Clinical trial results:
Somatropin Therapy for Short Children Born of Premature Gestation: A Controlled, Prospective Randomized, Multicenter Study with an Untreated Control Group

Summary

EudraCT number	2004-004781-33
Trial protocol	DE
Global end of trial date	24 March 2010

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	A6281273

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00174460
WHO universal trial number (UTN)	-

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., 1800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1800 7181021, 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	30 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether Growth Hormone (GH) therapy improves growth velocity and height Standard Deviation Score (SDS) after one year in very low birth weight (VLBW) preterm infants born appropriate-for-gestational age (AGA) with short stature.

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	29 August 2005
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	Germany: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	33
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study started on 29-Aug-2005 and ended on 30-Sep-2010.There were 33 subjects enrolled in this study in Germany.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Somatropin

Arm description:

The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation.

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

Dosage and administration details:

The children received 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals. (mg=milligrams, kg=kilograms).

Arm title	Control Arm

Arm description:

The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation.

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

Dosage and administration details:

Control group after 1 year underwent GH therapy with 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation.

Number of subjects in period 1	Somatropin	Control Arm
Started	18	15
Completed	18	14
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Somatropin
Reporting group description:	
The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation.	
Reporting group title	Control Arm
Reporting group description:	
The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation.	

Reporting group values	Somatropin	Control Arm	Total
Number of subjects	18	15	33
Age categorical			
1 subject in each treatment group was below the age of 4 at screening. However, both of them were 4 years old when treatment began; they did not violate the corresponding inclusion criterion.			
Units: Subjects			
Less than (<) 4 years	1	1	2
Greater than or equal to ≥ 4 years and < 8 years	14	11	25
≥ 8 years and < 12 years	3	3	6
Age continuous			
Units: years			
arithmetic mean	5.4	5.7	
standard deviation	± 1.6	± 1.9	-
Gender categorical			
Units: Subjects			
Female	9	7	16
Male	9	8	17

End points

End points reporting groups

Reporting group title	Somatropin
Reporting group description:	
The children were randomized into a treated group receiving subcutaneous somatropin according to exact body weight specific calculation.	
Reporting group title	Control Arm
Reporting group description:	
The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with subcutaneous somatropin according to exact body weight specific calculation.	

Primary: Change in Height Standard Deviation Score (SDS) After 1 Year

End point title	Change in Height Standard Deviation Score (SDS) After 1 Year
End point description:	
Change in Height SDS after 1 year where SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). Full Analysis Set (FAS); all randomized subjects who had at least 1 post-baseline efficacy measurement; Control group received Somatropin from Month 12 onwards.	
End point type	Primary
End point timeframe:	
Baseline to 1 year (Month 12)	

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters				
least squares mean (standard error)	1.099 (± 0.0714)	0.108 (± 0.0783)		

Statistical analyses

Statistical analysis title	Treatment difference for change in height SDS
Statistical analysis description:	
Results from analysis of covariance method (ANCOVA) adjusted for baseline height SDS and target height SDS; Last observation carried forward (LOCF).	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.991

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.773
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	0.1067

Primary: Change in Growth Velocity Standard Deviation Score (SDS) After 1 Year

End point title	Change in Growth Velocity Standard Deviation Score (SDS) After 1 Year

End point description:

Change in Growth Velocity (GV) SDS after 1 year where SDS= GV minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards.

End point type	Primary

End point timeframe:

Baseline to 1 year (Month 12)

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters per year				
least squares mean (standard error)	7.117 (± 0.4384)	1.502 (± 0.4814)		

Statistical analyses

Statistical analysis title	Treatment difference in growth velocity SDS

Statistical analysis description:

Results from ANCOVA adjusted for baseline growth velocity SDS and target height SDS; LOCF.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.615
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.266
upper limit	6.963

Variability estimate	Standard error of the mean
Dispersion value	0.6591

Secondary: Change From Baseline in Growth Velocity After 1 Year and After 2 Years

End point title	Change From Baseline in Growth Velocity After 1 Year and After 2 Years

End point description:

Growth velocity measured as centimeters per year. FAS; Control group received Somatropin from Month 12 onwards.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeter per year				
least squares mean (standard error)				
Month 12	5.11 (± 0.2623)	0.695 (± 0.2881)		
Month 24	3.049 (± 0.3546)	3.934 (± 0.3893)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline growth velocity, target height SDS, sex, and age; LOCF.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.415
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.605
upper limit	5.225
Variability estimate	Standard error of the mean
Dispersion value	0.395

Statistical analysis title	Treatment difference Month 24
Statistical analysis description:	
Results from ANCOVA adjusted for baseline growth velocity, target height SDS, sex, and age; LOCF.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.884
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.977
upper limit	0.208
Variability estimate	Standard error of the mean
Dispersion value	0.5327

Secondary: Change From Baseline in Growth Velocity SDS After 2 Years	
End point title	Change From Baseline in Growth Velocity SDS After 2 Years
End point description:	
Change in Growth Velocity SDS after 2 years (24 months) where SDS = growth velocity minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards.	
End point type	Secondary
End point timeframe:	
Baseline, Month 24	

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeter per year				
least squares mean (standard error)	4.751 (± 0.4716)	5.825 (± 0.5177)		

Statistical analyses

Statistical analysis title	Change From Baseline in Growth Velocity SDS
Statistical analysis description:	
Results from ANCOVA adjusted for baseline growth velocity SDS and target height SDS; LOCF.	

Comparison groups	Control Arm v Somatropin
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.524
upper limit	0.376
Variability estimate	Standard error of the mean
Dispersion value	0.7089

Secondary: Change From Baseline in Height After 1 Year and After 2 Years

End point title	Change From Baseline in Height After 1 Year and After 2 Years
End point description:	
FAS; Control group received Somatropin from Month 12 onwards.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12, Month 24	

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters				
least squares mean (standard error)				
Month 12	10.467 (± 0.2439)	5.927 (± 0.2677)		
Month 24	18.908 (± 0.6507)	14.844 (± 0.7149)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12
Statistical analysis description:	
Results from ANCOVA adjusted for baseline height, target height SDS, sex, and age; LOCF.	
Comparison groups	Somatropin v Control Arm

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.789
upper limit	5.291
Variability estimate	Standard error of the mean
Dispersion value	0.3661

Statistical analysis title	Treatment difference Month 24
Statistical analysis description:	
Results from ANCOVA adjusted for baseline height, target height SDS, sex, and age; LOCF.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.049
upper limit	6.08
Variability estimate	Standard error of the mean
Dispersion value	0.9822

Secondary: Change From Baseline in Height SDS After 2 Years

End point title	Change From Baseline in Height SDS After 2 Years
End point description:	
Change in Height SDS after 2 years (24 months) where SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards.	
End point type	Secondary
End point timeframe:	
Baseline, Month 24	

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters				
least squares mean (standard error)	1.71 (± 0.1075)	0.991 (± 0.1179)		

Statistical analyses

Statistical analysis title	Change From Baseline in Height SDS
Statistical analysis description:	
Results from ANCOVA adjusted for baseline height SDS and target height SDS; LOCF.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.719
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.047
Variability estimate	Standard error of the mean
Dispersion value	0.1606

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Triceps

End point title	Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Triceps
End point description:	
Body composition measured as skinfold thickness at tricep in millimeters (mm); measured halfway down the left upper arm with arm hanging in relaxed position at subject's side. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12, Month 24	

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: millimeters				
least squares mean (standard error)				
Month 12 (n=15, 14)	-2.2 (± 0.341)	0.5 (± 0.353)		
Month 24 (n=16, 14)	-1.3 (± 0.511)	-0.83 (± 0.548)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, age, and sex; LOCF. For the treatment comparison, results were presented for 29 Subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.73
upper limit	-1.68
Variability estimate	Standard error of the mean
Dispersion value	0.497

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, age, and sex; LOCF. For the treatment comparison, results were presented for 30 Subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.537
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	1.09
Variability estimate	Standard error of the mean
Dispersion value	0.758

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Subscapular

End point title	Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Subscapular

End point description:

Body composition measured as subscapular skinfold thickness in mm; measured laterally just below the angle of the left scapula. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: millimeters				
least squares mean (standard error)				
Month 12 (n= 15, 14)	0.51 (± 0.783)	0.45 (± 0.849)		
Month 24 (n=16, 14)	0.9 (± 0.688)	0.79 (± 0.774)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 29 subjects.

Comparison groups	Control Arm v Somatropin
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.364
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.405

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results are presented for 30 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.345

Secondary: Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Suprailiac

End point title	Change From Baseline in Body Composition (Skinfold Thickness) After 1 Year and After 2 Years: Suprailiac

End point description:

Body composition measured as suprailiac skinfold thickness in mm; measured just above the iliac crest in the middle-axillary line. FAS; Control group received Somatropin from Month 12 onwards. Here n signifies the number of subjects evaluable at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: millimeter(s)				
least squares mean (standard error)				
Month 12 (n=14, 12)	0.51 (± 0.783)	0.45 (± 0.849)		
Month 24 (n=15, 12)	0.9 (± 0.688)	0.79 (± 0.774)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 26 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.959
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	1.188

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline skinfold thickness, target height SDS, sex, and age; LOCF. For the treatment comparison, results were presented for 27 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	2.32

Variability estimate	Standard error of the mean
Dispersion value	1.065

Secondary: Change From Baseline in Volumetric Cortical Bone Mineral Density (BMD) Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and After 2 Years

End point title	Change From Baseline in Volumetric Cortical Bone Mineral Density (BMD) Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and After 2 Years

End point description:

Volumetric Cortical BMD measured as milligrams per cubic millimeter (mg/mm^3). BMD (proximal radius) SDS (number of standard deviations a subject's BMD differs from the average BMD of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln [test result/M]/ S); Ln=natural logarithm; M=age- or height- and sex-specific mean value; S=age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
month 12 (n=2, 6)	-1.055 (± 0.6802)	-0.162 (± 0.36)		
Month 24(n=2, 6)	0.284 (± 0.5023)	-0.433 (± 0.2658)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline volumetric cortical bone mineral density SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.892

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.158
upper limit	1.374
Variability estimate	Standard error of the mean
Dispersion value	0.8161

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline volumetric cortical bone mineral density SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.956
upper limit	2.391
Variability estimate	Standard error of the mean
Dispersion value	0.6027

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Cross-sectional Area (CSA)

End point title	Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Cross-sectional Area (CSA)

End point description:

Bone structure Cortical CSA measured as millimeters squared (mm^2). CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln(test result/M)]/S); Ln=natural logarithm; M=age- or height-) and sex-specific mean value; S=age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; n=number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
Month 12 (n=2, 5)	-0.465 (± 0.7799)	0.017 (± 0.4559)		
Month 24 (n=2, 6)	-0.595 (± 0.7462)	0.609 (± 0.3907)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline cortical cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results are presented for 7 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.653
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.558
upper limit	2.595
Variability estimate	Standard error of the mean
Dispersion value	0.9666

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline cortical cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results are presented for 8 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.205

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.701
upper limit	1.292
Variability estimate	Standard error of the mean
Dispersion value	0.8991

Secondary: Change From Baseline in Bone Structure Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and 2 Years: Total Cross-sectional Area (CSA)

End point title	Change From Baseline in Bone Structure Using Peripheral Quantitative Computed Tomography (pQCT) After 1 Year and 2 Years: Total Cross-sectional Area (CSA)

End point description:

Bone structure Total CSA measured as millimeters squared (mm^2). Total CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln [test result/M)] / S); Ln=natural logarithm; M = age- or height- and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
Month 12 (n=2, 5)	0.375 (± 0.9345)	0.239 (± 0.5537)		
Month 24 (n=2, 6)	0.243 (± 0.3694)	-0.049 (± 0.1955)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline total cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 7 subjects.

Comparison groups	Somatropin v Control Arm

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.914
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.524
upper limit	3.795
Variability estimate	Standard error of the mean
Dispersion value	1.1499

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline total cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.547
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.939
upper limit	1.522
Variability estimate	Standard error of the mean
Dispersion value	0.4432

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Muscle Cross-sectional Area (CSA)

End point title	Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Muscle Cross-sectional Area (CSA)

End point description:

Bone structure Muscle CSA measured as millimeters squared (mm^2). CSA (proximal radius) SDS (number of standard deviations a subject's CSA differs from the average CSA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln [test result/M] / S); Ln=natural logarithm; M = age- or height- and sex-specific mean value; S= age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
Month 12 (n=2, 6)	2.084 (± 0.3628)	-0.227 (± 0.1688)		
Month 24 (n=2, 6)	2.402 (± 0.5221)	0.776 (± 0.2428)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline muscle cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.049
upper limit	3.572
Variability estimate	Standard error of the mean
Dispersion value	0.4542

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline muscle cross-sectional area SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.

Comparison groups	Somatropin v Control Arm

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.626
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.189
upper limit	3.44
Variability estimate	Standard error of the mean
Dispersion value	0.6536

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Thickness (CT)

End point title	Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Cortical Thickness (CT)

End point description:

Cortical Thickness measured as millimeters (mm). CT (proximal radius) SDS (number of standard deviations a subject's CT differs from the average CT of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln (test result/ M)]/S); Ln = natural logarithm; M = age- or height-) and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards. Cortical thickness was not analyzed as planned.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: z-score				
least squares mean (standard deviation)	()	()		

Notes:

[1] - Cortical thickness was not analyzed as planned.

[2] - Cortical thickness was not analyzed as planned.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Marrow Area (MA)

End point title	Change From Baseline in Bone Structure Using pQCT After 1 Year and 2 Years: Marrow Area (MA)

End point description:

Marrow Area measured as millimeters squared (mm^2). MA (proximal radius) SDS (number of standard deviations a subject's MA differs from the average MA of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln(test result/M)]/S); Ln=natural logarithm; M=age- or height-) and sex-specific mean value; S = age-(or height-) and sex-specific coefficient of variation) then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards. Marrow Area was not analyzed as planned.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: z-score				
least squares mean (standard error)	()	()		

Notes:

[3] - Marrow Area was not analyzed as planned.

[4] - Marrow Area was not analyzed as planned.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Stability Using pQCT After 1 Year and After 2 Years: Strength-strain Index (SSI)

End point title	Change From Baseline in Bone Stability Using pQCT After 1 Year and After 2 Years: Strength-strain Index (SSI)

End point description:

Bone stability expressed as polar SSI in cubic millimeters (mm^3). SSI (proximal radius) SDS (number of standard deviations a subject's SSI differs from the average SSI of their age and sex). Baseline and post-baseline SDS values transformed to age and sex specific z-score (Ln [test result/M)] / S); Ln=natural logarithm; M=age- or height- and sex-specific mean value; S=age-(or height-) and sex-specific coefficient of variation then change from baseline is calculated. Positive values are above the average for subject's age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies number of subjects from FAS with evaluable pQCT data for somatropin and control arm groups, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
Month 12 (n=2, 6)	0.648 (± 0.4224)	0.088 (± 0.2243)		

Month 24 (n=2, 6)	0.477 (± 0.3925)	0.363 (± 0.2084)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12
Statistical analysis description:	
Results from ANCOVA adjusted for baseline strength-strain index SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.331
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.846
upper limit	1.965
Variability estimate	Standard error of the mean
Dispersion value	0.5061

Statistical analysis title	Treatment difference Month 24
Statistical analysis description:	
Results from ANCOVA adjusted for baseline strength-strain index SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 8 subjects.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.192
upper limit	1.42
Variability estimate	Standard error of the mean
Dispersion value	0.4703

Secondary: Change From Baseline in Muscle Strength: Hand Grip SDS After 1 Year and After 2 Years

End point title	Change From Baseline in Muscle Strength: Hand Grip SDS After 1 Year and After 2 Years

End point description:

Muscle strength determined by measuring grip force (kilograms) using hand grip dynamometer for subjects ≥6 years of age. Baseline and post-baseline SDS values transformed to age and sex specific z-score. Change in hand grip calculated as SDS where SDS = hand grip minus mean (age- and sex-matched reference) divided by SD (age- and sex-matched reference). Positive values are above the average for subjects age and sex; negative values are below the average. FAS; Control group received Somatropin from Month 12 onwards; Here n signifies the number of subjects ≥6 years of age with evaluable data at observation for Somatropin and Control Arm, respectively. SDS reference values used were for the right hand but the hand grip strength measured for this study was for the dominant hand (may not have been the right hand).

End point type	Secondary

End point timeframe:

Baseline, Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: z-score				
least squares mean (standard error)				
Month 12 (n=7, 5)	0.37 (± 0.268)	0.28 (± 0.318)		
Month 24 (n=7, 6)	1.14 (± 0.218)	0.92 (± 0.236)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from ANCOVA adjusted for baseline hand grip strength SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 12 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.844
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.05

Variability estimate	Standard error of the mean
Dispersion value	0.42

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from ANCOVA adjusted for baseline hand grip strength SDS and target height SDS; LOCF. For the treatment comparison, results were presented for 13 subjects.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	0.329

Secondary: Number of Subjects With Change in Insulin Sensitivity: Somatropin

End point title	Number of Subjects With Change in Insulin Sensitivity: Somatropin[5]

End point description:

Insulin sensitivity calculated as incidence of pathological glucose intolerance assessed prior to randomization (Screening Day -3 to Baseline Day 0) and at final visit (final visit: Somatropin treatment group = Month 24). Pathological glucose intolerance (oral glucose tolerance test) measured as venous (blood or plasma) with range minimum 120 milligrams per deciliter (mg/dL) to >140 mg/dL; capillary (blood) with range minimum 120 mg/dL to >120 mg/dL; or method not known with range minimum 120 mg/dL to >120 mg/dL. FAS population was analyzed for the endpoint.

End point type	Secondary

End point timeframe:

Baseline, Month 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Comparison between groups was not planned. Data was not collected at Month 24 for Control Arm.

End point values	Somatropin			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: subjects				
Baseline: tolerant	18			
Baseline: intolerant	0			
Month 24: tolerant	16			

Month 24: intolerant	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Insulin Sensitivity: Control Arm

End point title	Number of Subjects With Change in Insulin Sensitivity: Control Arm[6]

End point description:

Insulin sensitivity calculated as incidence of pathological glucose intolerance assessed prior to randomization (Screening Day -3 to Baseline Day 0) and at final visit (final visit: Control Arm=Month 36). Pathological glucose intolerance (oral glucose tolerance test) measured as venous (blood or plasma) with range minimum 120 milligrams per deciliter (mg/dL) to >140 mg/dL; capillary (blood) with range minimum 120 mg/dL to >120 mg/dL; or method not known with range minimum 120 mg/dL to >120 mg/dL. FAS; Control group received Somatropin from Month 12 onwards.

End point type	Secondary

End point timeframe:

Baseline, Month 36

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: comparison between groups was not planned. Data was not collected at Month 36 for Somatropin group.

End point values	Control Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: subjects				
Baseline: tolerant	14			
Baseline: intolerant	1			
Month 36: tolerant	11			
Month 36: intolerant	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Curve Comparison Based on Height SDS

End point title	Growth Curve Comparison Based on Height SDS

End point description:

Growth curve comparison with height SDS in centimeters as the dependent variable; SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). FAS; Control group received Somatropin from Month 12 onwards. Data for Month 36 (applicable only to the Control Arm) is reported in a separate outcome measure. Here n signifies the number of subjects evaluable at specific time point.

End point type	Secondary

End point timeframe:
Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters				
least squares mean (standard error)				
Month 12 (n=18, 15)	-2.26 (± 0.0735)	-3.259 (± 0.0802)		
Month 24 (n=18, 14)	-1.638 (± 0.1016)	-2.327 (± 0.1122)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12
Statistical analysis description:	
Results from repeated measures mixed models analysis adjusted for baseline height SDS, visit, visit*treatment and target height SDS.	
Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.778
upper limit	1.219
Variability estimate	Standard error of the mean
Dispersion value	0.1095

Statistical analysis title	Treatment difference Month 24
Statistical analysis description:	
Results from repeated measures mixed models analysis adjusted for baseline height SDS, visit, visit*treatment and target height SDS. For the treatment comparison, results were presented for 32 Subjects.	
Comparison groups	Somatropin v Control Arm

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	0.994
Variability estimate	Standard error of the mean
Dispersion value	0.1519

Secondary: Growth Curve Comparison Based on Height SDS: Control Arm

End point title	Growth Curve Comparison Based on Height SDS: Control

End point description:

Growth curve comparison with height SDS in centimeters as the dependent variable; SDS = height minus mean (age-and sex-matched reference) divided by SD (age and sex-matched reference). Control Arm final visit = Month 36. FAS; Control group received Somatropin from Month 12 onwards. Month 36 visit not applicable to Somatropin treatment group.

End point type	Secondary

End point timeframe:

Month 36

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Comparison between groups was not planned at Month 36. No data was available for Somatropin group at Month 36.

End point values	Control Arm			
Subject group type	Reporting group			
Number of subjects analysed	14[8]			
Units: centimeters				
least squares mean (standard error)	-1.794 (± 0.1318)			

Notes:

[8] - N=number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Curve Comparison Based on Height

End point title	Growth Curve Comparison Based on Height

End point description:

Growth curve comparison with height in centimeters as the dependent variable. FAS; Control group received Somatropin from Month 12 onwards. Data for Month 36 (applicable only to the Control Arm) is reported in a separate outcome measure. Here n signifies the number of subjects evaluable at specific

time point.

End point type	Secondary

End point timeframe:

Month 12, Month 24

End point values	Somatropin	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: centimeters				
least squares mean (standard error)				
Month 12	114.228 (± 0.333)	109.644 (± 0.3733)		
Month 24	123.351 (± 0.483)	119.788 (± 0.5255)		

Statistical analyses

Statistical analysis title	Treatment difference Month 12

Statistical analysis description:

Results from repeated measure mixed models analysis adjusted for baseline height, sex, age, visit, visit*treatment and target height SDS.

Comparison groups	Somatropin v Control Arm
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.806
upper limit	5.363
Variability estimate	Standard error of the mean
Dispersion value	0.3859

Statistical analysis title	Treatment difference Month 24

Statistical analysis description:

Results from repeated measure mixed models analysis adjusted for baseline height, sex, age, visit, visit*treatment and target height SDS. For the treatment comparison, results were presented for 32 subjects.

Comparison groups	Somatropin v Control Arm

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.563
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.134
upper limit	4.992
Variability estimate	Standard error of the mean
Dispersion value	0.708

Secondary: Growth curve comparison with height in centimeters as the dependent variable.

End point title	Growth curve comparison with height in centimeters as the dependent variable.[9]

End point description:

Growth curve comparison with height in centimeters as the dependent variable. FAS; Control group received Somatropin from Month 12 onwards. Month 36 visit not applicable to Somatropin treatment group.

End point type	Secondary

End point timeframe:

Month 36

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparison between groups was not planned at Month 36. No data was available for Somatropin group at Month 36.

End point values	Control Arm			
Subject group type	Reporting group			
Number of subjects analysed	14[10]			
Units: centimeters				
least squares mean (standard error)	128.049 (± 0.7821)			

Notes:

[10] - N = number of subjects with evaluable data at observation.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study treatment.

Adverse event reporting additional description:

Safety population=who received at least 1 dose of treatment. Same event may appear as AE, SAE.Distinct events are presented. Event may be categorized as serious in 1 subject, nonserious in another/subject may have experienced both serious, nonserious event during study. EU BR AE tables were generated as per EU format using latest coding dictionary.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Somatropin

Reporting group description:

The children were randomized into a treated group receiving 0.068 mg/kg/day (0.48 mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals.

Reporting group title	Control Arm

Reporting group description:

The children were randomized into control group and after 1 year underwent Growth Hormone (GH) therapy, with 0.068 mg/kg/day (0.48mg/kg/week) subcutaneous somatropin according to exact body weight specific calculation. Dose adjustments were made at 6 month intervals.

Serious adverse events	Somatropin	Control Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (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			
Acute tonsillitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 15 (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	Control Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	11 / 15 (73.33%)	
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tooth disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Attention deficit/hyperactivity disorder			

subjects affected / exposed	2 / 18 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 18 (5.56%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Arthritis allergic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nuchal rigidity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Scoliosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 15 (13.33%)	
occurrences (all)	3	3	
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Ear infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Erythema infectiosum			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Febrile infection			

subjects affected / exposed	2 / 18 (11.11%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 18 (11.11%)	2 / 15 (13.33%)	
occurrences (all)	2	4	
Oral herpes			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	1 / 18 (5.56%)	1 / 15 (6.67%)	
occurrences (all)	6	1	
Otitis media acute			
subjects affected / exposed	0 / 18 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 18 (11.11%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Scarlet fever			
subjects affected / exposed	1 / 18 (5.56%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			

subjects affected / exposed	4 / 18 (22.22%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Tooth abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	2 / 15 (13.33%)	
occurrences (all)	4	4	
Varicella			
subjects affected / exposed	1 / 18 (5.56%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2005	Amendment was made to specific study procedures, subject selection and laboratory assessments.

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.

Result values for the primary outcome measures were revised at the final analysis due to programmatic corrections: age rounded up if >6 months past last birthday. Height and height SDS not rounded for final analysis; rounded only for the reports.

Notes: