing the statural response observed with that obtained during the first therapeutic phase at a dose of 0.46 mg/kg/week, or 1.4 IU/kg/week.
2) in subjects initially in the control group of Study CTN 97-8129-016, by comparing the statural response observed with that of subjects in study CTN 94-8123-014.

-To assess the value of early treatment during the course of arthritic disease by comparing the height acquired in the medium term by subjects in the two dose groups: treated from the start or 1 year to 15 months after the diagnosis of Chronic Juvenile Arthritis (CJA), or treated for 4 years after the diagnosis.

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	26 March 2002
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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	0

months)	
Children (2-11 years)	18
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects included in previous study CTN 97-8129-016 were eligible for this study.

Pre-assignment

Screening details:

This study was conducted in France from 26 March 2002 to 28 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

Are arms mutually exclusive?	Yes
Arm title	Somatropin (Without Previous Somatropin Exposure)

Arm description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (<=) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (>=) 17 years for boys and 15 years for girls.

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

Dosage and administration details:

Subjects received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5.

Arm title	Somatropin (With Previous Somatropin Exposure)

Arm description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was <=1.5 cm per year during the preceding 12 months and bone age was >=17 years for boys and 15 years for girls.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
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Dosage and administration details:

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Number of subjects in period 1	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)
Started	10	11
Completed	4	6
Not completed	6	5
Consent withdrawn by subject	3	3
Study terminated by sponsor	-	1
Protocol Violation	2	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Somatropin (Without Previous Somatropin Exposure)

Reporting group description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (<=) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (>=) 17 years for boys and 15 years for girls.

Reporting group title	Somatropin (With Previous Somatropin Exposure)

Reporting group description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was <=1.5 cm per year during the preceding 12 months and bone age was >=17 years for boys and 15 years for girls.

Reporting group values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)	Total
Number of subjects	10	11	21
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	8.5	8.3	
standard deviation	± 3.3	± 2.6	-
Gender, Male/Female			
Units: subjects			
Female	4	6	10
Male	6	5	11

End points

End points reporting groups

Reporting group title	Somatropin (Without Previous Somatropin Exposure)

Reporting group description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 microgram/kilogram/day (mcg/kg/day), subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was less than or equal (<=) 1.5 centimeter (cm) per year during the preceding 12 months and bone age was greater than or equal to (>=) 17 years for boys and 15 years for girls.

Reporting group title	Somatropin (With Previous Somatropin Exposure)

Reporting group description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was <=1.5 cm per year during the preceding 12 months and bone age was >=17 years for boys and 15 years for girls.

Primary: Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Year 3

End point title	Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Year 3[1]

End point description:

Annual rate of growth SDS was obtained by measuring the annual growth rate, subtracting chronological age- and gender-appropriate mean annual growth rate and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. Full Analysis Set (FAS) included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

End point type	Primary

End point timeframe:

Baseline, Year 3

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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[2]	6[3]		
Units: SDS				
median (full range (min-max))				
Baseline	-2.96 (-6.4 to 1.5)	-0.21 (-3 to 4.5)		
Change at Year 3	3.52 (-5.1 to 11.2)	1.34 (-3.6 to 6.2)		

Notes:

[2] - Subjects who were evaluable for this measure.

[3] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Final Height

End point title	Change from Baseline in Annual Rate of Growth Standard Deviation Score (SDS) at Final Height[4]

End point description:

Annual rate of growth SDS was obtained by measuring the annual growth rate, subtracting chronological age- and gender-appropriate mean annual growth rate and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population.

End point type	Primary

End point timeframe:

Baseline, final height (assessed up to Year 9.5)

Notes:

[4] - 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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: SDS				
median (full range (min-max))	(to)	(to)		

Notes:

[5] - Data was not analyzed because of change in planned analysis after early termination of the study.

[6] - Data was not analyzed because of change in planned analysis after early termination of the study.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Height Standard Deviation Score (SDS) at Year 3

End point title	Change from Baseline in Height Standard Deviation Score (SDS) at Year 3[7]

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). Height SDS was obtained by measuring the height, subtracting chronological age- and gender-appropriate mean height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

End point type	Primary

End point timeframe:

Baseline, Year 3

Notes:

[7] - 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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[8]	6[9]		
Units: SDS				
median (full range (min-max))				
Baseline	-2.34 (-4.8 to -1.4)	-0.61 (-3.7 to 1.4)		
Change at Year 3	1.21 (-0.7 to 2.4)	0.73 (-2.4 to 2.6)		

Notes:

[8] - Subjects who were evaluable for this measure.

[9] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Height Standard Deviation Score (SDS) at Final Height

End point title	Change from Baseline in Height Standard Deviation Score (SDS) at Final Height[10]

End point description:

Height was measured using a wall mounted device (example, Harpenden stadiometer). Height SDS was obtained by measuring the height, subtracting chronological age- and gender-appropriate mean height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

End point type	Primary

End point timeframe:

Baseline, final height (assessed up to Year 9.5)

Notes:

[10] - 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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[11]	3[12]		
Units: SDS				
median (full range (min-max))				

Baseline	-0.94 (-1.4 to -0.5)	0.96 (-3.7 to 2.3)		
Change at Final Height	0.08 (-0.7 to 0.9)	-0.43 (-0.8 to 0.5)		

Notes:

[11] - Subjects who were evaluable for this measure.

[12] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Year 3

End point title	Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Year 3[13]

End point description:

Predicted height was calculated according to Greulich and Pyle using Bayley Pinneau method. Predicted height SDS was obtained by calculating the predicted height, subtracting chronological age- and gender-appropriate mean predicted height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

End point type	Primary

End point timeframe:

Baseline, Year 3

Notes:

[13] - 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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[14]	4[15]		
Units: SDS				
median (full range (min-max))				
Baseline	-2.43 (-2.6 to -1.6)	-0.76 (-1.8 to 0.7)		
Change at Year 3	1.63 (0.1 to 2.3)	0.68 (-2.6 to 2)		

Notes:

[14] - Subjects who were evaluable for this measure.

[15] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Final Height

End point title	Change from Baseline in Predicted Height Standard Deviation Score (SDS) at Final Height[16]

End point description:

Predicted height was calculated according to Greulich and Pyle using Bayley Pinneau method. Predicted height SDS was obtained by calculating the predicted height, subtracting chronological age- and gender-appropriate mean predicted height and dividing the result by standard deviation of that mean (as obtained from chronological age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject's value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement.

End point type	Primary

End point timeframe:

Baseline, final height (assessed up to Year 9.5)

Notes:

[16] - 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	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[17]	2[18]		
Units: SDS				
median (full range (min-max))				
Baseline	-1.74 (-2.4 to -1.1)	-0.84 (-1.8 to 0.1)		
Change at Final Height	0.71 (0.1 to 1.3)	-0.67 (-2.4 to 1)		

Notes:

[17] - Subjects who were evaluable for this measure.

[18] - Subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor-1 (IGF-1) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point title	Change From Baseline in Insulin-like Growth Factor-1 (IGF-1) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point description:

FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

End point type	Secondary

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: milligram per deciliter (mg/dL)				
median (full range (min-max))				
Baseline (n = 10, 11)	0.0165 (0.0075 to 0.0517)	0.0361 (0.0181 to 0.0868)		
Change at Year 0.5 (n = 10, 9)	0.0255 (-0.0145 to 0.039)	0.0017 (-0.0256 to 0.0681)		
Change at Year 1 (n = 10, 11)	0.0329 (-0.0061 to 0.0531)	0.0093 (-0.0358 to 0.0488)		
Change at Year 1.5 (n = 9, 11)	0.0406 (-0.0035 to 0.0754)	0.0066 (-0.0194 to 0.0599)		
Change at Year 2 (n = 9, 10)	0.0223 (0.0055 to 0.0673)	0.0221 (-0.0292 to 0.0534)		
Change at Year 2.5 (n = 8, 8)	0.0366 (-0.0109 to 0.0558)	0.0201 (-0.0237 to 0.047)		
Change at Year 3 (n = 9, 7)	0.0445 (-0.006 to 0.0557)	0.013 (-0.0049 to 0.0648)		
Change at Year 3.5 (n = 7, 7)	0.0396 (0.0014 to 0.0707)	0.01 (-0.0022 to 0.0436)		
Change at Year 4 (n = 7, 6)	0.0453 (0.0175 to 0.0646)	0.0212 (-0.0014 to 0.0485)		
Change at Year 4.5 (n = 6, 5)	0.0431 (0.008 to 0.1233)	0.0142 (0.0042 to 0.0303)		
Change at Year 5 (n = 7, 5)	0.0369 (0.0258 to 0.0902)	0.0236 (0.0164 to 0.053)		
Change at Year 5.5 (n = 5, 4)	0.0448 (0.0258 to 0.0965)	0.0186 (0.0119 to 0.0356)		
Change at Year 6 (n = 5, 4)	0.0454 (0.0155 to 0.0718)	0.0256 (0 to 0.0434)		
Change at Year 6.5 (n = 5, 2)	0.0593 (0.0512 to 0.0766)	0.0195 (0.0125 to 0.0264)		
Change at Year 7 (n = 5, 1)	0.0424 (0.0393 to 0.0766)	0.0254 (0.0254 to 0.0254)		
Change at Year 7.5 (n = 3, 0)	0.0529 (0.0527 to 0.0599)	99999 (99999 to 99999)		
Change at Year 8 (n = 2, 0)	0.0576 (0.0468 to 0.0683)	99999 (99999 to 99999)		
Change at Year 8.5 (n = 1, 0)	0.028 (0.028 to 0.028)	99999 (99999 to 99999)		
Change at Year 9 (n = 1, 2)	0.0403 (0.0403 to 0.0403)	0.0363 (0.0159 to 0.0567)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP3) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point title	Change From Baseline in Insulin-like Growth Factor Binding Protein 3 (IGFBP3) Concentration at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point description:

End point type	Secondary

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: mg/dL				
median (full range (min-max))	(to)	(to)		

Notes:

[19] - Data was not statistically summarized due to early termination of the study.

[20] - Data was not statistically summarized due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lean Mass and Fat Mass at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

End point title	Change from Baseline in Lean Mass and Fat Mass at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

End point description:

Lean mass and fat mass: measurements of body composition assessed using Dual Energy X-ray Absorptiometry (DEXA) scan.

End point type	Secondary

End point timeframe:

Baseline, Year 1, 2, 3, 4, 5, 6, 7, 8, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: kg				
median (full range (min-max))	(to)	(to)		

Notes:

[21] - Data was not statistically summarized due to early termination of the study.

[22] - Data was not statistically summarized due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Mineralization at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

End point title	Change from Baseline in Bone Mineralization at Year 1, 2, 3, 4, 5, 6, 7, 8 and 9

End point description:

Bone mineralization, an estimate of the amount of mineral (such as calcium) in the bone, was assessed using DEXA scan. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

End point type	Secondary

End point timeframe:

Baseline, Year 1, 2, 3, 4, 5, 6, 7, 8, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: grams				
median (full range (min-max))				
Baseline (n = 10, 11)	565.4 (136 to 1305)	643 (454 to 998)		
Change at Year 1 (n = 10, 11)	104.67 (9 to 340)	118.4 (-792.7 to 459.6)		
Change at Year 2 (n = 9, 10)	272.7 (63 to 590)	231.3 (-47.5 to 774.4)		
Change at Year 3 (n = 8, 7)	375.27 (106 to 1084.9)	403.8 (25 to 862.5)		
Change at Year 4 (n = 3, 4)	518.7 (450.8 to 1047.9)	903.2 (277.1 to 1448.1)		

Change at Year 5 (n = 7, 4)	829 (421.7 to 1245.8)	938.3 (591.8 to 1787.6)		
Change at Year 6 (n = 5, 4)	818.4 (112.5 to 1105.5)	998.05 (371.4 to 1984.2)		
Change at Year 7 (n = 5, 1)	1206.1 (739.6 to 1437.3)	1408.5 (1408.5 to 1408.5)		
Change at Year 8 (n = 2, 0)	1376 (1351.7 to 1400.4)	99999 (99999 to 99999)		
Change at Year 9 (n = 1, 2)	1376.3 (1376.3 to 1376.3)	1210.15 (898.6 to 1521.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Weight Standard Deviation Score (SDS) at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point title	Change from Baseline in Weight Standard Deviation Score (SDS) at Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point description:

Body weight was measured using a balance scale. Weight SDS was obtained by measuring the weight, subtracting age- and gender-
appropriate mean weight and dividing the result by standard deviation of that mean (as obtained from age- and gender-specific population reference data). SDS indicated how many standard deviations higher (in case of positive SDS) or lower (in case of negative SDS) subject’s value was relative to the mean of the reference population. FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

End point type	Secondary

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: SDS				
median (full range (min-max))				
Baseline (n = 10, 11)	-2.06 (-4 to 2.6)	0.04 (-5.4 to 5)		
Change at Year 0.5 (n = 10, 9)	0.25 (-0.7 to 0.4)	0.06 (-0.8 to 1.2)		
Change at Year 1 (n = 10, 11)	0.31 (-0.1 to 1.5)	0.25 (-1.1 to 0.9)		
Change at Year 1.5 (n = 9, 11)	0.62 (-0.3 to 2.3)	0.34 (-1.6 to 2.3)		

Change at Year 2 (n = 9, 10)	1.23 (-0.2 to 2.7)	0.46 (-1.1 to 2.2)		
Change at Year 2.5 (n = 8, 8)	1.51 (-0.9 to 3.2)	0.77 (-1.1 to 2.6)		
Change at Year 3 (n = 9, 7)	1.48 (-1.9 to 3.7)	0.61 (-1.2 to 2.7)		
Change at Year 3.5 (n = 7, 7)	1.56 (-1.9 to 3.7)	0.78 (-1.3 to 3)		
Change at Year 4 (n = 7, 6)	1.96 (-2.3 to 3.8)	0.58 (-1 to 2.4)		
Change at Year 4.5 (n = 6, 5)	1.78 (-2.7 to 4.1)	1.46 (-0.4 to 2.7)		
Change at Year 5 (n = 7, 5)	2.08 (-3 to 3.9)	2.06 (0.1 to 2.8)		
Change at Year 5.5 (n = 5, 3)	3.25 (1 to 3.8)	2.1 (1.7 to 2.6)		
Change at Year 6 (n = 5, 3)	2.95 (1.2 to 4.4)	1.89 (1.8 to 2.2)		
Change at Year 6.5 (n = 5, 2)	3.3 (0.8 to 5)	2.03 (1.9 to 2.2)		
Change at Year 7 (n = 5, 1)	2.91 (0.2 to 5.2)	1.7 (1.7 to 1.7)		
Change at Year 7.5 (n = 3, 0)	1.49 (0.3 to 3.1)	99999 (99999 to 99999)		
Change at Year 8 (n = 2, 0)	1.06 (0.5 to 1.6)	99999 (99999 to 99999)		
Change at Year 8.5 (n = 1, 0)	0.7 (0.7 to 0.7)	99999 (99999 to 99999)		
Change at Year 9 (n = 1, 1)	1.4 (1.4 to 1.4)	2 (2 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Corticosteroid Dose at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point title	Change from Baseline in Corticosteroid Dose at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9

End point description:

FAS included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height measurement. Here, 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. Here "99999" in the median and full range values signifies not estimable (NA), since none of the subjects were available in the group "Somatropin (With Previous Somatropin Exposure)" at given time point.

End point type	Secondary

End point timeframe:

Baseline, Year 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9

End point values	Somatropin (Without Previous Somatropin Exposure)	Somatropin (With Previous Somatropin Exposure)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: mg				
median (full range (min-max))				
Baseline (n = 10, 11)	4.75 (2 to 13.5)	7.5 (1 to 40)		
Change at Year 0.5 (n = 10, 9)	0 (-2.5 to 4.8)	0 (-11 to 0)		
Change at Year 1 (n = 9, 11)	-0.67 (-8.5 to 36)	0 (-15 to 20.3)		
Change at Year 1.5 (n = 8, 11)	0.5 (-5 to 8.8)	0 (-17 to 7.5)		
Change at Year 2 (n = 8, 10)	-0.5 (-6.3 to 11.9)	0 (-19 to 10.6)		
Change at Year 2.5 (n = 7, 8)	1.83 (-7.8 to 11.9)	0.04 (-28 to 7.5)		
Change at Year 3 (n = 7, 7)	1.75 (-9.5 to 19.4)	0 (-34.2 to 1)		
Change at Year 3.5 (n = 6, 7)	1.83 (-10.3 to 12.5)	-0.75 (-36 to 2.9)		
Change at Year 4 (n = 7, 6)	0.25 (-10 to 9.7)	-1.88 (-4.5 to 0)		
Change at Year 4.5 (n = 6, 5)	0.23 (-9 to 215.4)	-3.4 (-10 to 0)		
Change at Year 5 (n = 7, 5)	-2 (-9.5 to 15)	-3.5 (-10 to -0.6)		
Change at Year 5.5 (n = 5, 4)	0.25 (-9.5 to 18.3)	-1.83 (-4.5 to 486.5)		
Change at Year 6 (n = 5, 4)	-1 (-11 to 10.6)	-1.83 (-5.5 to 9)		
Change at Year 6.5 (n = 5, 2)	-1 (-11 to 3)	-2.46 (-3.7 to -1.3)		
Change at Year 7 (n = 5, 1)	-1 (-11 to 2)	-2.5 (-2.5 to -2.5)		
Change at Year 7.5 (n = 3, 0)	-7 (-12 to 0.5)	99999 (99999 to 99999)		
Change at Year 8 (n = 2, 0)	-3.25 (-7 to 5)	99999 (99999 to 99999)		
Change at Year 8.5 (n = 1, 0)	0.5 (0.5 to 0.5)	99999 (99999 to 99999)		
Change at Year 9 (n = 1, 2)	-7 (-7 to -7)	-3 (-3.5 to -2.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 7 days after last dose of 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. A n 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 generated separ ately 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	Somatropin (With Previous Somatropin Exposure)

Reporting group description:

Subjects who received low dose of somatropin (Genotonorm) for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was <=to 1.5 cm per year during the preceding 12 months and bone age was >=17 years for boys and 15 years for girls.

Reporting group title	Somatropin (Without Previous Somatropin Exposure)

Reporting group description:

Subjects who received matching placebo for 3 years during previous study CTN 97-8129-016, received somatropin (Genotonorm) up to 0.6 mg/kg/week, equivalent to 1.8 IU/kg/week, divided in 7 daily doses subcutaneously initially for first 3 years and then somatropin (Genotonorm) 0.46 mg/kg/week, equivalent to 1.4 IU/kg/week, divided in 7 daily doses subcutaneously until the additional study drug dose evaluation visit and thereafter received somatropin (Genotonorm) 50 mcg/kg/day, equivalent to 0.35 mg/kg/week or 1.05 IU/kg/week, subcutaneously until the final height was reached or up to Year 8.5. Final height was confirmed to have been achieved if the growth velocity was <=1.5 cm per year during the preceding 12 months and bone age was >=17 years for boys and 15 years for girls.

Serious adverse events	Somatropin (With Previous Somatropin Exposure)	Somatropin (Without Previous Somatropin Exposure)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	2 / 10 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Gastrostomy closure			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (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			
Lung disorder			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Lipoatrophy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile idiopathic arthritis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scoliosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Leishmaniasis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing fever			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Somatropin (With Previous Somatropin Exposure)	Somatropin (Without Previous Somatropin Exposure)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	9 / 10 (90.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Poor peripheral circulation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Knee operation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Ill-defined disorder			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Injection site haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nodule			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Social circumstances			
Walking disability			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Insomnia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Investigations			
Blood corticotrophin decreased			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Blood glucose decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood urine present			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Glucose tolerance test			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Insulin-like growth factor increased			
subjects affected / exposed	8 / 11 (72.73%)	6 / 10 (60.00%)	
occurrences (all)	17	12	
Weight decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Joint injury			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Procedural vomiting			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Congenital scoliosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hyporeflexia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypotonia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Loss of consciousness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Visual field defect			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Visual acuity reduced			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Aphthous stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Acanthosis nigricans			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Acne			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Ecchymosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lividity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pruritus generalised			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin atrophy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Hypercalciuria			

subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Amyotrophy			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 10 (30.00%)	
occurrences (all)	3	5	
Arthritis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Joint range of motion decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Juvenile idiopathic arthritis			
subjects affected / exposed	4 / 11 (36.36%)	4 / 10 (40.00%)	
occurrences (all)	6	5	
Osteonecrosis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Synovial cyst			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 11 (9.09%)	3 / 10 (30.00%)	
occurrences (all)	2	3	
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	2	
Herpes simplex			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infectious mononucleosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Laryngitis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Nail candida			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	4	
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Oral herpes			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Otitis externa			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Varicella			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	2 / 11 (18.18%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Glucose tolerance impaired			
subjects affected / exposed	5 / 11 (45.45%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Hyperinsulinaemia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Insulin resistance			
subjects affected / exposed	6 / 11 (54.55%)	5 / 10 (50.00%)	
occurrences (all)	7	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2004	1- Visits at month 3, month 9, month 15, month 21, month 27 and month 33 were not applicable for children who were not receiving Genotonorm due to the discontinuation of corticosteroid therapy. 2- If corticosteroid therapy was discontinued in children at the beginning or during the study for at least 6 months and the height was greater than (>) -2 Standard Deviation (SD) for chronological age, then Genotonorm treatment was stopped and could only be resumed if corticosteroid therapy was resumed for at least 3 months and the investigative doctor considered it beneficial for the child. 3- If 2 consecutive measurements of the level of IGF-1 were above 2 SD, then the daily dosage of Genotonorm was decreased by 20 percent (%). 4- If the measurement of glucose in the urine was found to be above 10 gram/24 hours on 3 occasions, then the dosage of the growth hormone was decreased by 20% and further metabolic monitoring (fasting blood glucose and glucose in the urine) was done in the month following the dose change.
04 February 2005	1- Every year, following examinations were required to be performed in addition to examinations performed during a six-month visit: Serum calcium; serum phosphorus; 25 hydroxy (OH) vitamin D3 and 1.25 dihydroxy (OH)2 vitamin D3 and Parathyroid hormone (PTH) levels; Oral glucose tolerance test (OGTT); Collection of 24-hour urine for calcium and creatinine; Collection of 2 mL of serum (4 x 0.5 mL); Bone age: radiography of 2 wrists. 2- The maximum dose administered was reduced to 0.46 mg 1.4 IU/kg/week from 0.6 mg 1.8 IU/kg/week. 3- Genotonorm treatment was adapted according to IGF-1 rates which were maintained below or equal to +2.5 SD for chronological age and If IGF-1 rates were above +2.5 SD the dose of growth hormone was decreased by 20%. 4- In the case of diabetes defined by blood glucose at time T120 mins of OGTT ≥11.1 millimole per liter (mmol/L) or fasting blood glucose >=7.0 mmol/L, the Genotonorm dose was reduced by 40% and another OGTT check was done after 3 months of dose adjustment. That diabetes was reported as an adverse event and If It persisted, Genotonorm treatment was interrupted and the event was reported as a serious adverse event.
29 November 2007	Genotonorm treatment was adapted according to IGF-1 levels which were maintained below or equal to +2 SD for chronological age and sex and If IGF-1 level was above +2 SD, then the growth hormone dose was decreased by 20%.
16 February 2011	The maximal dose of somatropin was limited up to 50 mcg/kg/day (0.35 mg [1.05 IU/kg/week]) in relation to the ongoing review of safety of somatropin- containing products.

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.

Data for bone mineral density (BMD), bone mineral content (BMC) and IGFBP3 were not analyzed because of change in planned analysis after the study was prematurely terminated due to Good Clinical Practice (GCP) non-compliance issues.

Notes: