Clinical trial results:
A Phase 2, Randomized, Open-Label, Safety and Dose-Finding Study Comparing 3 Different Doses of Weekly TV-1106 and Daily Recombinant Human Growth Hormone (Genotropin®) Therapy in Treatment-Naive, Pre-Pubertal, Growth Hormone-Deficient Children

Summary

EudraCT number	2013-004468-69
Trial protocol	HU CZ RO GR BG ES PL
Global end of trial date	29 April 2016

Results information

Result version number	v1 (current)
This version publication date	16 November 2016
First version publication date	16 November 2016

Trial information

Trial identification

Sponsor protocol code	TV1106-IMM-20001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02092077
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd.
Sponsor organisation address	5 Bazel Street, Petach Tikva, Israel,
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, info.era-clinical@teva.de

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	25 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the safety and tolerability of 3 different weekly doses of TV-1106 and a daily dose of Genotropin® in paediatric patients.

EARLY TERMINATION: the Sponsor Teva Pharmaceuticals Ltd. reassessed the benefit/risk balance of TV-1106 and the likelihood of regulatory success for TV-1106. As a consequence of this reassessment, the Sponsor took the decision to terminate the development of TV-1106 and stop all ongoing clinical trials. Notably, no new safety issues were identified with the administration of TV-1106.

Protection of trial subjects:

This study was conducted in full accordance with the International Council for 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 11, 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 good clinical practice 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 and parent(s) or other legally acceptable representative(s) in a language understandable by the patients and parent(s) or other legally acceptable representative(s). 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 parent(s) or other legally acceptable representative(s) and an oral or signed and dated (where applicable) assent form was obtained from each applicable minor patient before any study procedures or assessments were done. It was explained to the patients and parent(s) or other legally acceptable representative(s) 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 investigator kept the original consent and assent forms, and copies were given to the patients/parent(s)/other legally acceptable representative(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2014
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	Poland: 1
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Hungary: 1

Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	Georgia: 5
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 14
Worldwide total number of subjects	65
EEA total number of subjects	8

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 148 pediatric patients with isolated idiopathic GH insufficiency, GH insufficiency as part of multiple pituitary hormone deficiencies, or organic GH insufficiency (eg, due to pituitary tumor, pituitary or brain surgery, intracranial radiation therapy) were screened for enrollment into this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TV-1106 0.554 mg/kg/week

Arm description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Arm type	Experimental
Investigational medicinal product name	TV-1106
Investigational medicinal product code	
Other name	long-acting growth hormone
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All patients randomized to any one of the TV 1106 treatment arms began with a dose of 0.554 mg/kg/week. Two weeks after this initial dose, the patients who were assigned to the 0.554 mg/kg/week dose group continued on that dose for the remainder of the core period of the study. The remaining patients randomized to TV 1106 received the next higher dose, 0.924 mg/kg/week, for the next 2 weeks. After completing 2 weeks at this dose (4 weeks since beginning treatment), the patients assigned to the 0.924 mg/kg/week dose group continued on that dose until the end of the core period, and the patients assigned to the 1.20 mg/kg/week dose group began taking 1.20 mg/kg/week and continued with that dose until the end of the core period (6 months total).
Patients who continued into the core extension period of the study for an additional 6 months and the later 12 month safety period continued on the same treatment and dose of TV-1106. Adjustments could be made as agreed by DMC and sponsor.

Arm title	TV-1106 0.924 mg/kg/week

Arm description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks and then titrated up to 0.924 mg/kg/week for 5.5 months
(core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Arm type	Experimental
Investigational medicinal product name	TV-1106
Investigational medicinal product code	
Other name	long-acting growth hormone
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All patients randomized to any one of the TV 1106 treatment arms began with a dose of 0.554 mg/kg/week. Two weeks after this initial dose, the patients who were assigned to the 0.554 mg/kg/week dose group continued on that dose for the remainder of the core period of the study. The remaining patients randomized to TV 1106 received the next higher dose, 0.924 mg/kg/week, for the next 2 weeks. After completing 2 weeks at this dose (4 weeks since beginning treatment), the patients assigned to the 0.924 mg/kg/week dose group continued on that dose until the end of the core period, and the patients assigned to the 1.20 mg/kg/week dose group began taking 1.20 mg/kg/week and continued with that dose until the end of the core period (6 months total).
Patients who continued into the core extension period of the study for an additional 6 months and the later 12 month safety period continued on the same treatment and dose of TV-1106. Adjustments could be made as agreed by DMC and sponsor.

Arm title	TV-1106 1.2 mg/kg/week

Arm description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks, followed by TV-1106 0.924 mg/kg/week for study weeks 3-4, followed by the assigned dose of TV-1106 1.2 mg/kg/week for 5 months (core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Arm type	Experimental
Investigational medicinal product name	TV-1106
Investigational medicinal product code	
Other name	long-acting growth hormone
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All patients randomized to any one of the TV 1106 treatment arms began with a dose of 0.554 mg/kg/week. Two weeks after this initial dose, the patients who were assigned to the 0.554 mg/kg/week dose group continued on that dose for the remainder of the core period of the study. The remaining patients randomized to TV 1106 received the next higher dose, 0.924 mg/kg/week, for the next 2 weeks. After completing 2 weeks at this dose (4 weeks since beginning treatment), the patients assigned to the 0.924 mg/kg/week dose group continued on that dose until the end of the core period, and the patients assigned to the 1.20 mg/kg/week dose group began taking 1.20 mg/kg/week and continued with that dose until the end of the core period (6 months total).
Patients who continued into the core extension period of the study for an additional 6 months and the later 12 month safety period continued on the same treatment and dose of TV-1106. Adjustments could be made as agreed by DMC and sponsor.

Arm title	Genotropin 0.033 mg/kg/day

Arm description:

Participants were administered genotropin subcutaneously at a dosage of 0.033 mg/kg/day for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were made for safety reasons (e.g. dose decrease if the IGF-1 SDS for 2 consecutive peak IGF-1 levels exceeded +2.5 SDS), or as agreed by the DMC and sponsor.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	rhGH, recombinant human growth hormone
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A subcutaneous dose of 0.033 mg/kg/day for GENOTROPIN was chosen because it is the standard GENOTROPIN dose for the age of patients included. Injections were given in the evening at bedtime (between 1800 and 2200), except on days of in clinic visits when injections were given as part of the study procedures.

Number of subjects in period 1	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week
Started	16	15	17
Safety Analysis Set	16	15	17
Completed	0	0	0
Not completed	16	15	17
primarily termination of study	11	13	12
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	3	2	3
Lost to follow-up	1	-	-
Lack of efficacy	1	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Genotropin 0.033 mg/kg/day
Started	17
Safety Analysis Set	16
Completed	0
Not completed	17
primarily termination of study	15
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Lost to follow-up	-
Lack of efficacy	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	TV-1106 0.554 mg/kg/week
Reporting group description:	
Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.	
Reporting group title	TV-1106 0.924 mg/kg/week
Reporting group description:	
Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks and then titrated up to 0.924 mg/kg/week for 5.5 months (core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.	
Reporting group title	TV-1106 1.2 mg/kg/week
Reporting group description:	
Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks, followed by TV-1106 0.924 mg/kg/week for study weeks 3-4, followed by the assigned dose of TV-1106 1.2 mg/kg/week for 5 months (core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.	
Reporting group title	Genotropin 0.033 mg/kg/day
Reporting group description:	
Participants were administered genotropin subcutaneously at a dosage of 0.033 mg/kg/day for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were made for safety reasons (e.g. dose decrease if the IGF-1 SDS for 2 consecutive peak IGF-1 levels exceeded +2.5 SDS), or as agreed by the DMC and sponsor.	

Reporting group values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week
Number of subjects	16	15	17
Age categorical Units: Subjects			
<7 years	9	10	9
>=7 years	7	5	8
Age continuous Units: years			
arithmetic mean	6.1	5.8	6.5
standard deviation	± 2.47	± 1.9	± 2.1
Gender categorical Units: Subjects			
Female	9	7	6
Male	7	8	11
Race Units: Subjects			
White	16	15	16
Other	0	0	1
Body Mass Index Units: kg/m^2			
arithmetic mean	15.8	15.8	15.6
standard deviation	± 1.67	± 1.4	± 1.97

Gestation Age			
Units: weeks			
arithmetic mean	39.4	39.1	38.2
standard deviation	± 1.37	± 0.53	± 2.11
Birth weight			
Units: kg			
arithmetic mean	3.3	3.2	3
standard deviation	± 0.4	± 0.34	± 0.66
Birth height			
Units: cm			
arithmetic mean	51.2	50.5	49.8
standard deviation	± 1.97	± 1.68	± 2.7
Height standard deviation score			
H-SDS			
Units: standard deviations			
arithmetic mean	-3.1	-3.1	-3.2
standard deviation	± 0.81	± 0.99	± 1.04
Height velocity			
Units: cm/year			
arithmetic mean	3.5	3.5	3.7
standard deviation	± 1.73	± 1.7	± 2.75
Height velocity standard deviation score			
Units: standard deviation			
arithmetic mean	-2.7	-3	-2.3
standard deviation	± 1.85	± 1.62	± 3.12
Insulin-like growth factor-1 standard deviation score			
IGF-1-SDS			
Units: standard deviation			
arithmetic mean	-2.1	-1.7	-1.7
standard deviation	± 0.87	± 0.73	± 0.8

Reporting group values	Genotropin 0.033 mg/kg/day	Total	
Number of subjects	17	65	
Age categorical			
Units: Subjects			
<7 years	9	37	
>=7 years	8	28	
Age continuous			
Units: years			
arithmetic mean	6.4		
standard deviation	± 2.57	-	
Gender categorical			
Units: Subjects			
Female	4	26	
Male	13	39	
Race			
Units: Subjects			
White	17	64	
Other	0	1	

Body Mass Index Units: kg/m^2 arithmetic mean standard deviation	 15.8 ± 1.39	 -	
Gestation Age Units: weeks arithmetic mean standard deviation	 38.8 ± 1.23	 -	
Birth weight Units: kg arithmetic mean standard deviation	 3.2 ± 0.56	 -	
Birth height Units: cm arithmetic mean standard deviation	 50.7 ± 2.85	 -	
Height standard deviation score			
H-SDS			
Units: standard deviations arithmetic mean standard deviation	 -3.3 ± 0.75	 -	
Height velocity Units: cm/year arithmetic mean standard deviation	 3.6 ± 1.2	 -	
Height velocity standard deviation score Units: standard deviation arithmetic mean standard deviation	 -2.5 ± 1.25	 -	
Insulin-like growth factor-1 standard deviation score			
IGF-1-SDS			
Units: standard deviation arithmetic mean standard deviation	 -1.7 ± 0.99	 -	

End points

End points reporting groups

Reporting group title	TV-1106 0.554 mg/kg/week

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	TV-1106 0.924 mg/kg/week

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks and then titrated up to 0.924 mg/kg/week for 5.5 months
(core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	TV-1106 1.2 mg/kg/week

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks, followed by TV-1106 0.924 mg/kg/week for study weeks 3-4, followed by the assigned dose of TV-1106 1.2 mg/kg/week for 5 months (core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	Genotropin 0.033 mg/kg/day

Reporting group description:

Participants were administered genotropin subcutaneously at a dosage of 0.033 mg/kg/day for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were made for safety reasons (e.g. dose decrease if the IGF-1 SDS for 2 consecutive peak IGF-1 levels exceeded +2.5 SDS), or as agreed by the DMC and sponsor.

Primary: Height Velocity (HV) At Baseline and After 6 Months of Treatment

End point title	Height Velocity (HV) At Baseline and After 6 Months of Treatment[1]

End point description:

Height measurements were performed as follows: the patient was measured standing without shoes with head, shoulders, buttocks, and heels in contact with the vertical surface of the wall mounted stadiometer and the back as straight as possible. With the child looking straight ahead, the head projection of the stadiometer was placed at the crown of the head. At each determination, the measurement was performed in triplicate by the same person, and the 3 measurements were recorded.
HV at baseline computed as [(mean height at baseline - mean height at pre-study measurement)/interval (baseline - pre-study measurement)] *365.25
HV at 6 months computed as [(mean height at study visit - mean height at baseline)/interval (study visit - baseline)]*365.25

End point type	Primary

End point timeframe:

Pre-study (-6 weeks), Baseline (Day 1), Month 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the early termination of the study, no paediatric patients completed the study according to the protocol; thus limited efficacy analyses were completed and no conclusions can be drawn from these data. Thus no statistical analyses were performed.

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[2]	15[3]	16[4]	17[5]
Units: cm/year				
arithmetic mean (standard deviation)				
Baseline (n=16, 15, 16, 17)	3.5 (± 1.73)	3.5 (± 1.7)	3.7 (± 2.75)	3.6 (± 1.2)
Month 6 (n=13, 12, 12, 15)	11 (± 3.34)	12.8 (± 3.23)	16 (± 5.02)	13.4 (± 3.98)

Notes:

[2] - Randomized patients (ITT) with data at the timepoint.

[3] - Randomized patients (ITT) with data at the timepoint.

[4] - Randomized patients (ITT) with data at the timepoint.

[5] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Height Velocity After 12 Months of Treatment

End point title	Height Velocity After 12 Months of Treatment

End point description:

Height measurements were performed as follows: the patient was measured standing without shoes with head, shoulders, buttocks, and heels in contact with the vertical surface of the wall mounted stadiometer and the back as straight as possible. With the child looking straight ahead, the head projection of the stadiometer was placed at the crown of the head. At each determination, themeasurement was performed in triplicate by the same person, and the 3 measurements were recorded.

HV at 12 months computed as [(mean height at study visit - mean height at baseline)/interval (study visit - baseline)]*365.25

End point type	Secondary

End point timeframe:

Baseline (Day 1), Month 12

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[6]	4[7]	7[8]	3[9]
Units: cm/year				
arithmetic mean (standard deviation)	8.1 (± 0)	10.8 (± 2.37)	11.9 (± 3.5)	8.6 (± 2.32)

Notes:

[6] - Randomized patients (ITT) with data at the timepoint.

[7] - Randomized patients (ITT) with data at the timepoint.

[8] - Randomized patients (ITT) with data at the timepoint.

[9] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Height Velocity Standard Deviation Score (HV-SDS) after 6 and 12

Months of Treatment

End point title	Height Velocity Standard Deviation Score (HV-SDS) after 6 and 12 Months of Treatment

End point description:

HV at 6 and 12 months was computed as [(mean height at study visit - mean height at baseline)/interval (study visit - baseline)]*365.25

HV-SDS was based on Swiss Growth Reference Standard by Prader et al. 1989.

End point type	Secondary

End point timeframe:

Months 6 and 12

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[10]	15[11]	17[12]	17[13]
Units: standard deviation score				
arithmetic mean (standard deviation)				
Month 6 (n=13, 12, 12, 15)	5.2 (± 4.08)	7.2 (± 3.08)	11.4 (± 5.9)	7.6 (± 4.4)
Month 12 (n=1, 4, 7, 3)	1.9 (± 0)	4.1 (± 1.77)	6.2 (± 4.14)	3.2 (± 2.07)

Notes:

[10] - Randomized patients (ITT) with data at the timepoint.

[11] - Randomized patients (ITT) with data at the timepoint.

[12] - Randomized patients (ITT) with data at the timepoint.

[13] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Height Standard Deviation Score (H-SDS) After 6 and 12 Months of Treatment

End point title	Change from Baseline in Height Standard Deviation Score (H-SDS) After 6 and 12 Months of Treatment

End point description:

Height measurements were performed as follows: the patient was measured standing without shoes with head, shoulders, buttocks, and heels in contact with the vertical surface of the wall mounted stadiometer and the back as straight as possible. With the child looking straight ahead, the head projection of the stadiometer was placed at the crown of the head. At each determination, the measurement was performed in triplicate by the same person, and the 3 measurements were recorded.

H-SDS was based on CDC (2000) Growth Charts by Kuczmarski RJ et. al.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Months 6 and 12

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[14]	15[15]	17[16]	17[17]
Units: standard deviation score				
arithmetic mean (standard deviation)				
Month 6 (n=13, 12, 12, 15)	0.6 (± 0.41)	0.8 (± 0.37)	1.1 (± 0.46)	0.9 (± 0.46)
Month 12 (n=1, 4, 7, 3)	0.4 (± 0)	1 (± 0.55)	1.3 (± 0.58)	0.8 (± 0.37)

Notes:

[14] - Randomized patients (ITT) with data at the timepoint.

[15] - Randomized patients (ITT) with data at the timepoint.

[16] - Randomized patients (ITT) with data at the timepoint.

[17] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Adverse Events

End point title	Participants with Adverse Events

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 84

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[18]	15[19]	17[20]	16[21]
Units: participants				
>=1 adverse event	11	12	11	8
Severe adverse event	2	0	2	0
Treatment-related adverse event	7	8	9	2
Death	0	0	0	0
Other serious adverse event	0	1	0	1
Withdrawn from study due to adverse event	3	2	2	1

Notes:

[18] - Safety analysis population

[19] - Safety analysis population

[20] - Safety analysis population

[21] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Potentially Clinically Significant Abnormal Serum Chemistry, Hematology and Urinalysis Results

End point title	Participants with Potentially Clinically Significant Abnormal Serum Chemistry, Hematology and Urinalysis Results

End point description:

Significance criteria for parameters showing potentially clinically significant abnormal results are:
- Lactate Dehydrogenase High (U/L): >=3* upper limit of normal
- Hemoglobin Low Female (G/L): <=95
- Hemoglobin Low Male (G/L): <=115
- Hematocrit Low Male (1): <0.37
- Hematocrit Low Female (1): < 0.32
- Eosinophils//Leukocytes High (%): >=10.0
- Urine Ketones High: >=2 unit increase from baseline
- Urine Protein High: >=2 unit increase from baseline

End point type	Secondary

End point timeframe:

Day 1 to Week 84

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[22]	15[23]	17[24]	16[25]
Units: participants				
Lactate Dehydrogenase High	1	0	0	0
Hemoglobin Low Female	0	2	0	0
Hemoglobin Low Male	4	0	3	4
Hematocrit Low Male	5	1	5	5
Hematocrit Low Female	0	2	0	0
Eosinophils//Leukocytes High	1	4	2	0
Urine Ketones High	2	0	0	0
Urine Protein High	0	0	1	0

Notes:

[22] - Safety analysis population

[23] - Safety analysis population

[24] - Safety analysis population

[25] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Positive Anti-drug Antibodies (ADA) at Various Timepoints

End point title	Patients with Positive Anti-drug Antibodies (ADA) at Various Timepoints

End point description:

For TV-1106 randomized patients, blood samples for immunogenicity were taken on Day 7 after the last study drug administration, and prior to the next administration, to avoid interference of the treatment with the assay.

Counts indicate participants with positive ADA results.

Values of 999 = not applicable

End point type	Secondary

End point timeframe:

Week 2, Months 3, 6, 10, 12, 15, 18

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[26]	15[27]	17[28]	17[29]
Units: participants				
Week 2 (n=5, 3, 4, 13)	5	3	4	0
Month 3 (n=8, 9, 13, 11)	8	9	13	0
Month 6 (n=11, 7, 11, 12)	11	7	11	0
Month 10 (n=4, 5, 7, 1)	4	5	7	0
Month 12 (n=1, 1, 4, 2)	1	1	4	0
Month 15 (n=0, 1, 3, 0)	9999	1	3	9999
Month 18 (n=0, 0, 0, 1)	9999	9999	9999	0

Notes:

[26] - Randomized patients (ITT) with data at the timepoint.

[27] - Randomized patients (ITT) with data at the timepoint.

[28] - Randomized patients (ITT) with data at the timepoint.

[29] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Insulin-like Growth Factor-1 Standard Deviation Score (IGF-1 SDS) at Timepoints up to Month 12

End point title	Insulin-like Growth Factor-1 Standard Deviation Score (IGF-1 SDS) at Timepoints up to Month 12

End point description:

Peak IGF-I levels were collected on Day 3 following TV-1106 dose at Weeks 4, 6, 8, and Months 4, 5, and 8. Trough IGF-I levels were taken on Day 7 following TV 1106 dose at Week 2, Months 3, 6, 10, 12. For Genotropin®, samples were drawn at least 12 hours after the previous Genotropin® dose.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1) to Month 12

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[30]	15[31]	17[32]	17[33]
Units: standard deviation score				
arithmetic mean (standard deviation)				
Baseline (n=12, 12, 16, 16)	-2.1 (± 0.87)	-1.7 (± 0.73)	-1.7 (± 0.8)	-1.7 (± 0.99)
Week 2 (n=14, 13, 15, 8)	-2 (± 0.81)	-1.6 (± 0.92)	-1.4 (± 0.78)	-1.5 (± 1.09)
Week 4 (n=15, 14, 15, 14)	-0.3 (± 1.2)	0.5 (± 1.29)	0.5 (± 1.8)	-0.7 (± 1.27)
Week 6 (n=15, 14, 15, 13)	-0.9 (± 0.96)	0.6 (± 1.28)	0.8 (± 1.44)	-0.9 (± 1.28)
Week 8 (n=14, 13, 15, 13)	-0.5 (± 1.11)	0.8 (± 1.32)	0.9 (± 1.23)	-0.8 (± 1.11)
Month 3 (n=13, 13, 13, 15)	-1.5 (± 0.86)	-1.1 (± 0.95)	-1.1 (± 0.61)	-0.9 (± 1.21)
Month 4 (n=15, 14, 15, 14)	-0.1 (± 1.17)	0.4 (± 1.34)	0.6 (± 0.84)	-0.8 (± 0.8)
Month 5 (n=12, 14, 13, 14)	-0.5 (± 1.07)	0.3 (± 1.52)	0.5 (± 1.37)	-0.5 (± 1.35)
Month 6 (n=13, 11, 12, 14)	-1.8 (± 0.68)	-1.4 (± 0.49)	-1.3 (± 1.09)	-0.6 (± 1.42)
Month 8 (n=10, 9, 10, 11)	-0.5 (± 1.25)	0.8 (± 1.18)	1.3 (± 1.09)	-0.5 (± 1.8)
Month 10 (n=6, 7, 8, 8)	-1.4 (± 1.09)	-0.4 (± 1.53)	0.7 (± 1.6)	0.1 (± 2.34)
Month 12 (n=1, 4, 7, 3)	-0.3 (± 0)	-1.3 (± 0.94)	-1.5 (± 0.63)	-1.2 (± 1.72)

Notes:

[30] - Randomized patients (ITT) with data at the timepoint.

[31] - Randomized patients (ITT) with data at the timepoint.

[32] - Randomized patients (ITT) with data at the timepoint.

[33] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Peak Serum Concentration of TV-1106 at Week 4 and 6 and Month 15

End point title	Peak Serum Concentration of TV-1106 at Week 4 and 6 and Month 15

End point description:

Sampling times for peak serum concentrations of TV-1106 were taken approximately 72 hours (Day 3) after TV-1106 was administered. All pharmacokinetic (PK) blood samples were drawn during clinic visits at approximately the same time every morning between 6:00 and 10:00 AM (+ 4 hours).

Values of 9999 indicate 'not applicable'.

End point type	Other pre-specified

End point timeframe:

Weeks 4 and 6, Month 15

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[34]	15[35]	17[36]	0[37]
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4 (n=16, 14, 14, 0)	221.81 (± 277.96)	598.3 (± 767.06)	494.61 (± 679.31)	()
Week 6 (n=16, 15, 15, 0)	342.29 (± 483.26)	537.93 (± 648.46)	1351.53 (± 990.35)	()
Month 15 (n=0, 1, 3, 0)	9999 (± 9999)	50 (± 0)	1529.53 (± 1341.08)	()

Notes:

[34] - Randomized patients (ITT) with data at the timepoint.

[35] - Randomized patients (ITT) with data at the timepoint.

[36] - Randomized patients (ITT) with data at the timepoint.

[37] - Genotropin samples not collected at these timepoints.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Trough Serum Concentrations at Various Timepoints

End point title	Trough Serum Concentrations at Various Timepoints

End point description:

Sampling times for trough serum concentrations for TV-2206 were taken approximately 152 to 160 hours (Day 7) after the previous TV-1106 dose and prior to the next dose. Sample times for serum concentrations of Genotropin were at least 12 hours after the previous Genotropin® dose. All pharmacokinetic (PK) blood samples were drawn during clinic visits at approximately the same time every morning between 6:00 and 10:00 AM (+ 4 hours).

Values of 9999 indicate 'not applicable'.

End point type	Other pre-specified

End point timeframe:

Week 2, Months 3, 6, 12 and 18

End point values	TV-1106 0.554 mg/kg/week	TV-1106 0.924 mg/kg/week	TV-1106 1.2 mg/kg/week	Genotropin 0.033 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[38]	15[39]	17[40]	17[41]
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 2 (n=5, 3, 4, 13)	25 (± 26.63)	7.8 (± 2.66)	6.98 (± 1.56)	3.8 (± 8.22)
Month 3 (n=8, 9, 13,11)	33.18 (± 21.46)	35.28 (± 31.14)	27.38 (± 29.09)	1.37 (± 0.81)
Month 6 (n=11, 7, 11, 12)	55.92 (± 39.36)	34.04 (± 33.02)	164.95 (± 354.66)	0.9 (± 0.33)
Month 12 (n=1, 1, 4, 2)	33.2 (± 0)	19.6 (± 0)	36.43 (± 17.37)	1.89 (± 0.82)
Month 18 (n=0, 0, 0, 1)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	0.7 (± 0)

Notes:
[38] - Randomized patients (ITT) with data at the timepoint.
[39] - Randomized patients (ITT) with data at the timepoint.
[40] - Randomized patients (ITT) with data at the timepoint.
[41] - Randomized patients (ITT) with data at the timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 84

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	TV1106 0.554 mg/kg/week

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	TV1106 0.924 mg/kg/week

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks and then titrated up to 0.924 mg/kg/week for 5.5 months
(core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	TV1106 1.2 mg/kg/eek

Reporting group description:

Participants were administered TV-1106 subcutaneously at a dosage of 0.554 mg/kg/week for 2 weeks, followed by TV-1106 0.924 mg/kg/week for study weeks 3-4, followed by the assigned dose of TV-1106 1.2 mg/kg/week for 5 months (core period), and remained at the assigned dose for an additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were allowed for low HV and/or new information showing clear benefit or risk of any specific dosage.

Reporting group title	Genotropin

Reporting group description:

Participants were administered genotropin subcutaneously at a dosage of 0.033 mg/kg/day for 6 months (core period), and additional 6 months (core extension period), and a 12 month safety period. Dose adjustments were made for safety reasons (e.g. dose decrease if the IGF-1 SDS for 2 consecutive peak IGF-1 levels exceeded +2.5 SDS), or as agreed by the DMC and sponsor.

Serious adverse events	TV1106 0.554 mg/kg/week	TV1106 0.924 mg/kg/week	TV1106 1.2 mg/kg/eek
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (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

Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (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

Serious adverse events	Genotropin		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	TV1106 0.554 mg/kg/week	TV1106 0.924 mg/kg/week	TV1106 1.2 mg/kg/eek
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)	12 / 15 (80.00%)	11 / 17 (64.71%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Injection site erythema			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	2 / 17 (11.76%)
occurrences (all)	16	18	12
Injection site pruritus			

subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 17 (5.88%)
occurrences (all)	1	8	3
Injection site swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	2 / 17 (11.76%)
occurrences (all)	0	3	5
Injection site warmth			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 17 (5.88%)
occurrences (all)	0	11	1
Injection site hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	2 / 17 (11.76%)
occurrences (all)	1	1	3
Irritability			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Asthma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Psychiatric disorders			
Fear of injection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Investigations			

Drug specific antibody present			
subjects affected / exposed	2 / 16 (12.50%)	5 / 15 (33.33%)	2 / 17 (11.76%)
occurrences (all)	2	5	2
Neutralising antibodies positive			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	1 / 17 (5.88%)
occurrences (all)	1	2	1
Red blood cell target cells present			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Red blood cell elliptocytes present			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Skin injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Animal bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Odontogenic cyst			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Psychomotor hyperactivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Aphthous stomatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Erythema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Endocrine disorders			

Precocious puberty			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	1 / 17 (5.88%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Posture abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Infections and infestations			
Laryngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pyoderma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Ear infection			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Acute tonsillitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	3 / 17 (17.65%)
occurrences (all)	0	1	4
Bronchitis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	0 / 17 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Non-serious adverse events	Genotropin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Fatigue			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site erythema			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site pruritus			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site swelling			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site warmth			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Asthma			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Fear of injection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Investigations			
Drug specific antibody present			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Neutralising antibodies positive			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Red blood cell target cells present			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Red blood cell elliptocytes present			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Animal bite			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Odontogenic cyst			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Psychomotor hyperactivity			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Aphthous stomatitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Dermatitis allergic			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

Erythema			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Precocious puberty			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Posture abnormal			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Laryngitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Pyoderma			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Otitis media acute			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Acute tonsillitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2014	Amendment 1 (dated 09 April 2014) to the protocol was issued before any patients were enrolled into the study. The following changes (not all-inclusive) were made to the protocol: • The addition of 2 health-related quality of life scales, in order to assess other QoL aspects in this patient population. • References to growth standards for H-SDS and HV-SDS were added.
15 July 2014	Amendment 2 (dated 15 July 2014) to the protocol was issued before any patients were enrolled into the study. The following changes (not all-inclusive) were made to the protocol: • The addition of alternative sites for injections in order to emphasize the importance of rotating injection sites • Removal of in-clinic administration of TV 1106 where the weekly dosing did not coincide with the visit schedule.
19 November 2015	Amendment 3 (dated 19 November 2015) to the protocol was issued after 65 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. This amendment was issued as a follow-up to the notification, dated 06 July 2015, submitted to all concerned Health Authorities concerning the identification of increased antibody response (ADA) in 11 pediatric patients treated with TV-1106 in this ongoing study. The following changes were made to the protocol: • The addition of extra visits to monitor immunogenicity. • Treatment discontinuation criteria were revised following expert advice and increased frequency of monitoring of nAb, if required. • The local amendment (described above) concerning the request to have only 1 single venipuncture was incorporated into the global amendment.

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.

As the study was terminated early, no paediatric patients completed the study according to the protocol. Thus limited efficacy analyses were completed and no conclusions can be drawn from these data. The focus of the clinical trial summary is safety.

Notes: