



Clinical trial results:

RECOMBINANT HUMAN GROWTH HORMONE (RHGH) AND RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-1 (RHIGF-1) COMBINATION THERAPY IN CHILDREN WITH SHORT STATURE ASSOCIATED WITH IGF-1 DEFICIENCY: A SIX-YEAR, RANDOMIZED, MULTI-CENTER, OPEN LABEL, PARALLEL-GROUP, ACTIVE TREATMENT CONTROLLED, DOSE SELECTION TRIAL.

Summary

EudraCT number	2019-000843-29
Trial protocol	Outside EU/EEA
Global end of trial date	01 March 2012

Results information

Result version number	v1 (current)
This version publication date	22 September 2019
First version publication date	22 September 2019

Trial information

Trial identification

Sponsor protocol code	MS316
-----------------------	-------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00572156
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 Quai Georges Gorse, Boulogne Billancourt, France, 92100
Public contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Pharma, clinical.trials@ipsen.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	01 March 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 March 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy and safety of three combinations of recombinant human growth hormone (rhGH) and recombinant human insulin-like growth factor-1 (rhIGF-1) compared to that of rhGH alone in the treatment of short stature associated with IGF-1 deficiency.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice, the ethical principles that have their origins in the Declaration of Helsinki, and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator:

Under standard United States (US) clinical practice, children in this study could expect to be prescribed long-term rhGH treatment following a diagnosis of idiopathic short stature. The use of a placebo group would be unethical where a viable treatment option exists; hence rhGH monotherapy (45 micrograms per kilogram [$\mu\text{g}/\text{kg}$] per day) was included as a comparator in this study.

Actual start date of recruitment	01 January 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	106
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	95
Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase II, multicenter, randomized, open-label, parallel-group, active treatment controlled, dose selection study in prepubertal children, aged ≥ 5 years, with short stature associated with low IGF-1 and normal stimulated GH response. The study was conducted at 27 centers in the US from January 2008 to March 2012.

Pre-assignment

Screening details:

Eligible subjects were randomized to one of four treatment groups, stratified by age ≤ 9 years and IGF-1 standard deviation score (SDS) ≤ -2 , in a 1:1:1:1 ratio. The planned treatment duration for each subject was six years, however, the study was prematurely terminated by the Sponsor after the last subject completed Year 3.

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	45 $\mu\text{g}/\text{kg}$ rhGH Alone

Arm description:

Subjects received 45 $\mu\text{g}/\text{kg}$ rhGH alone, administered once daily by injection. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Arm type	Active comparator
Investigational medicinal product name	rhGH
Investigational medicinal product code	
Other name	Somatropin, Nutropin AQ®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to rotate the injection sites daily to minimize the potential for injection site reactions.

Arm title	45 $\mu\text{g}/\text{kg}$ rhGH + 50 $\mu\text{g}/\text{kg}$ rhIGF-1
------------------	--

Arm description:

Subjects received 45 $\mu\text{g}/\text{kg}$ rhGH and 50 $\mu\text{g}/\text{kg}$ rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Arm type	Experimental
Investigational medicinal product name	rhGH
Investigational medicinal product code	
Other name	Somatropin, Nutropin AQ®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	Mecasermin, Increlex®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Arm title	45 µg/kg rhGH + 100 µg/kg rhIGF-1
------------------	-----------------------------------

Arm description:

Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Arm type	Experimental
Investigational medicinal product name	rhGH
Investigational medicinal product code	
Other name	Somatropin, Nutropin AQ®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	Mecasermin, Increlex®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Arm title	45 µg/kg rhGH + 150 µg/kg rhIGF-1
------------------	-----------------------------------

Arm description:

Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).

Arm type	Experimental
Investigational medicinal product name	rhGH
Investigational medicinal product code	
Other name	Somatropin, Nutropin AQ®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhGH once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	Mecasermin, Increlex®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of rhIGF-1 once daily. Injections were to be administered shortly before or shortly after (20 minutes) breakfast into the upper thigh, upper arm, abdomen or buttock. Subjects were instructed to inject each drug (rhGH and rhIGF-1) into opposite sides of the body, and the injection sites were rotated daily to minimize the potential for injection site reactions.

Number of subjects in period 1	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Started	26	27	27
Completed	0	1	0
Not completed	26	26	27
Adverse event, non-fatal	3	1	5
Subject/Parent Decision	1	6	4
Sponsor Decision	20	16	17
Lost to follow-up	1	1	1
Protocol deviation	1	2	-

Number of subjects in period 1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Started	26
Completed	1
Not completed	25
Adverse event, non-fatal	1
Subject/Parent Decision	3
Sponsor Decision	19
Lost to follow-up	-
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	45 µg/kg rhGH Alone
Reporting group description: Subjects received 45 µg/kg rhGH alone, administered once daily by injection. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 50 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).	

Reporting group values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Number of subjects	26	27	27
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	9.2	8.4	9.0
standard deviation	± 2.0	± 2.0	± 2.2
Gender categorical Units: Subjects			
Female	5	5	7
Male	21	22	20
Race Units: Subjects			
Asian	2	4	1
Black	1	1	1
Hispanic	4	1	3
White	17	20	19
Hispanic/White	1	1	3
Hawaiian or Pacific Islander/ White	1	0	0

Reporting group values	45 µg/kg rhGH + 150 µg/kg rhIGF-1	Total	
Number of subjects	26	106	

Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	8.8 ± 2.3	-	
Gender categorical Units: Subjects			
Female	4	21	
Male	22	85	
Race Units: Subjects			
Asian	1	8	
Black	0	3	
Hispanic	2	10	
White	23	79	
Hispanic/White	0	5	
Hawaiian or Pacific Islander/ White	0	1	

End points

End points reporting groups

Reporting group title	45 µg/kg rhGH Alone
Reporting group description: Subjects received 45 µg/kg rhGH alone, administered once daily by injection. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 50 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).	
Reporting group title	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Reporting group description: Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections. Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).	

Primary: Height Velocity During the First Year of Treatment

End point title	Height Velocity During the First Year of Treatment
End point description: Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to the end-of-year-one visit. First-year height velocity (growth in centimeters [cm]) is presented for the Modified Intent-To-Treat (MITT) population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year-one height measurements were imputed using the last observation carried forward (LOCF) method.	
End point type	Primary
End point timeframe: Baseline (Day 1) and at Year 1 (Week 52).	

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: cm/year				
arithmetic mean (standard deviation)	9.3 (± 1.7)	10.1 (± 1.3)	9.7 (± 2.5)	11.2 (± 2.1)

Statistical analyses

Statistical analysis title	45 rhGH + 50 rhIGF-1 vs 45 rhGH Alone
Statistical analysis description: Comparison of 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using an analysis of covariance (ANCOVA), with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.	
Comparison groups	45 µg/kg rhGH Alone v 45 µg/kg rhGH + 50 µg/kg rhIGF-1
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 ^[1]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	1.91

Notes:

[1] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's test.

Statistical analysis title	45 rhGH + 100 rhIGF-1 vs 45 rhGH Alone
Statistical analysis description: Comparison of 45 µg/kg rhGH + 100 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.	
Comparison groups	45 µg/kg rhGH Alone v 45 µg/kg rhGH + 100 µg/kg rhIGF-1
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.722 ^[2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.5

Notes:

[2] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's test.

Statistical analysis title	45 rhGH + 150 rhIGF-1 vs 45 rhGH Alone
-----------------------------------	--

Statistical analysis description:

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 combination treatment versus 45 µg/kg rhGH monotherapy using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

Comparison groups	45 µg/kg rhGH Alone v 45 µg/kg rhGH + 150 µg/kg rhIGF-1
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.01

Notes:

[3] - The two-sided p-values for the comparisons are adjusted for multiple comparisons using Dunnett's method.

Statistical analysis title	45 rhGH + 100 rhIGF-1 vs 45 rhGH + 50 rhIGF-1
-----------------------------------	---

Statistical analysis description:

Comparison of 45 µg/kg rhGH + 100 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

Comparison groups	45 µg/kg rhGH + 50 µg/kg rhIGF-1 v 45 µg/kg rhGH + 100 µg/kg rhIGF-1
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.427
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	0.61

Statistical analysis title	45 rhGH + 150 rhIGF-1 vs 45 rhGH + 50 rhIGF-1
-----------------------------------	---

Statistical analysis description:

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 50 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

Comparison groups	45 µg/kg rhGH + 50 µg/kg rhIGF-1 v 45 µg/kg rhGH + 150 µg/kg rhIGF-1
-------------------	--

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	2.12

Statistical analysis title	45 rhGH + 150 rhIGF-1 vs 45 rhGH + 100 rhIGF-1
-----------------------------------	--

Statistical analysis description:

Comparison of 45 µg/kg rhGH + 150 µg/kg rhIGF-1 versus 45 µg/kg rhGH + 100 µg/kg rhIGF-1 combination treatments using ANCOVA, with Year 1 height velocity as the dependent variable and with randomization strata defined by baseline age and IGF-1 SDS as covariates.

Comparison groups	45 µg/kg rhGH + 100 µg/kg rhIGF-1 v 45 µg/kg rhGH + 150 µg/kg rhIGF-1
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.54

Secondary: Height Velocity During the Second, Third and Fourth Year of Treatment

End point title	Height Velocity During the Second, Third and Fourth Year of Treatment
-----------------	---

End point description:

Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to end of study. Second, third and fourth-year height velocity (growth in cm) is presented for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year height measurements were imputed for Years 2, 3 and 4 only if a subject had at least one height value recorded in the specified year (imputation by LOCF method).

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 2, 3 and 4 (Weeks 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: cm/year				
arithmetic mean (standard deviation)				
Year 2 (n=24,25,22,24)	8.4 (± 1.3)	9.1 (± 1.2)	9.4 (± 1.6)	10.1 (± 1.8)
Year 3 (n=22,22,20,22)	8.0 (± 1.1)	8.4 (± 1.0)	8.9 (± 1.3)	9.2 (± 1.5)
Year 4 (n=17,16,15,16)	7.7 (± 0.9)	8.1 (± 0.8)	8.4 (± 1.2)	8.3 (± 1.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Change in Height SDS During the First, Second, Third and Fourth Year of Treatment

End point title	Cumulative Change in Height SDS During the First, Second, Third and Fourth Year of Treatment
-----------------	--

End point description:

Height was measured standing, without shoes, as the average of three measurements (the subject being repositioned each time) by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer which was calibrated prior to measurement of each subject and a calibration log kept. Height was evaluated at each study visit from screening up to end of study. Height SDS was calculated using the National Center for Health Statistics 2000 data as provided by the Center for Disease Control. Mean change from baseline in height SDS at Years 1, 2, 3 and 4 is presented for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. Missing end-of-year-one height SDS was imputed using last LOCF method; height SDS was imputed for Years 2, 3 and 4 only if a subject had at least one height value recorded in the specified year.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: SDS				
arithmetic mean (standard deviation)				
Year 1 (n=25,27,27,26)	0.7 (± 0.3)	0.9 (± 0.2)	0.8 (± 0.4)	1.0 (± 0.4)
Year 2 (n=24,25,22,24)	1.0 (± 0.4)	1.4 (± 0.4)	1.4 (± 0.5)	1.6 (± 0.6)
Year 3 (n=22,22,20,22)	1.3 (± 0.5)	1.6 (± 0.4)	1.8 (± 0.7)	1.9 (± 0.6)
Year 4 (n=17,16,15,16)	1.5 (± 0.5)	1.8 (± 0.5)	2.1 (± 0.8)	2.0 (± 0.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Predicted Adult Height (PAH) at Years 1, 2, 3 and 4

End point title	Predicted Adult Height (PAH) at Years 1, 2, 3 and 4
-----------------	---

End point description:

PAH was calculated by the Roche-Wainer-Thissen (RWT) method, as refined by Khamis and Guo and adjusted for growth after age 18 according to Roche and Davila, and was summarized for subjects completing the year in the context of baseline height SDS and mid-parental target height SDS. The mid-parental target height SDS was defined as:

$0.4 * (\text{Mother's height SDS} + \text{Father's height SDS})$.

RWT PAH SDS at baseline (Day 1) and at Years 1, 2, 3 and 4, as well as mid-parental target height SDS, are presented for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: SDS				
arithmetic mean (standard deviation)				
Baseline (n=25,27,27,26)	-1.67 (± 0.51)	-1.83 (± 0.58)	-1.69 (± 0.59)	-1.76 (± 0.73)
Year 1 (n=24,25,22,25)	-1.12 (± 0.57)	-1.22 (± 0.58)	-0.99 (± 0.55)	-1.01 (± 0.80)
Year 2 (n=22,21,20,22)	-0.96 (± 0.56)	-0.81 (± 0.55)	-0.66 (± 0.56)	-0.69 (± 0.91)
Year 3 (n=21,19,19,20)	-0.78 (± 0.63)	-0.65 (± 0.60)	-0.42 (± 0.62)	-0.64 (± 0.98)
Year 4 (n=3,4,4,3)	-1.22 (± 0.59)	-0.44 (± 0.81)	0.49 (± 0.60)	-0.07 (± 0.89)
Mid-parental target height (n=25,27,27,26)	-0.51 (± 0.38)	-0.64 (± 0.52)	-0.53 (± 0.50)	-0.47 (± 0.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Change from Baseline in Body Mass Index (BMI) SDS at Years 1, 2, 3, 4 and End of Study

End point title	Total Change from Baseline in Body Mass Index (BMI) SDS at Years 1, 2, 3, 4 and End of Study
-----------------	--

End point description:

Weight in kilograms (kg) was recorded from a single observation of the subject in light clothing or dressing gown with shoes removed. BMI was calculated by weight divided by height squared and measured as kg per square meter (kg/m^2). Height and weight were evaluated at each study visit from screening up to the end of study. Mean change from baseline in BMI SDS at Years 1, 2, 3 and 4, and at end of study is presented for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

End point type Secondary

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: SDS				
arithmetic mean (standard deviation)				
Change to Year 1 (n=24,25,22,25)	0.24 (± 0.43)	0.31 (± 0.39)	0.36 (± 0.41)	0.54 (± 0.40)
Change to Year 2 (n=22,21,20,22)	0.31 (± 0.49)	0.57 (± 0.41)	0.49 (± 0.44)	0.59 (± 0.46)
Change to Year 3 (n=21,19,19,20)	0.35 (± 0.58)	0.62 (± 0.43)	0.49 (± 0.59)	0.71 (± 0.54)
Change to Year 4 (n=3,5,5,4)	0.27 (± 0.52)	0.64 (± 0.58)	0.65 (± 0.90)	1.20 (± 0.91)
Change to End of Study (n=25,27,27,26)	0.34 (± 0.54)	0.45 (± 0.45)	0.42 (± 0.53)	0.64 (± 0.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal Maturation (Bone Age) at Years 1, 2, 3 and 4

End point title Skeletal Maturation (Bone Age) at Years 1, 2, 3 and 4

End point description:

Plain X-rays of the left hand and wrist exposed for bone age appraisal were sent to a central facility for standardized evaluation. Bone age was evaluated at screening and each end-of-year visit up to the end of study. Bone age is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the completer population, consisting of all subjects that remained in the study until a specific time point (ie, Year 1, Year 2, Year 3 and Year 4).

n = number of subjects with data available for analysis for each indicated timepoint.

End point type Secondary

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: years				
arithmetic mean (standard deviation)				
Baseline (n=25,27,27,26)	7.6 (± 1.8)	7.3 (± 1.9)	7.2 (± 2.0)	7.4 (± 2.0)
Year 1 (n=24,25,22,25)	9.0 (± 1.9)	8.5 (± 1.9)	8.4 (± 2.2)	8.5 (± 2.1)
Year 2 (n= 22,21,20,22)	10.3 (± 2.0)	9.6 (± 2.1)	9.8 (± 2.4)	9.9 (± 2.2)
Year 3 (n=21,19,19,20)	11.4 (± 2.0)	10.9 (± 2.2)	11.4 (± 2.4)	10.9 (± 2.2)
Year 4 (n=3,4,5,3)	12.4 (± 1.0)	10.9 (± 1.8)	12.2 (± 3.0)	12.5 (± 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of GH at Years 1, 2, 3 and 4

End point title	Serum Concentration of GH at Years 1, 2, 3 and 4
End point description:	Growth factor panels for measuring GH were evaluated at each study visit from screening up to the end-of-year-four visit. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for GH is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement. n = number of subjects with data available for analysis for each indicated timepoint.
End point type	Secondary
End point timeframe:	Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=23,25,18,25)	1.1 (± 2.2)	2.9 (± 8.1)	2.4 (± 4.5)	1.9 (± 2.3)
Year 1 (Trough) (n=23,25,18,25)	1.7 (± 2.1)	3.5 (± 12.9)	2.1 (± 3.2)	1.4 (± 2.1)
Year 2 (Trough) (n=21,20,16,20)	4.0 (± 6.0)	2.2 (± 4.2)	2.7 (± 3.9)	1.4 (± 1.2)
Year 3 (Trough) (n=20,18,15,20)	2.8 (± 5.1)	1.3 (± 1.6)	1.5 (± 1.4)	1.9 (± 3.5)
Year 4 (Trough) (n=3,5,4,3)	1.2 (± 0.3)	0.5 (± 0.4)	3.0 (± 2.9)	1.1 (± 0.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of IGF-1 at Years 1, 2, 3 and 4

End point title	Serum Concentration of IGF-1 at Years 1, 2, 3 and 4
-----------------	---

End point description:

Growth factor panels for measuring IGF-1 were evaluated at each study visit from screening up to the end of study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGF-1 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=24,25,22,25)	108.3 (± 39.8)	87.1 (± 31.0)	100.2 (± 41.4)	96.7 (± 38.8)
Year 1 (Trough) (n=24,25,22,25)	278.2 (± 95.5)	326.9 (± 108.9)	397.8 (± 185.4)	296.0 (± 126.8)
Year 2 (Trough) (n=22,21,20,22)	312.8 (± 97.2)	427.2 (± 178.5)	539.3 (± 195.9)	466.4 (± 178.6)
Year 3 (Trough) (n=21,19,19,20)	335.3 (± 110.0)	404.9 (± 140.4)	462.2 (± 156.4)	441.3 (± 226.0)
Year 4 (Trough) (n=3,5,5,3)	347.7 (± 130.7)	363.6 (± 125.4)	546.2 (± 265.8)	607.7 (± 65.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1) at Years 1, 2, 3 and 4

End point title	Serum Concentration of Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1) at Years 1, 2, 3 and 4
-----------------	--

End point description:

Growth factor panels for measuring IGFBP-1 were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGFBP-1 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=24,24,21,24)	87.8 (± 54.5)	102.5 (± 37.2)	95.7 (± 50.0)	122.4 (± 53.7)
Year 1 (Trough) (n=24,24,21,24)	45.7 (± 38.0)	63.8 (± 50.1)	68.2 (± 61.6)	88.8 (± 47.4)
Year 2 (Trough) (n=22,21,19,20)	59.4 (± 45.6)	58.2 (± 47.7)	53.3 (± 35.3)	71.7 (± 46.1)
Year 3 (Trough) (n=21,19,18,19)	46.1 (± 35.2)	60.4 (± 52.5)	53.2 (± 34.8)	84.7 (± 53.5)
Year 4 (Trough) (n=3,5,5,3)	100.0 (± 60.4)	46.8 (± 58.0)	49.2 (± 20.7)	49.0 (± 26.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) at Years 1, 2, 3 and 4

End point title	Serum Concentration of Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) at Years 1, 2, 3 and 4
-----------------	--

End point description:

Growth factor panels for measuring IGFBP-3 were evaluated at each study visit from screening up to the end of study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for IGFBP-3 is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=24,25,22,25)	2204.2 (± 387.3)	2160.0 (± 421.3)	2113.6 (± 486.3)	2196.0 (± 612.0)
Year 1 (Trough) (n=24,25,22,25)	2954.2 (± 618.5)	2784.0 (± 755.9)	2677.3 (± 548.5)	2624.0 (± 598.8)
Year 2 (Trough) (n=22,21,20,22)	2813.6 (± 399.2)	2942.9 (± 552.8)	3060.0 (± 703.7)	2754.5 (± 600.6)
Year 3 (Trough) (n=21,19,19,20)	3404.8 (± 476.9)	3431.6 (± 718.1)	3373.7 (± 479.4)	3260.0 (± 908.1)

Year 4 (Trough) (n=3,5,5,3)	3733.3 (± 378.6)	3260.0 (± 709.2)	3620.0 (± 957.6)	3466.7 (± 461.9)
-----------------------------	------------------	------------------	------------------	------------------

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Acid-Labile Subunit (ALS) at Years 1, 2, 3 and 4

End point title	Serum Concentration of Acid-Labile Subunit (ALS) at Years 1, 2, 3 and 4
-----------------	---

End point description:

Growth factor panels for measuring ALS were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for ALS is presented at baseline (Day 1) and at Years 1, 2, 3 and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: milligrams per liter				
arithmetic mean (standard deviation)				
Baseline (n=25,26,26,25)	10.6 (± 3.0)	10.0 (± 3.4)	10.9 (± 3.0)	11.0 (± 4.1)
Year 1 (Trough) (n=24,24,21,24)	16.0 (± 4.0)	12.7 (± 2.3)	14.0 (± 3.9)	11.5 (± 2.8)
Year 2 (Trough) (n=22,21,19,20)	15.2 (± 4.3)	14.3 (± 5.2)	15.7 (± 4.0)	13.7 (± 4.5)
Year 3 (Trough) (n=21,18,18,19)	13.7 (± 2.3)	13.0 (± 3.2)	12.9 (± 2.7)	11.2 (± 4.0)
Year 4 (Trough) (n=3,5,5,3)	13.7 (± 1.5)	12.0 (± 2.2)	12.0 (± 3.0)	13.7 (± 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Growth Hormone Binding Protein (GHBP) at Years 1, 2, 3 and 4

End point title	Serum Concentration of Growth Hormone Binding Protein (GHBP) at Years 1, 2, 3 and 4
-----------------	---

End point description:

Growth factor panels for measuring GHBP were evaluated at baseline and various visits during the study. Samples were assayed at a central laboratory from a single blood sample collected during the appropriate visit. Serum concentration for GHBP is presented at baseline (Day 1) and at Years 1, 2, 3

and 4 for the MITT population, consisting of all subjects who were randomized and had at least one post-baseline height measurement.

n = number of subjects with data available for analysis for each indicated timepoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and at Years 1, 2, 3 and 4 (Weeks 52, 104, 156 and 208, respectively).

End point values	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1	45 µg/kg rhGH + 150 µg/kg rhIGF-1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	27	26
Units: picomoles per liter				
arithmetic mean (standard deviation)				
Baseline (n=25,26,25,25)	785.8 (± 291.1)	735.8 (± 343.5)	698.8 (± 212.2)	719.0 (± 261.5)
Year 1 (Trough) (n=23,24,20,24)	729.4 (± 229.5)	576.9 (± 211.0)	598.9 (± 187.3)	530.5 (± 233.5)
Year 2 (Trough) (n=22,21,18,21)	725.6 (± 308.4)	589.3 (± 171.6)	562.5 (± 184.4)	564.6 (± 171.9)
Year 3 (Trough) (n=21,17,17,19)	672.0 (± 224.4)	646.9 (± 204.1)	614.3 (± 210.9)	554.9 (± 197.0)
Year 4 (Trough) (n=3,5,5,3)	714.0 (± 38.5)	516.9 (± 252.5)	798.2 (± 336.1)	519.7 (± 141.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from randomization (Day 1) until 30 days after the subject was terminated from the study. Overall timeframe up to a maximum of approximately 4 years.

Adverse event reporting additional description:

Safety population consisted of all subjects who were randomized.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	11.0
--------------------	------

Reporting groups

Reporting group title	45 µg/kg rhGH Alone
-----------------------	---------------------

Reporting group description:

Subjects received 45 µg/kg rhGH alone, administered once daily by injection.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Reporting group title	45 µg/kg rhGH + 50 µg/kg rhIGF-1
-----------------------	----------------------------------

Reporting group description:

Subjects received 45 µg/kg rhGH and 50 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Reporting group title	45 µg/kg rhGH + 100 µg/kg rhIGF-1
-----------------------	-----------------------------------

Reporting group description:

Subjects received 45 µg/kg rhGH and 100 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned dose. Full doses commenced on the day immediately following Day 15 (Visit 3).

Reporting group title	45 µg/kg rhGH + 150 µg/kg rhIGF-1
-----------------------	-----------------------------------

Reporting group description:

Subjects received 45 µg/kg rhGH and 150 µg/kg rhIGF-1, administered once daily as separate injections.

Treatment commenced on Day 1 (Visit 2) at 50% of the assigned doses. Full doses commenced on the day immediately following Day 15 (Visit 3).

Serious adverse events	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	1 / 27 (3.70%)	2 / 27 (7.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Evans syndrome			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	45 µg/kg rhGH + 150 µg/kg rhIGF-1		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 26 (3.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Evans syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	45 µg/kg rhGH Alone	45 µg/kg rhGH + 50 µg/kg rhIGF-1	45 µg/kg rhGH + 100 µg/kg rhIGF-1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	27 / 27 (100.00%)	27 / 27 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 26 (7.69%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 26 (34.62%)	15 / 27 (55.56%)	4 / 27 (14.81%)
occurrences (all)	17	27	22
Injection site pain			
subjects affected / exposed	4 / 26 (15.38%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences (all)	4	2	0
Malaise			
subjects affected / exposed	1 / 26 (3.85%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Injection site bruising			
subjects affected / exposed	4 / 26 (15.38%)	4 / 27 (14.81%)	4 / 27 (14.81%)
occurrences (all)	4	5	4
Injection site hypertrophy			
subjects affected / exposed	0 / 26 (0.00%)	6 / 27 (22.22%)	7 / 27 (25.93%)
occurrences (all)	0	8	13
Injection site induration			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 1	2 / 27 (7.41%) 2
Influenza like illness subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Injection site urticaria subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	3 / 27 (11.11%) 3	1 / 27 (3.70%) 2
Fatigue subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	3 / 27 (11.11%) 3	0 / 27 (0.00%) 0
Feeling hot subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 27 (3.70%) 1	0 / 27 (0.00%) 0
Seasonal allergy subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 27 (11.11%) 4	3 / 27 (11.11%) 3
Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 7	14 / 27 (51.85%) 18	9 / 27 (33.33%) 16
Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	7 / 27 (25.93%) 11	7 / 27 (25.93%) 10
Nasal congestion			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 27 (7.41%) 2	3 / 27 (11.11%) 6
Asthma subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 1	3 / 27 (11.11%) 4
Epistaxis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 5	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	2 / 27 (7.41%) 2	1 / 27 (3.70%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 1	2 / 27 (7.41%) 2
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 27 (7.41%) 2	1 / 27 (3.70%) 1
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 27 (3.70%) 1	0 / 27 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Attention subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Investigations			
Insulin-like growth factor increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Body temperature increased			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	3 / 27 (11.11%) 4	3 / 27 (11.11%) 3
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Thyroxine free decreased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Weight decreased subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
Injury, poisoning and procedural complications			
Procedural pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Arthropod sting subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	1 / 27 (3.70%) 2	0 / 27 (0.00%) 0
Skin laceration subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Upper limb fracture subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Concussion subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
Joint sprain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 27 (7.41%) 2	3 / 27 (11.11%) 4
Limb injury			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Orthodontic appliance complication subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	14 / 26 (53.85%) 40	14 / 27 (51.85%) 43	17 / 27 (62.96%) 39
Dizziness subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 27 (7.41%) 4	0 / 27 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	3 / 27 (11.11%) 3	3 / 27 (11.11%) 3
Tremor subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 7	1 / 27 (3.70%) 1	3 / 27 (11.11%) 3
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 27 (7.41%) 2	1 / 27 (3.70%) 1
Eye disorders Eye pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 1	0 / 27 (0.00%) 0
Myopia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2

Vision blurred subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	4 / 27 (14.81%) 4	0 / 27 (0.00%) 0
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	9 / 26 (34.62%) 17	5 / 27 (18.52%) 6	6 / 27 (22.22%) 12
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 11	5 / 27 (18.52%) 8	3 / 27 (11.11%) 7
Diarrhoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	3 / 27 (11.11%) 4	2 / 27 (7.41%) 2
Nausea subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 10	4 / 27 (14.81%) 5	4 / 27 (14.81%) 7
Abdominal pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	4 / 27 (14.81%) 4	4 / 27 (14.81%) 6
Dyspepsia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 27 (11.11%) 3	0 / 27 (0.00%) 0
Stomach discomfort subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 27 (7.41%) 2	3 / 27 (11.11%) 4
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	2 / 27 (7.41%) 2	0 / 27 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
Skin and subcutaneous tissue disorders			

Dermatitis contact subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 27 (3.70%) 2	1 / 27 (3.70%) 1
Skin hypertrophy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 2	0 / 27 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 27 (3.70%) 1	3 / 27 (11.11%) 6
Eczema subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Keratosis pilaris subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Alopecia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Hair texture abnormal subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 27 (3.70%) 1	2 / 27 (7.41%) 2
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 27 (3.70%) 1	2 / 27 (7.41%) 2
Pollakiuria subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 8	4 / 27 (14.81%) 7	5 / 27 (18.52%) 5
Pain in extremity subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 7	8 / 27 (29.63%) 11	7 / 27 (25.93%) 8
Back pain			

subjects affected / exposed	3 / 26 (11.54%)	5 / 27 (18.52%)	1 / 27 (3.70%)
occurrences (all)	4	5	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Scoliosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)	3 / 27 (11.11%)	1 / 27 (3.70%)
occurrences (all)	0	4	2
Myalgia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	2	4	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 26 (38.46%)	10 / 27 (37.04%)	9 / 27 (33.33%)
occurrences (all)	23	19	31
Otitis media			
subjects affected / exposed	4 / 26 (15.38%)	5 / 27 (18.52%)	3 / 27 (11.11%)
occurrences (all)	4	7	5
Viral infection			
subjects affected / exposed	6 / 26 (23.08%)	3 / 27 (11.11%)	6 / 27 (22.22%)
occurrences (all)	10	6	6
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)	3 / 27 (11.11%)	5 / 27 (18.52%)
occurrences (all)	2	3	9
Pharyngitis streptococcal			
subjects affected / exposed	5 / 26 (19.23%)	12 / 27 (44.44%)	7 / 27 (25.93%)
occurrences (all)	13	17	9
Gastroenteritis viral			
subjects affected / exposed	6 / 26 (23.08%)	3 / 27 (11.11%)	2 / 27 (7.41%)
occurrences (all)	7	9	4

Influenza			
subjects affected / exposed	2 / 26 (7.69%)	3 / 27 (11.11%)	5 / 27 (18.52%)
occurrences (all)	2	4	6
Ear infection			
subjects affected / exposed	3 / 26 (11.54%)	2 / 27 (7.41%)	4 / 27 (14.81%)
occurrences (all)	5	4	6
Otitis externa			
subjects affected / exposed	1 / 26 (3.85%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Molluscum contagiosum			
subjects affected / exposed	2 / 26 (7.69%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Bronchitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 27 (3.70%)	2 / 27 (7.41%)
occurrences (all)	1	3	4
Nasopharyngitis			
subjects affected / exposed	3 / 26 (11.54%)	4 / 27 (14.81%)	4 / 27 (14.81%)
occurrences (all)	4	5	15
Pharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	0	3	0
Sinusitis			
subjects affected / exposed	5 / 26 (19.23%)	7 / 27 (25.93%)	3 / 27 (11.11%)
occurrences (all)	25	14	5
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	3
Varicella			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 27 (3.70%)	3 / 27 (11.11%)
occurrences (all)	1	1	3
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	3 / 27 (11.11%)	0 / 27 (0.00%)
occurrences (all)	1	3	0

Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	0 / 27 (0.00%) 0	0 / 27 (0.00%) 0
---	---------------------	---------------------	---------------------

Non-serious adverse events	45 µg/kg rhGH + 150 µg/kg rhIGF-1		
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 26 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	13 / 26 (50.00%) 19		
Injection site pain subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 6		
Malaise subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Injection site bruising subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 5		
Injection site hypertrophy subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4		
Injection site induration subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4		
Influenza like illness subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Injection site erythema			

<p>subjects affected / exposed occurrences (all)</p> <p>Injection site urticaria subjects affected / exposed occurrences (all)</p> <p>Fatigue subjects affected / exposed occurrences (all)</p> <p>Feeling hot subjects affected / exposed occurrences (all)</p>	<p>2 / 26 (7.69%) 3</p> <p>2 / 26 (7.69%) 5</p> <p>1 / 26 (3.85%) 1</p> <p>0 / 26 (0.00%) 0</p>		
<p>Immune system disorders</p> <p>Hypersensitivity subjects affected / exposed occurrences (all)</p> <p>Seasonal allergy subjects affected / exposed occurrences (all)</p>	<p>2 / 26 (7.69%) 2</p> <p>0 / 26 (0.00%) 0</p>		
<p>Reproductive system and breast disorders</p> <p>Gynaecomastia subjects affected / exposed occurrences (all)</p>	<p>1 / 26 (3.85%) 1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough subjects affected / exposed occurrences (all)</p> <p>Pharyngolaryngeal pain subjects affected / exposed occurrences (all)</p> <p>Nasal congestion subjects affected / exposed occurrences (all)</p> <p>Asthma subjects affected / exposed occurrences (all)</p> <p>Epistaxis</p>	<p>10 / 26 (38.46%) 14</p> <p>5 / 26 (19.23%) 5</p> <p>3 / 26 (11.54%) 3</p> <p>2 / 26 (7.69%) 2</p>		

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 4		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Attention deficit/hyperactivity disorder subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Attention subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Investigations			
Insulin-like growth factor increased subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 4		
Body temperature increased subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Thyroxine free decreased			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Arthropod sting			
subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Contusion			
subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Skin laceration			
subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Upper limb fracture			
subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Concussion			
subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Joint sprain			
subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Limb injury			
subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Orthodontic appliance complication			
subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	18 / 26 (69.23%) 50		
Dizziness subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3		
Migraine subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 7		
Tremor subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Eye disorders Eye pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Myopia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Vision blurred subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	12 / 26 (46.15%)		
occurrences (all)	19		
Abdominal pain upper			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
Stomach discomfort			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	6		
Skin hypertrophy			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Urticaria			

subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Eczema subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Keratosis pilaris subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Alopecia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Hair texture abnormal subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Renal and urinary disorders			
Enuresis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Pollakiuria subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 12		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 12		
Back pain subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Neck pain			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Scoliosis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	13 / 26 (50.00%) 37		
Otitis media subjects affected / exposed occurrences (all)	9 / 26 (34.62%) 19		
Viral infection subjects affected / exposed occurrences (all)	8 / 26 (30.77%) 21		
Gastroenteritis subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 10		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 14		
Gastroenteritis viral subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Influenza subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Ear infection subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4		

Otitis externa			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Molluscum contagiosum			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Varicella			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2008	<ul style="list-style-type: none">• The adiponectin test was deleted after failure to validate that assay;• The number of sites was increased to 30;• Language regarding the use of gonadotropin agonists (e.g., Lupron®) was clarified;• Safety lab follow up for subjects with sustained IGF-1 SDS +4 was added;• The possibility to use single injections of combination rhGH and rhIGF-1 during the first year was deleted;• Addition of serum chemistry panel at Visit 4;• Addition of gamma glutamyl transferase and creatine phosphokinase to the safety laboratory assessments, and additional growth factors as needed;• Additional language added to risk management and reduction section regarding intracranial hypertension symptoms.
11 August 2010	<p>Amendment came into effect after all subjects had completed 1 year of treatment and following the availability of the first year height data contained in the interim report.</p> <ul style="list-style-type: none">• The study duration for individual subjects was extended from 3 to 6 years to provide safety and efficacy data on longer-term use of combination rhGH and rhIGF-1. Updates to the protocol were made to reflect the extension to a six-year study;• Minor changes were made to the wording of some of the study's secondary objectives.• The primary efficacy endpoint of the study was clarified to only comprise the first year of the study and secondary efficacy endpoints for the subsequent years of the study were added;• A new table of study assessments was added to reflect the extension to a six-year study. Insulin testing was removed from all future visits and collection of month and year of first menarche was added;• The growth factor panel to be evaluated was modified to also include IGF-2 and insulin-like growth factor binding proteins other than IGF-1;• The composition of the Data Monitoring Committee was changed;• Text regarding resumption of study treatment after generalised allergic reaction, intracranial hypertension, hypoglycemia and subject monitoring was added to the Risk Management and reduction section;• Protocol sections describing study assessments for each visit were modified in that pubertal status was added and specification of growth factors was replaced by "growth factor panel";• Two additional protocol sections describing the study assessments to be performed at Visits 15 to 23 were added;• Description of statistical method for assessment of total treatment effect for subjects with data beyond Year 1 and text regarding handling of missing data were added.

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.

The study was prematurely terminated once the last subject had completed 3 years of treatment (compared to the 6 years planned) for strategic reasons.

Notes: