Clinical trial results:
A 64-Week (12-week core phase and 52-week safety extension), Phase II, Multicenter, Randomized, Open Label Study to Evaluate the Safety, Tolerability and Efficacy of Weekly TV-1106 in Adults with Growth Hormone Deficiency

Summary

EudraCT number	2012-004975-37
Trial protocol	HU CZ SK GR SI DE SE
Global end of trial date	23 June 2015

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	14 July 2016

Trial information

Trial identification

Sponsor protocol code	TV1106-GHD-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01811576
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd.
Sponsor organisation address	5 Bazel St., Petach Tikva, Israel,
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, ustevatrials@tevapharm.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the clinical effect of weekly doses of Albutropin (TV-1106), as measured by the change from baseline in insulin-like growth factor 1 (IGF-I), in growth hormone deficient (GHD) adults following 12 weeks of treatment.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use).
Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2013
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	Israel: 1
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 21
Worldwide total number of subjects	52
EEA total number of subjects	46

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	49
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 93 patients with GHD were screened for enrollment into this study. Of the 93 patients screened, 52 patients at 16 centers in Europe, the Middle East and the US met entry criteria.

Pre-assignment

Screening details:

Of the 41 patients not enrolled, 32 were excluded due to inclusion/exclusion criteria, 3 withdrew consent, 2 were lost to follow-up before the baseline visit, 1 experienced an AE, and 3 were excluded for 'other' reasons. Eligible patients were randomized on a 4:1 basis to either albutropin or genotropin.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Albutropin

Arm description:

Patients began with a starting weekly dose of Albutropin based on the conversion calculations (previous daily rhGH dose ×28 ×0.6). Up or down titration was allowed based on the IGF-1 SDS obtained on day 7 of weeks 3, 6, and 9 with the goal for each patient to achieve an IGF-1 SDS by the time of trough level during
week 12 that was within ±0.5 SDS of the patient's pre-washout IGF-1 SDS and a Cmax IGF-1 SDS level during week 12 that was below +2.0 SDS. Doses increased or decreased by 2.8 mg if the current dose was < 15 mg, and adjusted by 5.8 mg otherwise.
At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin.

Arm type	Experimental
Investigational medicinal product name	Albutropin
Investigational medicinal product code	TV-1106
Other name	human serum albumin-human growth hormone (HSA-hGH)
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose and titration dose levels of Albutropin were up to 50 mg given as weekly subcutaneous (sc) injections in the formulation buffer. Doses in excess of 50 mg
were not allowed for titration and resulted in early termination. Except on in-clinic visit days, the patient was responsible for injections of the specified dose of Albutropin once weekly between 6:00 and 10:00 AM in the abdomen or thigh, rotating the site with each injection.
The starting Albutropin dose was 60% of the albutropin dose considered 'comparable' to the dose of rhGH previously administered.
Dose adjustments were accomplished using a titration algorithm based on IGF-1 levels evaluated by a central reader who directed the investigator in choosing the titration dose. Ultimately, the investigator was responsible for making the final decision regarding the dose administered.

Arm title	Genotropin

Arm description:

The initial dose of Genotropin was based on the previous daily rhGH dose in use prior to washout. Up and down titrations were performed at the same time points and according to the same algorithm as that described for Albutropin, using either 0.2 mg/day of the Genotropin if the current dose of Genotropin was greater than 0.5 mg/day or 0.1 mg/day if the current dose of Genotropin was less than or equal to 0.5 mg/day.

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of Genotropin.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	somatropin (rDNA origin), rhGH (recombinant human Growth Hormone)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients injected their specified dose of Genotropin once daily between 6:00 and 10:00 AM except on days of in-clinic visits when the dose was injected in the arm by a qualified site staff member after the planned activities were performed by the site staff. The dose levels available for achieving the appropriate final daily dose ranged from 0.2 mg to 1.8 mg and were administered using a variable, multi-dose injection device.

Number of subjects in period 1	Albutropin	Genotropin
Started	41	11
Completed	41	11

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Albutropin

Arm description:

At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin for an additional 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Albutropin
Investigational medicinal product code	TV-1106
Other name	human serum albumin-human growth hormone (HSA-hGH)
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose and titration dose levels of Albutropin were up to 50 mg given as weekly subcutaneous (sc) injections in the formulation buffer. Except on in-clinic visit days, the patient was responsible for injections of the specified dose of Albutropin once weekly between 6:00 and 10:00 AM in the abdomen or thigh, rotating the site with each injection.

Arm title	Genotropin

Arm description:

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of Genotropin for an additional 52 weeks.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	somatropin (rDNA origin), rhGH (recombinant human Growth Hormone)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients injected their specified dose of Genotropin once daily between 6:00 and 10:00 AM except on days of in-clinic visits when the dose was injected in the arm by a qualified site staff member after the planned activities were performed by the site staff. The dose levels available for achieving the appropriate final daily dose ranged from 0.2 mg to 1.8 mg and were administered using a variable, multi-dose injection device.

Number of subjects in period 2	Albutropin	Genotropin
Started	41	11
Completed	33	9
Not completed	8	2
Consent withdrawn by subject	4	1
Adverse event, non-fatal	1	1
Not specified	1	-
Lack of efficacy	1	-
Noncompliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Albutropin

Reporting group description:

Patients began with a starting weekly dose of Albutropin based on the conversion calculations (previous daily rhGH dose ×28 ×0.6). Up or down titration was allowed based on the IGF-1 SDS obtained on day 7 of weeks 3, 6, and 9 with the goal for each patient to achieve an IGF-1 SDS by the time of trough level during
week 12 that was within ±0.5 SDS of the patient's pre-washout IGF-1 SDS and a Cmax IGF-1 SDS level during week 12 that was below +2.0 SDS. Doses increased or decreased by 2.8 mg if the current dose was < 15 mg, and adjusted by 5.8 mg otherwise.
At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin.

Reporting group title	Genotropin

Reporting group description:

The initial dose of Genotropin was based on the previous daily rhGH dose in use prior to washout. Up and down titrations were performed at the same time points and according to the same algorithm as that described for Albutropin, using either 0.2 mg/day of the Genotropin if the current dose of Genotropin was greater than 0.5 mg/day or 0.1 mg/day if the current dose of Genotropin was less than or equal to 0.5 mg/day.

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of Genotropin.

Reporting group values	Albutropin	Genotropin	Total
Number of subjects	41	11	52
Age categorical Units: Subjects			
20 to <=40	16	4	20
>40 to <=60	18	6	24
>60	7	1	8
Age continuous Units: years			
arithmetic mean	45.9	44	
standard deviation	± 13.11	± 13.08	-
Gender categorical Units: Subjects			
Female	15	5	20
Male	26	6	32
Race Units: Subjects			
White	41	11	52
Not White	0	0	0
Ethnicity Units: Subjects			
Not Hispanic or Latino	41	11	52
Hispanic or Latino	0	0	0
Normal IGF SDS			
Range: -1.5 to 2.0			
Units: Subjects			
Yes	41	11	52
No	0	0	0

Weight			
Units: kg			
arithmetic mean	80.5	72.5	
standard deviation	± 17.42	± 19.04	-
Height			
Units: cm			
arithmetic mean	170.1	165.1	
standard deviation	± 11.38	± 10.94	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	27.6	26.3	
standard deviation	± 4.45	± 4.51	-
Insulin-like Growth Factor 1 (IGF-1)			
Units: ng/mL			
arithmetic mean	167.83	198.82	
standard deviation	± 50.563	± 42.211	-
IGF-1 Standard Deviation Score (SDS) Level			
Units: SDS level			
arithmetic mean	0.32	0.67	
standard deviation	± 0.622	± 0.593	-
Fasting blood glucose			
Units: mmol/L			
arithmetic mean	4.65	4.77	
standard deviation	± 0.429	± 0.39	-
Triiodothyronine			
Units: pmol/L			
arithmetic mean	1404.57	1490.91	
standard deviation	± 299.862	± 430.011	-
Triiodothyronine, Free			
Units: pmol/L			
arithmetic mean	15.64	15.56	
standard deviation	± 3.334	± 3.112	-
Thyroid stimulating hormones			
Units: mU/L			
arithmetic mean	0.27	0.79	
standard deviation	± 0.602	± 1.46	-
Cortisol, serum random			
Units: nmol/L			
arithmetic mean	317.74	311.6	
standard deviation	± 276.846	± 214.783	-

End points

End points reporting groups

Reporting group title	Albutropin

Reporting group description:

Patients began with a starting weekly dose of Albutropin based on the conversion calculations (previous daily rhGH dose ×28 ×0.6). Up or down titration was allowed based on the IGF-1 SDS obtained on day 7 of weeks 3, 6, and 9 with the goal for each patient to achieve an IGF-1 SDS by the time of trough level during
week 12 that was within ±0.5 SDS of the patient's pre-washout IGF-1 SDS and a Cmax IGF-1 SDS level during week 12 that was below +2.0 SDS. Doses increased or decreased by 2.8 mg if the current dose was < 15 mg, and adjusted by 5.8 mg otherwise.
At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin.

Reporting group title	Genotropin

Reporting group description:

The initial dose of Genotropin was based on the previous daily rhGH dose in use prior to washout. Up and down titrations were performed at the same time points and according to the same algorithm as that described for Albutropin, using either 0.2 mg/day of the Genotropin if the current dose of Genotropin was greater than 0.5 mg/day or 0.1 mg/day if the current dose of Genotropin was less than or equal to 0.5 mg/day.

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of Genotropin.

Reporting group title	Albutropin

Reporting group description:

At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin for an additional 52 weeks.

Reporting group title	Genotropin

Reporting group description:

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of Genotropin for an additional 52 weeks.

Subject analysis set title	Albutropin: Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A paired t-test in Albutropin subjects to assess the magnitude of change from baseline to maximum IGF-1 SDS (Cmax) value during week 12. Baseline data are reported in this column.

Subject analysis set title	Albutropin: Cmax at Week 12
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A paired t-test in Albutropin subjects to assess the magnitude of change from baseline to maximum IGF-1 SDS (Cmax) value during week 12. IGF-1 SDS data at maximum concentration during Week 12 are reported in this column.

Primary: Insulin-Like Growth Factor 1 (IGF-1) Standard Deviation Score (SDS) at Baseline and Cmax Level During Week 12

End point title	Insulin-Like Growth Factor 1 (IGF-1) Standard Deviation Score (SDS) at Baseline and Cmax Level During Week 12

End point description:

The study hypotheses are defined as follows:
H0: μD = 0
H1: μD ≠ 0
Where μD = expected value of IGF-1 SDS difference (Cmax at week 12 - baseline) in Albutropin group.

Observed values are reported here. The statistical analysis was based on the within-subject change from baseline to Cmax during week 12.

End point type	Primary

End point timeframe:

Baseline (Day 0), Week 12; samples drawn between 6:00 and 10:00 AM prior to dosing on Days 0, 78, 79, 80, 81 and 84

End point values	Albutropin: Baseline	Albutropin: Cmax at Week 12		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	41		
Units: standard deviation score				
arithmetic mean (standard error)	-1.5 (± 0.14)	0.8 (± 0.12)		

Statistical analyses

Statistical analysis title	IGF-1 SDS Change Baseline to Cmax Week 12

Statistical analysis description:

The null hypothesis was tested based on a paired t – test with n-1 degrees of freedom, where n refers to the total number of subjects in the Albutropin group with baseline and Cmax at week 12.
n=41 since this is a within subject change.

Comparison groups	Albutropin: Baseline v Albutropin: Cmax at Week 12
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	t-test, 2-sided

Notes:

[1] - The significance level of the paired t-test was 5% (2-sided).

Secondary: Percentage of Patients Whose Week 12 Trough IGF-1 SDS Value Is Within +/- 0.5 of screening IGF-1 SDS Value and Cmax <+2.0

End point title	Percentage of Patients Whose Week 12 Trough IGF-1 SDS Value Is Within +/- 0.5 of screening IGF-1 SDS Value and Cmax <+2.0

End point description:

Percentage of patients who meet both conditions:
1) Week 12 trough IGF-1 SDS within +/- 0.5 of screening IGF-1 SDS
2) Cmax Level During Week 12 Is Below +2.0 SDS.

Both protocol and SAP document that 95% CI ranges will only be calculated for the Albutropin group. Values of 9999 indicate values were not calculated.

End point type	Secondary

End point timeframe:

Screening (Weeks -8 to -5), Week 12

End point values	Albutropin	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[2]	11[3]		
Units: percentage of patients				
number (confidence interval 95%)	37 (22.12 to 53.06)	36 (-9999 to 9999)		

Notes:

[2] - ITT

[3] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Adverse Events (AE)

End point title	Patients with Adverse Events (AE)

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relationship of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day 1 to Week 64

End point values	Albutropin	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[4]	11[5]		
Units: patients				
Any AE	26	5		
Severe AE	2	1		
Treatment-related AE	10	1		
Deaths	0	0		
Other serious AE	7	1		
Withdrawn from study due to AE	1	1		

Notes:

[4] - Safety

[5] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Endpoint in Lipid Profile

End point title	Change from Baseline to Endpoint in Lipid Profile

End point description:

Change from baseline to endpoint values are offered for total cholesterol, very-low-density lipoprotein

(VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Endpoint in this context is referring to the last observed, post-baseline value for each patient.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Endpoint (up to Week 64)

End point values	Albutropin	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[6]	11[7]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Total cholesterol	-0.1 (± 0.83)	0 (± 1.04)		
VLDL cholesterol	0 (± 0.2)	0 (± 0.28)		
LDL cholesterol	-0.1 (± 0.64)	-0.1 (± 0.81)		
HDL cholesterol	0 (± 0.24)	0 (± 0.23)		
Triglycerides	0 (± 0.88)	0 (± 0.6)		

Notes:

[6] - ITT

[7] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Treatment-Emergent Anti-drug Antibodies (ADA)

End point title	Patients with Treatment-Emergent Anti-drug Antibodies (ADA)

End point description:

The testing scheme for patients treated with Albutropin (TV-1106) was multi-tiered, with testing for inhibition by TV-1106, by human growth hormone (hGH), and by human serum albumin (HSA). Confirmed positive assays were titered and tested for neutralizing antibodies (NAbs). All patients treated with Genotropin were tested for anti- recombinant human growth hormone (anti-rhGH) ADA. Values of 9999 = not applicable

End point type	Secondary

End point timeframe:

Day 1 to Week 64

End point values	Albutropin	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[8]	11[9]		
Units: patients				
ADA response	13	0		
Anti-TV-1106 NAb response	1	9999		

Notes:

[8] - PK analysis set

[9] - PK analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 64

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Albutropin

Reporting group description:

Patients began with a starting weekly dose of Albutropin based on the conversion calculations (previous daily rhGH dose ×28 ×0.6). Up or down titration was allowed based on the IGF-1 SDS obtained on day 7 of weeks 3, 6, and 9 with the goal for each patient to achieve an IGF-1 SDS by the time of trough level during week 12 that was within ±0.5 SDS of the patient's pre-washout IGF-1 SDS and a Cmax IGF-1 SDS level during week 12 that was below +2.0 SDS. Doses increased or decreased by 2.8 mg if the current dose was < 15 mg, and adjusted by 5.8 mg otherwise.

At the end of week 12, patients were expected to continue into the extension phase on their current dose of weekly Albutropin.

Reporting group title	Genotropin

Reporting group description:

The initial dose of Genotropin was based on the previous daily rhGH dose in use prior to washout. Up and down titrations were performed at the same time points and according to the same algorithm as that described for TV-1106, using either 0.2 mg/day of the Genotropin if the current dose of Genotropin was greater than 0.5 mg/day or 0.1 mg/day if the current dose of Genotropin was less than or equal to 0.5 mg/day.

At the end of week 12, patients were expected to continue into the extension phase on their current daily dose of genotropin.

Serious adverse events	Albutropin	Genotropin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 41 (17.07%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Neutralising antibodies positive			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod bite			

subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis contact			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 41 (2.44%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Albutropin	Genotropin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 41 (36.59%)	5 / 11 (45.45%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 41 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 41 (2.44%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injection site atrophy			
subjects affected / exposed	4 / 41 (9.76%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	3 / 41 (7.32%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Osteoarthritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Arthralgia			

subjects affected / exposed	3 / 41 (7.32%)	0 / 11 (0.00%)	
occurrences (all)	8	0	
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 41 (9.76%)	1 / 11 (9.09%)	
occurrences (all)	5	1	
Conjunctivitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 41 (7.32%)	0 / 11 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2013	Amendment 1 (dated 04 March 2013) to the protocol was issued before any patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: Added monitoring procedures (MRI/CT imaging) Clarified the inclusion/exclusion criteria Clarified the study design Clarified study drug dosing
21 July 2013	Amendment 2 (dated 21 July 2013) to the protocol was issued before any patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: Modified inclusion criterion d: the intent of inclusion criterion d was to establish that patients with GHD had been receiving stable rhGH therapy. However, patients with GHD that had been clinically stable over an extended period of time may have had infrequent monitoring of their IGF-1 levels, and still have been an appropriate clinical candidate for the study. Therefore, clarification of this criterion was necessary to reduce patient burden in terms of time and inconvenience of additional blood draws, as well as to clarify to investigators how to proceed with patients with long standing GHD in whom frequent monitoring was not indicated. Modified / amended exclusion criteria Electrocardiography was modified so that the methodology of ECG collection could support further development work for QT analysis. Digital ECGs with a central reader were used for the core phase of the study. For the safety extension phase, traditional ECGs were performed with investigator interpretation. Lipid profile was changed from a secondary endpoint to a safety endpoint . Clarified that the MRI/CT scan should have been performed prior to baseline (visit 3) so that the results could have been obtained prior to the baseline visit, in which the first dose of study drug was administered.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported