Clinical trial results:
RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-1 (rhIGF-1) TREATMENT OF PREPUBERTAL CHILDREN WITH GROWTH FAILURE ASSOCIATED WITH PRIMARY IGF-1 DEFICIENCY: A PHASE 3, RANDOMIZED, OPEN LABEL, OBSERVATION-CONTROLLED, MULTICENTER, PARALLEL-DOSE COMPARISON TRIAL.

Summary

EudraCT number	2019-001020-36
Trial protocol	Outside EU/EEA
Global end of trial date	02 July 2008

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	MS301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00125164
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	02 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the safety and efficacy of recombinant human insulin-like growth factor-1 (rhIGF-1) in promoting the growth of children with growth failure associated with Primary IGF-1 deficiency (IGFD).

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: -

Actual start date of recruitment	14 March 2004
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	United States: 137
Worldwide total number of subjects	137
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)	133
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3, randomised, open-label, observation-controlled, multi-centre, parallel-dose comparison trial of rhIGF-1 in prepubertal male and female subjects with growth failure associated with Primary IGFD. The trial was conducted at 30 clinical sites in the United States from 02 July 2008 to 14 March 2014.

Pre-assignment

Screening details:

Subjects were initially randomised to 40 micrograms (µg) rhIGF-1 per kilogram (kg) twice a day (BID), 80 µg rhIGF-1 per kg BID, or untreated control. Following a protocol amendment, a 120 µg/kg BID arm was added, randomisation to the 40 µg/kg BID arm was discontinued and on-going subjects in this arm were reassigned to receive 120 µg/kg BID.

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	Untreated Control

Arm description:

Subjects were randomised to the untreated control group and did not receive any investigational medical product for the duration of the 1 year study period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	40 µg/kg rhIGF-1 BID

Arm description:

Subjects were initially randomised to receive 40 µg/kg rhIGF-1 BID. Following a protocol amendment, the 11 subjects in this arm who had not already completed the study at this dose were reassigned to receive 120 µg/kg rhIGF-1 BID for the remainder of the 1 year study period. All 16 subjects initially randomised to this arm were excluded from the efficacy analyses.

Arm type	Experimental
Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	mecasermin
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of 40 µg/kg rhIGF-1, BID, for up to 1 year or until dose group was discontinued following protocol amendment. Doses were up-titrated from 20 µg/kg rhIGF-1 to the final dose of 40 µg/kg rhIGF-1 over the first 2 weeks of the study. Injections were given immediately before breakfast and dinner. After the protocol amendment, subjects on-going in this group r commenced therapy at 80 µg/kg rhIFG-1 BID for 2 weeks followed by 120 µg/kg rhIFG-1 BID for the remainder of the trial. Dose adjustments were made every 3 months based upon the subject's weight.

Arm title	80 µg/kg rhIGF-1 BID

Arm description:

Subjects were randomised to receive 80 µg/kg rhIGF-1 BID for the duration of the 1 year study period.

Arm type	Experimental

Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	mecasermin
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of 80 µg/kg rhIGF-1 BID, for up to 1 year. Doses were up-titrated from 20 µg/kg rhIGF-1 to the final dose of 80 µg/kg rhIGF-1 over the first 4 weeks of the study. Injections were given immediately before breakfast and dinner. Dose adjustments were made every 3 months based upon the subject's weight.

Arm title	120 µg/kg rhIGF-1 BID

Arm description:

Subjects were randomised to receive 120 µg/kg rhIGF-1 BID for the duration of the 1 year study period.

Arm type	Experimental
Investigational medicinal product name	rhIGF-1
Investigational medicinal product code	
Other name	mecasermin
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous injections of 120 µg/kg rhIGF-1 BID, for up to 1 year. Doses were up-titrated from 40 µg/kg rhIGF-1 to the final dose of 120 µg/kg rhIGF-1 over the first 4 weeks of the study. Injections were given immediately before breakfast and dinner. Dose adjustments were made every 3 months based upon the subject's weight.

Number of subjects in period 1[1]	Untreated Control	40 µg/kg rhIGF-1 BID	80 µg/kg rhIGF-1 BID
Started	25	16	44
Completed	23	16	40
Not completed	2	0	4
Consent withdrawn by subject	2	-	1
Adverse event, non-fatal	-	-	2
Lost to follow-up	-	-	1

Number of subjects in period 1[1]	120 µg/kg rhIGF-1 BID
Started	51
Completed	45
Not completed	6
Consent withdrawn by subject	1
Adverse event, non-fatal	4
Lost to follow-up	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Consent for one randomised subject was withdrawn prior to any study measurements. This subject was excluded from the baseline population.

Baseline characteristics

Reporting groups	
Reporting group title	Untreated Control
Reporting group description:	
Subjects were randomised to the untreated control group and did not receive any investigational medical product for the duration of the 1 year study period.	
Reporting group title	40 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were initially randomised to receive 40 µg/kg rhIGF-1 BID. Following a protocol amendment, the 11 subjects in this arm who had not already completed the study at this dose were reassigned to receive 120 µg/kg rhIGF-1 BID for the remainder of the 1 year study period. All 16 subjects initially randomised to this arm were excluded from the efficacy analyses.	
Reporting group title	80 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 80 µg/kg rhIGF-1 BID for the duration of the 1 year study period.	
Reporting group title	120 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 120 µg/kg rhIGF-1 BID for the duration of the 1 year study period.	

Reporting group values	Untreated Control	40 µg/kg rhIGF-1 BID	80 µg/kg rhIGF-1 BID
Number of subjects	25	16	44
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	7.0	7.6	7.7
standard deviation	± 2.4	± 2.4	± 2.4
Gender categorical Units: Subjects			
Female	10	4	14
Male	15	12	30
Race/Ethnicity Units: Subjects			
Asian	1	0	1
Black	0	0	0
Native Hawaiian or Pacific Islander	0	0	0
White	22	16	38
Hispanic	2	0	4

Other	0	0	1

Reporting group values	120 µg/kg rhIGF-1 BID	Total	
Number of subjects	51	136	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	7.6		
standard deviation	± 2.7	-	
Gender categorical Units: Subjects			
Female	8	36	
Male	43	100	
Race/Ethnicity Units: Subjects			
Asian	2	4	
Black	2	2	
Native Hawaiian or Pacific Islander	1	1	
White	41	117	
Hispanic	4	10	
Other	1	2	

End points

End points reporting groups

Reporting group title	Untreated Control
Reporting group description:	
Subjects were randomised to the untreated control group and did not receive any investigational medical product for the duration of the 1 year study period.	
Reporting group title	40 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were initially randomised to receive 40 µg/kg rhIGF-1 BID. Following a protocol amendment, the 11 subjects in this arm who had not already completed the study at this dose were reassigned to receive 120 µg/kg rhIGF-1 BID for the remainder of the 1 year study period. All 16 subjects initially randomised to this arm were excluded from the efficacy analyses.	
Reporting group title	80 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 80 µg/kg rhIGF-1 BID for the duration of the 1 year study period.	
Reporting group title	120 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 120 µg/kg rhIGF-1 BID for the duration of the 1 year study period.	
Subject analysis set title	Untreated Control
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to the untreated control group.	
Subject analysis set title	80 µg/kg rhIGF-1 BID
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to the 80 µg/kg rhIGF-1 BID group.	
Subject analysis set title	120 µg/kg rhIGF-1 BID
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomised to the 120 µg/kg rhIGF-1 BID group.	

Primary: Height Velocity at 1 Year

End point title	Height Velocity at 1 Year
End point description:	
Height was measured standing, without shoes, as the average of 3 measurements by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer at Day 1 (baseline) and each study visit up to 1 year (12 months). First-year height velocity (growth in centimetres [cm]) is presented for all subjects with a baseline height measurement and at least 1 on-treatment height measurement. Missing first-year (Month 12) height measurements were imputed using the last observation carried forward method.	
End point type	Primary
End point timeframe:	
Baseline and at 1 year.	

End point values	Untreated Control	80 µg/kg rhIGF-1 BID	120 µg/kg rhIGF-1 BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	42	49	
Units: cm/year				
arithmetic mean (standard deviation)	5.2 (± 1.0)	6.9 (± 1.0)	7.7 (± 1.5)	

Statistical analyses

Statistical analysis title	80 µg/kg rhIGF-1 BID versus Untreated Control

Statistical analysis description:

Comparison of 80 µg/kg rhIGF-1 BID group with the untreated control group using analysis of covariance (ANCOVA), where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	Untreated Control v 80 µg/kg rhIGF-1 BID
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	2.39

Notes:

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

Statistical analysis title	120 µg/kg rhIGF-1 BID versus Untreated Control

Statistical analysis description:

Comparison of 120 µg/kg rhIGF-1 BID group with the untreated control group using ANCOVA, where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	Untreated Control v 120 µg/kg rhIGF-1 BID
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.99
upper limit	3.16

Notes:

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

Statistical analysis title	80 µg/kg rhIGF-1 BID versus 120 µg/kg rhIGF-1 BID

Statistical analysis description:

Comparison of the 80 µg/kg rhIGF-1 BID group with the 120 µg/kg rhIGF-1 BID group using ANCOVA, where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	80 µg/kg rhIGF-1 BID v 120 µg/kg rhIGF-1 BID
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.31

Notes:

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

Secondary: Mean Change From Baseline in Height Standard Deviation (SD) Score at 1 Year

End point title	Mean Change From Baseline in Height Standard Deviation (SD) Score at 1 Year

End point description:

Height was measured standing without shoes as the average of 3 measurements by the same observer using identical technique with a Harpenden or other wall-mounted stadiometer at Day 1 (baseline) and each study visit up to 1 year (12 months). Height SD score was calculated using the National Center for Health Statistics 2000 data as provided by the Center for Disease Control as the subject value minus the mean divided by the standard deviation. The mean and the standard deviation could vary depending on the age and sex of the subject. Mean change from baseline in height SD score at 1 year is presented for all subjects with a baseline height measurement and at least 1 on-treatment height measurement. Missing first-year (Month 12) height measurements were imputed using the last observation carried forward method.

End point type	Secondary

End point timeframe:

Baseline and at 1 year.

End point values	Untreated Control	80 µg/kg rhIGF-1 BID	120 µg/kg rhIGF-1 BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	42	49	
Units: SD score/year				
arithmetic mean (standard deviation)	0.02 (± 0.24)	0.38 (± 0.17)	0.48 (± 0.32)	

Statistical analyses

Statistical analysis title	80 µg/kg rhIGF-1 BID versus Untreated Control

Statistical analysis description:

Comparison of 80 µg/kg BID group with the untreated control group using ANCOVA, where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	Untreated Control v 80 µg/kg rhIGF-1 BID
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.5

Notes:

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

Statistical analysis title	120 µg/kg rhIGF-1 BID versus Untreated Control

Statistical analysis description:

Comparison of 120 µg/kg rhIGF-1 BID group with the untreated control group using ANCOVA, where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	Untreated Control v 120 µg/kg rhIGF-1 BID
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.6

Notes:

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

Statistical analysis title	80 µg/kg rhIGF-1 BID versus 120 µg/kg rhIGF-1 BID

Statistical analysis description:

Comparison of 80 µg/kgrhIGF-1 BID group with the 120 µg/kg rhIGF-1 BID group using ANCOVA, where the covariates are the baseline height SD score stratum used in the randomisation, the pretreatment height velocity, the baseline bone age, the baseline chronological age, and sex.

Comparison groups	120 µg/kg rhIGF-1 BID v 80 µg/kg rhIGF-1 BID

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0495 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.22

Notes:

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

Secondary: Mean Change from Baseline in Bone Age at 1 Year

End point title	Mean Change from Baseline in Bone Age at 1 Year

End point description:

Plain X-rays of the left hand and wrist exposed were taken at baseline and at 1 year for bone age appraisal. The films were sent to a central facility for standardised evaluation. The mean change in bone age from baseline at 1 year (Month 12) is presented for all subjects with both baseline and 1 year bone age measurements.

End point type	Secondary

End point timeframe:

Baseline and at 1 year.

End point values	Untreated Control	80 µg/kg rhIGF-1 BID	120 µg/kg rhIGF-1 BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	40	44	
Units: Years				
arithmetic mean (standard deviation)	0.8 (± 0.3)	1.1 (± 0.4)	1.2 (± 0.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Change From Baseline in Serum Growth Factor Concentrations at 1 Year

End point title	Mean Percent Change From Baseline in Serum Growth Factor Concentrations at 1 Year

End point description:

Growth factor panels were drawn at various visits during the study. Blood samples were collected while subjects were in a fasting state for measuring the level of serum IGF-1 and IGF binding protein (IGFBP)-3 and in a non-fasting state for IGF-2 and IGFBP-2. Mean percent change from baseline for each of the growth factor panels 1 year are presented.

n = number of subjects with baseline measurement and 1 year measurements for each of the growth factor panels.

End point type	Secondary

End point timeframe:

Baseline and at 1 year.

End point values	Untreated Control	80 µg/kg rhIGF-1 BID	120 µg/kg rhIGF-1 BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25[7]	44[8]	51[9]	
Units: Percent change				
arithmetic mean (standard deviation)				
IGF-1	64 (± 120)	227 (± 220)	266 (± 215)	
IGF-2	14 (± 28)	-38 (± 37)	-37 (± 32)	
IGFBP-2	-16 (± 26)	58 (± 84)	61 (± 79)	
IGFBP-3	13 (± 33)	-19 (± 22)	-19 (± 28)	

Notes:

[7] - IGF-1, n=18; IGF-2, n=17; IGFBP-2, n=15; IGFBP-3, n=18

[8] - IGF-1, n=34; IGF-2, n=35; IGFBP-2, n=32; IGFBP-3, n=34

[9] - IGF-1, n=42; IGF-2, n=40; IGFBP-2, n=34; IGFBP-3, n=42

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected until 30 days after last subject visit or until resolution (up to approximately 13 months overall).	
Adverse event reporting additional description:	
All subjects initially randomised to receive 40 µg/kg rhIGF-1 BID were analysed together, regardless of actual dose received.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Untreated Control
Reporting group description:	
Subjects were randomised to the untreated control group and did not receive any investigational medical product for the duration of the 1 year study period.	
Reporting group title	40 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were initially randomised to receive 40 µg/kg rhIGF-1 BID. Following a protocol amendment, subjects in this arm who had not already completed the study at this dose were reassigned to receive 120 µg/kg rhIGF-1 BID for the remainder of the 1 year study period.	
Reporting group title	80 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 80 µg/kg rhIGF-1 BID and received this dose for the duration of the 1 year study period.	
Reporting group title	120 µg/kg rhIGF-1 BID
Reporting group description:	
Subjects were randomised to receive 120 µg/kg rhIGF-1 BID for the duration of the 1 year study period.	

Serious adverse events	Untreated Control	40 µg/kg rhIGF-1 BID	80 µg/kg rhIGF-1 BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	1 / 16 (6.25%)	2 / 44 (4.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Cor triatriatum			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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
Nervous system disorders			
Benign intracranial hypertension			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (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 escherichia coli			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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

Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (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

Serious adverse events	120 µg/kg rhIGF-1 BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Cor triatriatum			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis escherichia coli			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypoglycaemic seizure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Untreated Control	40 µg/kg rhIGF-1 BID	80 µg/kg rhIGF-1 BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	16 / 16 (100.00%)	40 / 44 (90.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Dysplastic Naevus Syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Melanocytic Naevus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Orthodontic Procedure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	0 / 25 (0.00%)	3 / 16 (18.75%)	6 / 44 (13.64%)
occurrences (all)	0	3	10
Injection site pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	7 / 44 (15.91%)
occurrences (all)	0	2	7
Chest Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Feeling Abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0

) H H O LHOD LS&E 5 R U + V X 1 0 0 1 0 0 cm 1 w 0 J 0 0 0 RG Π 0 d 54 128 m 54 18 l S Π0 d 2 J 1 0 0 1 0 0 cm 1 0 0 1 0 0 cm 1 w 0 J 0 0 0 RG Π 0

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	2
Flank Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Influenza Like Illness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Injection Site Erythema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	4 / 44 (9.09%)
occurrences (all)	0	0	4
Injection Site Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Injection Site Haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Injection Site Hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	2 / 44 (4.55%)
occurrences (all)	0	3	2
Injection Site Irritation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Injection Site Rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	4
Injection Site Reaction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Injection Site Swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Injection Site Urticaria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Irritability			

subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	4 / 25 (16.00%)	2 / 16 (12.50%)	11 / 44 (25.00%)
occurrences (all)	6	5	15
Immune system disorders			
Drug Eruption			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Multiple Allergies			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Seasonal Allergy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	2 / 44 (4.55%)
occurrences (all)	0	1	2
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Precocious Puberty			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 25 (16.00%)	4 / 16 (25.00%)	10 / 44 (22.73%)
occurrences (all)	7	6	16
Nasal Congestion			
subjects affected / exposed	0 / 25 (0.00%)	4 / 16 (25.00%)	5 / 44 (11.36%)
occurrences (all)	0	5	6
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	3 / 16 (18.75%)	4 / 44 (9.09%)
occurrences (all)	0	3	4
Adenoidal Hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Allergic Respiratory Symptom			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Asthma			
subjects affected / exposed	2 / 25 (8.00%)	2 / 16 (12.50%)	0 / 44 (0.00%)
occurrences (all)	3	3	0
Bronchial Hyperreactivity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Dyspnoea Exertional			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Productive Cough			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Pulmonary Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Rhinitis Allergic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	1	0	2

Rhinitis Seasonal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	4
Sinus Congestion			
subjects affected / exposed	1 / 25 (4.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	1	6	0
Snoring			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Tonsillar Hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Upper Respiratory Tract Congestion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	2 / 44 (4.55%)
occurrences (all)	0	1	5
Wheezing			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Mental Status Changes			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Investigations			
Blood Glucose Decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Blood Glucose Increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Body Temperature Increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Eosinophil Count Increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Heart Rate Irregular			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Accidental Poisoning			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Arthropod Bite			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Clavicle Fracture			

subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Concussion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Excoriation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Foreign Body Trauma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Head Injury			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Heat Exhaustion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Joint Injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Joint Sprain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Post Procedural Discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Procedural Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Skin Laceration			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Thermal Burn			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tooth Fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Upper Limb Fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Wrist Fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 25 (16.00%)	8 / 16 (50.00%)	13 / 44 (29.55%)
occurrences (all)	9	16	30
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Migraine			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tension Headache			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	4	0
Tremor			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	1 / 25 (4.00%)	3 / 16 (18.75%)	0 / 44 (0.00%)
occurrences (all)	1	3	0
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Ear pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 16 (6.25%)	3 / 44 (6.82%)
occurrences (all)	2	1	3
Ear Congestion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Hypoacusis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Middle Ear Effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Hypermetropia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pseudopapilloedema			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Superficial Injury Of Eye			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	4 / 16 (25.00%)	6 / 44 (13.64%)
occurrences (all)	0	5	7
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	3 / 16 (18.75%)	4 / 44 (9.09%)
occurrences (all)	0	4	7
Abdominal Discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Abdominal Pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	2 / 44 (4.55%)
occurrences (all)	0	2	3
Abdominal Pain Upper			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	1 / 44 (2.27%)
occurrences (all)	0	2	1
Breath Odour			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Chapped Lips			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	2	0

Dyspepsia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Gastritis			
subjects affected / exposed	0 / 25 (0.00%)	4 / 16 (25.00%)	4 / 44 (9.09%)
occurrences (all)	0	4	4
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Gingival Hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Inguinal Hernia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Mouth Ulceration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Procedural Nausea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Stomach Discomfort			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	5 / 16 (31.25%)	9 / 44 (20.45%)
occurrences (all)	1	6	17
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Blister			

subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Dermatitis Allergic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	3
Dermatitis Contact			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	3 / 44 (6.82%)
occurrences (all)	1	0	3
Eczema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Hair Texture Abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Hyperkeratosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Lip Blister			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Lip Swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Pityriasis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pruritus			

subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	0	0	2
Rash Generalised			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rash Macular			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rash Papular			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Rash Pruritic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Skin Exfoliation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Skin Hypopigmentation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	3 / 44 (6.82%)
occurrences (all)	0	1	3
Varicella			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0

Urinary Tract Infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 25 (4.00%)	1 / 16 (6.25%)	3 / 44 (6.82%)
occurrences (all)	1	1	5
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	1 / 44 (2.27%)
occurrences (all)	0	1	2
Back Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tendon Disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 25 (24.00%)	3 / 16 (18.75%)	10 / 44 (22.73%)
occurrences (all)	7	5	17
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	2 / 16 (12.50%)	5 / 44 (11.36%)
occurrences (all)	3	3	5
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	3 / 16 (18.75%)	8 / 44 (18.18%)
occurrences (all)	0	4	10
Pharyngitis streptococcal			

subjects affected / exposed	2 / 25 (8.00%)	1 / 16 (6.25%)	4 / 44 (9.09%)
occurrences (all)	2	1	6
Influenza			
subjects affected / exposed	1 / 25 (4.00%)	1 / 16 (6.25%)	4 / 44 (9.09%)
occurrences (all)	1	1	7
Otitis media			
subjects affected / exposed	3 / 25 (12.00%)	3 / 16 (18.75%)	2 / 44 (4.55%)
occurrences (all)	3	3	3
Sinusitis			
subjects affected / exposed	3 / 25 (12.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	4	0	1
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 16 (12.50%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Cellulitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	2	0	0
Croup Infectious			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Ear Infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	1	0	3
Hordeolum			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Labyrinthitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Molluscum Contagiosum			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	1	0	2
Oral Herpes			

subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Otitis Externa			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	3	0	0
Otitis Media Acute			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 16 (6.25%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	3 / 44 (6.82%)
occurrences (all)	0	0	7
Rotavirus Infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Skin Papilloma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Staphylococcal Skin Infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Tinea Infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tooth Abscess			
subjects affected / exposed	2 / 25 (8.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	2	0	0
Viral Infection			

subjects affected / exposed	2 / 25 (8.00%)	1 / 16 (6.25%)	2 / 44 (4.55%)
occurrences (all)	2	1	2
Viral Upper Respiratory Tract			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 16 (12.50%)	3 / 44 (6.82%)
occurrences (all)	1	4	3
Anorexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	3
Decreased Appetite			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	2 / 44 (4.55%)
occurrences (all)	1	0	3
Hyperlipidaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Increased Appetite			
subjects affected / exposed	0 / 25 (0.00%)	0 / 16 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Lactose Intolerance			
subjects affected / exposed	1 / 25 (4.00%)	0 / 16 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	120 µg/kg rhIGF-1 BID		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	50 / 51 (98.04%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Dysplastic Naevus Syndrome			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Melanocytic Naevus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Orthodontic Procedure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	7		
Injection site pain			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Chest Pain			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Feeling Abnormal			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Feeling Hot			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Flank Pain			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Influenza Like Illness			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Injection Site Erythema			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injection Site Haematoma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injection Site Haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injection Site Hypertrophy			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Injection Site Irritation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injection Site Rash			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Injection Site Reaction			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	19		
Injection Site Swelling			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injection Site Urticaria			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Malaise			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	13 / 51 (25.49%)		
occurrences (all)	18		
Immune system disorders			
Drug Eruption			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Multiple Allergies			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Seasonal Allergy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Precocious Puberty			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	7		
Nasal Congestion			

subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	7		
Pharyngolaryngeal pain			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Adenoidal Hypertrophy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Allergic Respiratory Symptom			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Bronchial Hyperreactivity			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dyspnoea Exertional			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Productive Cough			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Pulmonary Hypertension			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rhinitis Allergic			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Rhinitis Seasonal			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	3		
Sinus Congestion			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Snoring			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Tonsillar Hypertrophy			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Upper Respiratory Tract Congestion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Psychiatric disorders			
Anger			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Disturbance in attention			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Mental Status Changes			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Nervousness			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Investigations			
Blood Glucose Decreased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Blood Glucose Increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Body Temperature Increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Eosinophil Count Increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Heart Rate Irregular			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Accidental Poisoning			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Arthropod Bite			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Clavicle Fracture			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Concussion			

subjects affected / exposed	0 / 51 (0.00%)			
occurrences (all)	0			
Contusion				
subjects affected / exposed	3 / 51 (5.88%)			
occurrences (all)	3			
Excoriation				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences (all)				

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Tooth Fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Upper Limb Fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Wrist Fracture			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 51 (41.18%)		
occurrences (all)	35		
Dizziness			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hypoaesthesia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tension Headache			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	8		
Ear pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Ear Congestion			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Middle Ear Effusion			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Eye disorders			
Hypermetropia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pseudopapilloedema			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Superficial Injury Of Eye			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Abdominal Discomfort			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Abdominal Pain			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	12		
Breath Odour			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Chapped Lips			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		

Gastritis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Gingival Hypertrophy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Inguinal Hernia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Mouth Ulceration			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Procedural Nausea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Stomach Discomfort			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	21		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blister			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Dermatitis Allergic			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dermatitis Contact			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hair Texture Abnormal			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Hyperkeratosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lip Blister			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lip Swelling			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Pityriasis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Pityriasis Rosea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Rash			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Rash Generalised			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rash Macular			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Rash Papular			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Rash Pruritic			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin Exfoliation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Skin Hypopigmentation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Urinary Tract Infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Back Pain			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		
Tendon Disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 51 (23.53%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	12		
Gastroenteritis viral			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Pharyngitis streptococcal			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	9		
Influenza			

subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	10		
Otitis media			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Sinusitis			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	8		
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Croup Infectious			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Ear Infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Labyrinthitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Molluscum Contagiosum			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Oral Herpes			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Otitis Externa			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Otitis Media Acute			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Rotavirus Infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Skin Papilloma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Staphylococcal Skin Infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Tinea Infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tooth Abscess			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Viral Infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Viral Upper Respiratory Tract			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	10		
Anorexia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Decreased Appetite			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Increased Appetite			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Lactose Intolerance			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2004	Change in randomisation ratio, number of arms, and dose levels. Subjects were randomised in a 2:3:3 ratio to the untreated control arm or to one of two rhIGF-1 treatment arms at two dose levels: subcutaneous injections BID at 40 or 80 µg/kg body weight. The randomisation ratio was changed to enhance the power of the test. Anthropometry (hand, foot, and jaw lengths) was added to the safety endpoints to detect acromegalic growth. Dose adjustments were revised to allow up-titration of doses to the new specified doses.Certain exclusion criterion were updated and timing of blood draws revised.
15 July 2004	Other sponsor-approved stimulants were allowed in addition to arginine-clonidine GH stimulation tests. Visits 3 and 4 could be combined if all eligibility criteria were met prior to Visit 3. The rhIGF-1 dosing instructions were changed to instruct the subject to eat a meal within 30 minutes of the injection, either before or after.
01 December 2004	Age range was expanded from 4-10 to 3-10 years for girls, and from 4-11 to 3-11 years for boys.
10 November 2005	Dose levels were increased from 40 or 80 µg/kg body weight BID to 80 or 120 µg/kg body weight BID. In addition, subjects who were already assigned to a BID of 40µg/kg body weight, prior to Amendment 4, were reassigned to a BID dose of 120 µg/kg body weight. Dose adjustments were also revised. Funduscopic examination was added to safety endpoints.

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.

Following a protocol amendment on 10 November 2005 subjects assigned to 40 µg/kg rhIGF-1 BID arm were excluded from all efficacy analyses.

Notes: