Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label, Comparator-Controlled Study to Assess Safety and Tolerability of Weekly TV-1106 Compared to Daily rhGH (GENOTROPIN®1) in Adults with Growth Hormone-Deficiency

Summary

EudraCT number	2014-002736-13
Trial protocol	DE HU SE IT AT ES SI LT GR CZ PL SK HR
Global end of trial date	18 December 2015

Results information

Result version number	v1 (current)
This version publication date	26 December 2016
First version publication date	26 December 2016

Trial information

Trial identification

Sponsor protocol code	TV1106-IMM-30022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02410356
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd.
Sponsor organisation address	5 Bazel Street, Petach Tikva, Israel, 49131
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	19 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2015
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 compare the safety and tolerability of weekly TV-1106 with daily Genotropin.

Based on evolving data from the two ongoing global Phase III studies in adults (TV1106-IMM-30021 and -30022) and the ongoing pediatric Phase II study (TV1106-IMM-20001) and as well as the recently completed adult Phase II study (TV1106-GHD-201), 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 Title 21, Parts 50, 54, 56, 312, and 314; 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	01 April 2015
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	Hungary: 2
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	34
EEA total number of subjects	2

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)	25
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

78 patients with GHD were screened for enrollment. 34 patients at 10 centers in the US and Hungary met entry criteria and were considered eligible for randomization. 44 patients who were not randomly assigned to study treatment: 18 were excluded due to inclusion/exclusion criteria and 26 were excluded for "other" reasons.

Pre-assignment

Screening details:

Eligible patients were randomly assigned to receive treatment with TV-1106 or GENOTROPIN in a 4:1 allocation ratio stratified by a combination of gender and oral estrogen use at screening (female using oral estrogen, female not using oral estrogen, and male).

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

Arm description:

TV-1106 was injected once weekly on the same day and at approximately the same time (between 1800 and 2200) for the 48-week open-label treatment.

The starting dose of TV-1106 was determined by multiplying the individual starting dose of previously taken daily rhGH (eg, GENOTROPIN) by a conversion
factor of 28. The TV-1106 dose was adjusted so that the patient's dose resulted in IGF-1 SDS between -0.5 and +1.5.

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

Dosage and administration details:

TV-1106 was administered on a weekly basis subcutaneously, either self-administered or administered during visits to the study site. The TV-1106 dose was adjusted so that the patient's dose resulted in IGF-1 SDS between -0.5 and +1.5. Dose increments were 2.5 mg or 5.0 mg based on patient demographics.

Arm title	Genotropin

Arm description:

The dose levels of GENOTROPIN were the same as the stable rhGH dose taken by each patient before the study, and were expected to range from 0.2 to 1.8 mg. GENOTROPIN was given as a daily subcutaneous injection for 48 weeks.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	GENOTROPIN®, somatropin [rDNA origin]
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The dose levels of GENOTROPIN were the same as the stable rhGH dose taken by each patient before

the study, and were expected to range from 0.2 to 1.8 mg. GENOTROPIN was given as a daily subcutaneous injection.

Number of subjects in period 1	TV-1106	Genotropin
Started	27	7
Completed	0	0
Not completed	27	7
Consent withdrawn by subject	-	1
Sponsor terminated the study	27	6

Baseline characteristics

Reporting groups	
Reporting group title	TV-1106

Reporting group description:

TV-1106 was injected once weekly on the same day and at approximately the same time (between 1800 and 2200) for the 48-week open-label treatment.

The starting dose of TV-1106 was determined by multiplying the individual starting dose of previously taken daily rhGH (eg, GENOTROPIN) by a conversion
factor of 28. The TV-1106 dose was adjusted so that the patient's dose resulted in IGF-1 SDS between -0.5 and +1.5.

Reporting group title	Genotropin

Reporting group description:

The dose levels of GENOTROPIN were the same as the stable rhGH dose taken by each patient before the study, and were expected to range from 0.2 to 1.8 mg. GENOTROPIN was given as a daily subcutaneous injection for 48 weeks.

Reporting group values	TV-1106	Genotropin	Total
Number of subjects	27	7	34
Age categorical Units: Subjects			
<40 years	1	2	3
>=40 years	26	5	31
Age continuous Units: years			
arithmetic mean	56.1	55.9	
standard deviation	± 13.31	± 16.59	-
Gender categorical Units: Subjects			
Female	11	3	14
Male	16	4	20
Race Units: Subjects			
White	21	7	28
Black	2	0	2
Asian	2	0	2
Missing	2	0	2
Growth-Hormone Deficiency Onset Units: Subjects			
Adult (>+18 years)	24	6	30
Childhood (<18 years)	3	1	4
Cause of Growth-Hormone Deficiency Units: Subjects			
Traumatic brain injury	2	0	2
Non-secreting pituitary adenoma	8	2	10
Idiopathic	15	3	18
Craniopharyngioma	1	1	2
Other	1	1	2
Prior Treatment for Growth-Hormone Deficiency			

Units: Subjects			
Yes	27	7	34
No	0	0	0
Weight			
Units: kg			
arithmetic mean	86.31	81.343	
standard deviation	± 15.5853	± 20.5136	-
Height			
Units: cm			
arithmetic mean	172.77	166.729	
standard deviation	± 9.5527	± 14.5053	-
Body Mass Index			
Units: kg/m^2			
arithmetic mean	28.732	28.926	
standard deviation	± 3.4828	± 4.6681	-
Insulin-like Growth Factor 1 Standard Deviation Score			
IGF-1 SDS represents the standard deviation from a 'normal' population.			
Units: standard deviations			
arithmetic mean	0.36	0.41	
standard deviation	± 0.644	± 0.495	-
Duration of Growth-Hormone Deficiency Diagnosis			
Units: years			
arithmetic mean	9.56	12.734	
standard deviation	± 9.7143	± 12.4567	-

End points

End points reporting groups

Reporting group title	TV-1106

Reporting group description:

TV-1106 was injected once weekly on the same day and at approximately the same time (between 1800 and 2200) for the 48-week open-label treatment.

The starting dose of TV-1106 was determined by multiplying the individual starting dose of previously taken daily rhGH (eg, GENOTROPIN) by a conversion
factor of 28. The TV-1106 dose was adjusted so that the patient's dose resulted in IGF-1 SDS between -0.5 and +1.5.

Reporting group title	Genotropin

Reporting group description:

The dose levels of GENOTROPIN were the same as the stable rhGH dose taken by each patient before the study, and were expected to range from 0.2 to 1.8 mg. GENOTROPIN was given as a daily subcutaneous injection for 48 weeks.

Primary: Percentage of Participants with Treatment-emergent Adverse Events

End point title	Percentage of Participants with Treatment-emergent Adverse Events[1]

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 usual 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	Primary

End point timeframe:

Day 1 up to Week 35

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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[2]	7[3]		
Units: percentage of total participants				
number (not applicable)				
>=1 adverse event	51.9	57.1		
Severe adverse event	0	0		
Treatment-related adverse event	14.8	14.3		
Deaths	0	0		
Other serious adverse events	0	0		
Discontinued from study drug due to adverse events	0	0		

Notes:

[2] - Safety population

[3] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Potentially Clinically Significant Abnormal Blood and Urine Test Results

End point title	Percentage of Participants with Potentially Clinically Significant Abnormal Blood and Urine Test Results[4]

End point description:

Parameters with potentially clinically significant abnormal test results include
- Serum chemistry: gamma glutamyl transferase
- Hematology: leukocytes, eosinophils/leukocytes
- Urinalysis: ketones

Significance criteria are listed below with the test. ULN = upper limit of normal

End point type	Primary

End point timeframe:

Day 1 up to Week 35

Notes:

[4] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[5]	7[6]		
Units: percentage of total participants				
number (not applicable)				
Gamma glutamyl transferase: >=3*ULN	3.7	0		
Leukocytes: <=3.0 10^9/L	3.7	0		
Eosinophils/leukocytes: >=10.0%	7.4	0		
Ketones: >=2 unit increase from baseline	0	14.3		

Notes:

[5] - Safety population

[6] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Potentially Clinically Significant Vital Signs

End point title	Percentage of Participants with Potentially Clinically Significant Vital Signs[7]

End point description:

Significance criteria for vital signs that showed potentially clinically significant findings are:
- Pulse rate: decrease 15 beats per minute (bpm) to <= 50 bpm
- Diastolic blood pressure: decrease 15 mmHg to <= 50 mmHg

End point type	Primary

End point timeframe:

Day 1 up to Week 35

Notes:

[7] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[8]	7[9]		
Units: percentage of total participants				
number (not applicable)				
Pulse rate	3.7	14.3		
Diastolic blood pressure	0	14.3		

Notes:

[8] - Safety population

[9] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Shift From Baseline To Endpoint in Electrocardiogram Findings

End point title	Shift From Baseline To Endpoint in Electrocardiogram

End point description:

Shifts represented as baseline - endpoint value (last observed post-baseline value). Endpoint is the last observed value.

Abnormal NCS indicates an abnormal but not clinically significant finding. Abnormal CS indicates an abnormal and clinically significant finding.

Values of 'Missing' indicate patients who did not have both a baseline and treatment finding.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[10] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[11]	7[12]		
Units: participants				
Normal - Normal	14	3		
Normal - Abnormal NCS	4	1		
Normal - Abnormal CS	0	0		
Abnormal NCS - Normal	0	0		
Abnormal NCS - Abnormal NCS	8	2		
Abnormal NCS - Abnormal CS	0	0		

Missing	1	1		

Notes:

[11] - Safety population

[12] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Thyroid Stimulating Hormone (TSH) Values at Baseline and Endpoint

End point title	Thyroid Stimulating Hormone (TSH) Values at Baseline and Endpoint[13]

End point description:

Observed values of TSH which is the first of three thyroid hormones measured.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[13] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[14]	7[15]		
Units: MIU/L				
arithmetic mean (standard deviation)				
Baseline (n=27, 5)	1.593 (± 1.5431)	1.702 (± 0.6426)		
Endpoint (n=27, 6)	1.522 (± 1.1972)	1.592 (± 1.3742)		

Notes:

[14] - Safety population

[15] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Free Thyroxin (free T4) Values at Baseline and Endpoint

End point title	Free Thyroxin (free T4) Values at Baseline and Endpoint[16]

End point description:

Observed values of Free T4 which is the second of three thyroid hormones measured.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[16] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27

of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[17]	7[18]		
Units: PMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=27, 7)	14.71 (± 2.597)	15.61 (± 3.09)		
Endpoint (n=27, 6)	15.27 (± 2.384)	15.45 (± 4.457)		

Notes:

[17] - Safety population

[18] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Triiodothyronine (Total T3) Values at Baseline and Endpoint

End point title	Triiodothyronine (Total T3) Values at Baseline and Endpoint[19]

End point description:

Observed values of Total T3 which is the third of three thyroid hormones measured.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[19] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[20]	7[21]		
Units: NMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=27, 7)	1.54 (± 0.283)	1.21 (± 0.406)		
Endpoint (n=27, 6)	1.48 (± 0.283)	1.33 (± 0.393)		

Notes:

[20] - Safety population

[21] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Glycated Hemoglobin (HbA1c) Values at Baseline and Endpoint

End point title	Glycated Hemoglobin (HbA1c) Values at Baseline and

End point description:

Glycated Hemoglobin (HbA1c) is a measure of glucose homeostasis.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[22] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[23]	7[24]		
Units: percentage of total hemoglobin				
arithmetic mean (standard deviation)				
Baseline (n=26, 7)	5.62 (± 0.583)	5.79 (± 0.861)		
Endpoint (n=27, 6)	5.62 (± 0.672)	5.9 (± 1.203)		

Notes:

[23] - Safety population

[24] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Fasting Blood Glucose Values at Baseline and Endpoint

End point title	Fasting Blood Glucose Values at Baseline and Endpoint[25]

End point description:

Fasting blood glucose is another measure of glucose homeostasis.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[25] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[26]	7[27]		
Units: MMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=27, 7)	5.56 (± 1.361)	5.51 (± 1.271)		
Endpoint (n=27, 6)	5.43 (± 1.106)	5.88 (± 1.533)		

Notes:

[26] - Safety population

[27] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Insulin Values at Baseline and Endpoint

End point title	Insulin Values at Baseline and Endpoint[28]

End point description:

Insulin is another measure of glucose homeostasis.

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 35)

Notes:

[28] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[29]	7[30]		
Units: PMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=27, 7)	81.1 (± 57.34)	76.3 (± 54.19)		
Endpoint (n=27, 6)	83.3 (± 49.63)	52 (± 17.66)		

Notes:

[29] - Safety population

[30] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Local Tolerability Assessed by Injection Site Reactions

End point title	Local Tolerability Assessed by Injection Site Reactions[31]

End point description:

Participants reporting at least one injection site reaction.

End point type	Primary

End point timeframe:

Day 1 up to Week 35

Notes:

[31] - 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: Because the study was terminated while enrollment was ongoing, the sample size was smaller than the planned 140 patients; 34 patients enrolled, 7 of whom received GENOTROPIN and 27 of whom received TV-1106 . Thus limited analyses were completed and no conclusions were reached.

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[32]	7[33]		
Units: percentage of total participants				
number (not applicable)				
Pain	0	14.3		
Tenderness	0	0		
Erythema	0	0		

Warmth	0	0		
Swelling	0	0		

Notes:

[32] - Safety population

[33] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Peak and Trough Insulin-Like Growth Factor 1 Standard Deviation Scores (IGF-I SDS) During the Study

End point title	Peak and Trough Insulin-Like Growth Factor 1 Standard Deviation Scores (IGF-I SDS) During the Study

End point description:

Peak reflects maximum value of IGF-I SDS from samples taken on Days 1 or 2 following TV-1106 dose (at Weeks 4, 8, & 16). For Genotropin, peak is the maximum IGF-I SDS value across the entire study.

Trough reflects minimum value of IGF-I SDS results from samples taken on Day 7, just prior to the next dose of TV-1106 (at Weeks 12 and 24).
For Genotropin, trough is the minimum IGF-I SDS value across the entire study.

End point type	Secondary

End point timeframe:

Day 1 up to Week 35

End point values	TV-1106	Genotropin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[34]	7[35]		
Units: standard deviations				
arithmetic mean (standard deviation)				
Peak IGF-1 SDS (n=20, 6)	0.91 (± 0.934)	1.32 (± 0.591)		
Trough IGF-1 SDS (n=17, 6)	0.25 (± 0.571)	0.5 (± 0.707)		

Notes:

[34] - Safety population

[35] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to Week 35	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	TV-1106

Reporting group description:

TV-1106 was injected once weekly on the same day and at approximately the same time (between 1800 and 2200) for the 48-week open-label treatment.

The starting dose of TV-1106 was determined by multiplying the individual starting dose of previously taken daily rhGH (eg, GENOTROPIN) by a conversion factor of 28. The TV-1106 dose was adjusted so that the patient's dose resulted in IGF-1 SDS between -0.5 and +1.5.

Reporting group title	Genotropin

Reporting group description:

The dose levels of GENOTROPIN were the same as the stable rhGH dose taken by each patient before the study, and were expected to range from 0.2 to 1.8 mg. GENOTROPIN was given as a daily subcutaneous injection for 48 weeks.

Serious adverse events	TV-1106	Genotropin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	TV-1106	Genotropin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 27 (33.33%)	4 / 7 (57.14%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 27 (7.41%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 27 (7.41%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 27 (14.81%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Injection site pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eye disorders			
Ocular discomfort			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Large intestine polyp			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			
Viral sinusitis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Conjunctivitis			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	1 / 7 (14.29%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sample size was smaller than the planned 140 patients; 34 patients enrolled. Limited analyses were completed and no conclusions reached.

Notes: