



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy, Safety and Tolerability Study of TV-1106 in Growth Hormone Deficient Adults Who Are Not Current Users of rhGH Treatment

Summary

EudraCT number	2014-003796-32
Trial protocol	DE HU CZ IT AT ES SI LT GR PL BG RO 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-30021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02410343
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd.
Sponsor organisation address	5 Bazel St., 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	01 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 determine the efficacy of 6 months of treatment with TV-1106 compared with placebo on body fat composition.

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	Austria: 1
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	United States: 9

Worldwide total number of subjects	14
EEA total number of subjects	5

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)	11
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 46 patients screened, 14 patients at 10 centers located in the US and Europe (Austria, Greece, Hungary) met entry criteria and were considered eligible for randomization. Of the 32 patients not randomly assigned to study treatment, 26 were excluded on the basis of inclusion/exclusion criteria and 6 were excluded for "other" reasons

Pre-assignment

Screening details:

Participants were randomly allocated to 1 of 2 treatment groups (TV-1106 or placebo) in a 2:1 allocation to prevent selection bias.

Period 1

Period 1 title	Core Period (24 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The 24-week core phase of the study was double-blind, and therefore, the sponsor, investigators, patients, and site staff did not have knowledge of treatment assignment. Blinded persons remained blinded until last patient randomized completed the core phase, at which time analysis of the accrued data from the core phase was to be performed. The central reader was unblinded, as were the bioanalytical scientists.

The 48-week extension phase of the study was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. To maintain the blind, placebo could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 to match the effect of dose titration.

Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Matching placebo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo treatment was administered in a blinded fashion and titrated on weeks 4, 8, 12 and 16 to mimic the active treatment.

Arm title	TV-1106
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Arm description:

TV-1106 was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. A common starting dose was 5.0 mg. Doses could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 until the participant's insulin-like growth factor 1 (IGF-1) standard deviation score (SDS) was within the range of -0.5 to +1.5.

Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.

Arm type	Experimental
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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	Intravenous use

Dosage and administration details:

A starting dose of 5.0 mg was expected to be appropriate for most patients because the daily recommended starting dose of recombinant human growth hormone (rhGH) treatments (e.g. somatropin) is 0.2 mg/day, and the conversion factor was 28. Dosage could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 until the participant's insulin-like growth factor 1 (IGF-1) standard deviation score (SDS) was within the range of -0.5 to +1.5.

Number of subjects in period 1	Placebo	TV-1106
Started	6	8
Completed	1	1
Not completed	5	7
Adverse event, non-fatal	1	-
Early termination of study by sponsor	4	7

Period 2

Period 2 title	Extension Period (12 Months)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	TV-1106 - Extension Period
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Arm description:

Participants from both the Placebo and TV-1106 groups who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106. Due to early termination of the study, two participants spent a maximum of two weeks in the extension period.

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	Intravenous use

Dosage and administration details:

After completion of the core phase and at initiation of the extension phase (visit 7), all patients were to revert to the starting dose of TV-1106, as determined by the unblinded central reader, to ensure the core phase of the study remained blinded during the transition to the open-label period.

Number of subjects in period 2	TV-1106 - Extension Period
Started	2
Completed	0
Not completed	2
Early termination of study by sponsor	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. To maintain the blind, placebo could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 to match the effect of dose titration. Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.	
Reporting group title	TV-1106
Reporting group description:	
TV-1106 was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. A common starting dose was 5.0 mg. Doses could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 until the participant's insulin-like growth factor 1 (IGF-1) standard deviation score (SDS) was within the range of -0.5 to +1.5. Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.	

Reporting group values	Placebo	TV-1106	Total
Number of subjects	6	8	14
Age categorical Units: Subjects			
<40 years	1	1	2
≥40 years	5	7	12
Age continuous Units: years arithmetic mean standard deviation	49.3 ± 12.86	56.4 ± 17.7	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	3	4	7
Race Units: Subjects			
White	5	7	12
Missing	1	1	2
Growth-Hormone Deficiency Onset Units: Subjects			
Adult (>+18 years)	5	7	12
Childhood (<18 years)	1	1	2
Cause of Growth-Hormone Deficiency Units: Subjects			
Secreting pituitary adenoma	0	1	1
Non-secreting pituitary adenoma	3	2	5
Idiopathic	0	1	1
Other	3	4	7
Prior Treatment for Growth-Hormone Deficiency Units: Subjects			
Yes	2	1	3

No Missing	0 4	0 7	0 11
Weight Units: kg arithmetic mean standard deviation	80.963 ± 24.1867	80.448 ± 13.3406	-
Height Units: cm arithmetic mean standard deviation	175.093 ± 9.1702	170.13 ± 8.5363	-
Body Mass Index Units: kg/m ² arithmetic mean standard deviation	26.04 ± 6.1675	27.716 ± 3.3512	-
Insulin-like Growth Factor 1 Standard Deviation Score			
IGF-1 SDS represents the standard deviation from a 'normal' population			
Units: standard deviations arithmetic mean standard deviation	-2 ± 0.978	-1.4 ± 0.545	-
Duration of Growth-Hormone Deficiency Diagnosis Units: years arithmetic mean standard deviation	9.27 ± 9.312	11.104 ± 13.1631	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. To maintain the blind, placebo could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 to match the effect of dose titration. Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.	
Reporting group title	TV-1106
Reporting group description: TV-1106 was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. A common starting dose was 5.0 mg. Doses could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 until the participant's insulin-like growth factor 1 (IGF-1) standard deviation score (SDS) was within the range of -0.5 to +1.5. Participants who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106.	
Reporting group title	TV-1106 - Extension Period
Reporting group description: Participants from both the Placebo and TV-1106 groups who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106. Due to early termination of the study, two participants spent a maximum of two weeks in the extension period.	

Primary: Body Fat Mass at Baseline, Week 24 and Endpoint in Core Period

End point title	Body Fat Mass at Baseline, Week 24 and Endpoint in Core Period ^[1]
End point description: The primary efficacy measure for the study was body fat mass (kg) measured by DXA imaging. The primary outcome as defined in the protocol was the change from baseline to week 24 in body fat mass. Due to the early termination of the study, observed values including endpoint values are reported. Endpoint is the last observed value. Values of 999 indicate not estimable due to single patient being reported.	
End point type	Primary
End point timeframe: Baseline (Day 1, pre-dose), Week 24, Endpoint in Core period	

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: As the study was terminated early, limited efficacy analyses are included. Because the study was terminated while enrollment was ongoing, the sample size was smaller than planned; 14 patients enrolled, 6 of whom received placebo and 8 of whom received TV-1106 during the core phase of the study. Thus, limited efficacy analyses were completed and, as only 2 patients (1 in each treatment group) completed the core phase of the study, no efficacy conclusions were reached.

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[2]	8 ^[3]		
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	24.38 (± 7.495)	29.5 (± 10.922)		

Week 24 (n=1, 1)	28.9 (± 999)	34.8 (± 999)		
Endpoint (n=3, 6)	23.37 (± 7.389)	31.05 (± 13.256)		

Notes:

[2] - Intent to treat population (ITT)

[3] - Intent to treat population (ITT)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Trunk Fat at Baseline, Week 24 and Endpoint in Core Period

End point title	Total Trunk Fat at Baseline, Week 24 and Endpoint in Core Period
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End point description:

Trunk fat (kg) was assessed based on DXA results. Trunk fat was defined as fat mass - (total arm fat + total leg fat + total head fat). The outcome as defined in the protocol was the within-patient change from baseline to week 24 in trunk fat. Due to the early termination of the study, observed values including endpoint values are reported.

Endpoint is the last observed value.

Values of 999 indicate not estimable due to reporting a single patient.

End point type	Secondary
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End point timeframe:

Baseline (Day 1, pre-dose), Week 24, Endpoint in Core Period

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[4]	8 ^[5]		
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	12.02 (± 4.716)	15.05 (± 5.041)		
Week 24 (n=1, 1)	15.6 (± 999)	12.6 (± 999)		
Endpoint (n=3, 6)	11.2 (± 4.173)	15.05 (± 6.369)		

Notes:

[4] - ITT

[5] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin-Like Growth Factor 1 Standard Deviation Score (IGF-I SDS) at Baseline, Week 24 and Endpoint in Core Period

End point title	Insulin-Like Growth Factor 1 Standard Deviation Score (IGF-I SDS) at Baseline, Week 24 and Endpoint in Core Period
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End point description:

IGF-I SDS, as reported by the central laboratory, was a key secondary variable. The week 24 value is a trough value as it was taken 7 days after the last TV-1106 or placebo injection.

The outcome as defined in the protocol was the within-patient change from baseline to week 24. Due to the early termination of the study, observed values including endpoint values are reported.

Endpoint is the last observed value and is of variable length of time since last TV-1106 or placebo

injection.

Values of 999 = not estimable due to reporting a single patient.

End point type	Secondary
End point timeframe:	
Baseline (Day 1, pre-dose), Week 24, Endpoint in Core Period	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[6]	8 ^[7]		
Units: standard deviation score				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	-2 (± 0.978)	-1.4 (± 0.545)		
Week 24 (n=1, 1)	-2 (± 999)	-1.3 (± 999)		
Endpoint (n=5, 6)	-1.66 (± 0.493)	-0.67 (± 0.896)		

Notes:

[6] - ITT

[7] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Scored Analysis of Quality of Life Assessment of GH Deficiency in Adults (QoL-AGHDA) at Baseline, Week 24 and Endpoint in Core Period

End point title	Scored Analysis of Quality of Life Assessment of GH Deficiency in Adults (QoL-AGHDA) at Baseline, Week 24 and Endpoint in Core Period
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End point description:

The AGHDA instrument is comprised of 25 questions, with yes or no answers. To each of the 25 questions comprising QOL AGHDA, a score of 1 was assigned if the answer was affirmative and 0 if the answer was negative. Data reported is the total score across the 25 questions for a total range of 0-25 with higher scores representing a poorer quality of life. The outcome as defined in the protocol was the within-patient change from baseline to week 24. Due to the early termination of the study, observed values including endpoint values are reported.

Endpoint is the last observed value.

Values of 999 = not estimable since reporting on a single patient.

End point type	Secondary
End point timeframe:	
Baseline (Day 1, pre-dose), Week 24, Endpoint in Core Period	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[8]	8 ^[9]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	3.8 (± 5.46)	9.6 (± 8.14)		
Week 24 (n=1, 1)	1 (± 999)	0 (± 999)		

Endpoint (n=6, 8)	2.8 (± 4.62)	6.5 (± 6.12)		
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Notes:

[8] - ITT

[9] - ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Adverse Events During the Core Period

End point title	Participants With Adverse Events During the Core Period
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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	Secondary
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End point timeframe:

Day 1 up to 24 Weeks

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[10]	8 ^[11]		
Units: participants				
>=1 adverse event	3	4		
Severe adverse event	1	0		
Treatment-related adverse event	0	2		
Deaths	0	0		
Other serious adverse events	1	0		
Discontinued from study drug due to adverse events	1	0		

Notes:

[10] - Safety population

[11] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Potentially Clinically Significant Abnormal Blood and Urine Test Results

End point title	Participants With Potentially Clinically Significant Abnormal Blood and Urine Test Results
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End point description:

Parameters with potentially clinically significant abnormal test results include
Serum chemistry: blood urea nitrogen, creatinine and bilirubin

Hematology: leukocytes, hemoglobin, hematocrit, platelets and neutrophils
Urinalysis: none

Significance criteria are listed below with the test.

End point type	Secondary
End point timeframe:	
Day 1 up to 24 Weeks	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[12]	8 ^[13]		
Units: participants				
Blood urea nitrogen: ≥ 10.71 mmol/L	0	1		
Creatinine: ≥ 177 mmol/L	0	1		
Bilirubin: ≥ 34.2 mmol/L	2	0		
Leukocytes: $\leq 3.0 \times 10^9/L$	1	0		
Hemoglobin: (male) ≤ 115 g/L	1	0		
Hematocrit: (male) < 0.37 L/L	1	0		
Platelets: $\leq 75 \times 10^9/L$	1	0		
Neutrophils: $\leq 1.0 \times 10^9/L$	1	0		

Notes:

[12] - Safety

[13] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Shift From Baseline To Endpoint in Core Period in Electrocardiogram Findings

End point title	Shift From Baseline To Endpoint in Core Period in Electrocardiogram Findings
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End point description:

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

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

End point type	Secondary
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End point timeframe:

Baseline (Day 1, pre-dose), up to Week 24

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[14]	8 ^[15]		
Units: participants				
Normal - Normal	4	6		
Normal - Abnormal NCS	1	0		
Normal - Abnormal CS	0	0		

Abnormal NCS - Normal	1	1		
Abnormal NCS - Abnormal NCS	0	1		
Abnormal NCS - Abnormal CS	0	0		

Notes:

[14] - Safety

[15] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Thyroid Stimulating Hormone (TSH) at Baseline and Endpoint

End point title	Thyroid Stimulating Hormone (TSH) at Baseline and Endpoint
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 24)

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[16]	8 ^[17]		
Units: MIU/L				
arithmetic mean (standard deviation)				
Baseline (n=6, 6)	0.365 (± 0.3791)	1.028 (± 2.0259)		
Endpoint (n=6, 7)	0.545 (± 0.5439)	0.796 (± 1.6971)		

Notes:

[16] - Safety

[17] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Free Thyroxin (Free T4) at Baseline and Endpoint

End point title	Free Thyroxin (Free T4) at Baseline and Endpoint
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline (Day 1, pre-dose), Endpoint (up to Week 24)

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[18]	8 ^[19]		
Units: PMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=6, 7)	17.22 (± 5.375)	15.26 (± 1.696)		
Endpoint (n=6, 8)	15.65 (± 2.18)	14.54 (± 3.259)		

Notes:

[18] - Safety

[19] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Triiodothyronine (Total T3) at Baseline and Endpoint

End point title	Triiodothyronine (Total T3) at Baseline and Endpoint
End point description:	Observed values of Total T3 which is the third of three thyroid hormones measured.
End point type	Secondary
End point timeframe:	Baseline (Day 1, pre-dose), Endpoint (up to Week 24)

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[20]	8 ^[21]		
Units: NMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=6, 7)	1.8 (± 1.228)	1.71 (± 0.302)		
Endpoint (n=6, 7)	1.32 (± 0.133)	1.64 (± 0.351)		

Notes:

[20] - Safety

[21] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Glycated Hemoglobin (HbA1c) at Baseline and Endpoint

End point title	Glycated Hemoglobin (HbA1c) at Baseline and Endpoint
End point description:	Glycated Hemoglobin (HbA1c) is a measure of glucose homeostasis.
End point type	Secondary
End point timeframe:	Baseline (Day 1, pre-dose), Endpoint (up to Week 24)

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[22]	8 ^[23]		
Units: percentage of total hemoglobin				
arithmetic mean (standard deviation)				
Baseline (n=6, 7)	5.53 (± 0.647)	5.49 (± 0.422)		
Endpoint (n=6, 7)	5.45 (± 0.797)	5.51 (± 0.358)		

Notes:

[22] - Safety population

[23] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting Blood Glucose at Baseline and Endpoint

End point title	Fasting Blood Glucose at Baseline and Endpoint
End point description:	
Fasting blood glucose is another measure of glucose homeostasis.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1, pre-dose), Endpoint (up to Week 24)	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[24]	8 ^[25]		
Units: MMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	5.37 (± 2.38)	4.83 (± 0.32)		
Endpoint (n=6, 8)	4.82 (± 0.818)	5.01 (± 0.344)		

Notes:

[24] - Safety

[25] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin at Baseline and Endpoint

End point title	Insulin at Baseline and Endpoint
End point description:	
Insulin is another measure of glucose homeostasis.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1, pre-dose), Endpoint (up to Week 24)	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[26]	8 ^[27]		
Units: PMOL/L				
arithmetic mean (standard deviation)				
Baseline (n=6, 8)	68 (± 68.9)	57 (± 22.68)		
Endpoint (n=6, 7)	65 (± 49.68)	94.3 (± 89.04)		

Notes:

[26] - Safety

[27] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Local Tolerability Assessed by Injection Site Reactions

End point title	Local Tolerability Assessed by Injection Site Reactions
End point description:	
Participants reporting at least one injection site reaction.	
End point type	Secondary
End point timeframe:	
Day 1 up to Week 24	

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[28]	8 ^[29]		
Units: participants				
Pain (n=6, 7)	0	2		
Tenderness (n=6, 8)	0	1		
Erythema (n=6, 7)	0	0		
Warmth (n=6, 7)	0	0		
Swelling (n=6, 7)	0	0		

Notes:

[28] - Safety

[29] - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Serum Concentration of TV1106 by Nominal Sampling Timepoints

End point title	Pharmacokinetic Serum Concentration of TV1106 by Nominal Sampling Timepoints
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End point description:

Weeks 4 and 8 serum samples obtained 2 days after TV1106 administration. Weeks 12 and 24 serum samples obtained 7 days after TV1106 administration. Week 16 serum samples obtained 1 day after TV1106 administration.

In study documentation, only minimum and maximum values are presented at visits where more than 50% of results are below the limit of quantitation. The lower limit of quantification was 4 ng/mL. However EudraCT requires a median value so 'zero' has been entered in Baseline, Week 4, Week 12 and Week 24 as a placeholder.

End point type	Secondary
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End point timeframe:

Baseline (Day 1, pre-dose), Weeks 4, 8, 12, 16, 24

End point values	Placebo	TV-1106		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[30]	8 ^[31]		
Units: ng/mL				
median (full range (min-max))				
Baseline (n=0, 8)	(to)	0 (0 to 0)		
Week 4 (n=0, 4)	(to)	0 (0 to 5.8)		
Week 8 (n=0, 3)	(to)	4.5 (0 to 4.7)		
Week 12 (n=0, 2)	(to)	0 (0 to 0)		
Week 16 (n=0, 2)	(to)	9.05 (6.6 to 11.5)		
Week 24 (n=0, 1)	(to)	0 (0 to 0)		

Notes:

[30] - Not performed on placebo group

[31] - Safety

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core Period: Day 1 to Week 24

Extension Period: Week 25-26

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Placebo - Core Period
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Reporting group description:

Placebo was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. To maintain the blind, placebo could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 to match the effect of dose titration.

Reporting group title	TV-1106 - Core Period
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Reporting group description:

TV-1106 was injected subcutaneously once weekly on the same day and time for 24 weeks during the Core Period. A common starting dose was 5.0 mg. Doses could be titrated by an unblinded central reader on weeks 4, 8, 12 and 16 until the participant's insulin-like growth factor 1 (IGF-1) standard deviation score (SDS) was within the range of -0.5 to +1.5.

Reporting group title	TV-1106 - Extension Period
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Reporting group description:

Participants from both the Placebo and TV-1106 groups who completed the Core Period were eligible to enter an open-label extension phase for 12 additional months where all participants received treatment with TV-1106. Due to early termination of the study, two participants spent a maximum of two weeks in the extension period.

Serious adverse events	Placebo - Core Period	TV-1106 - Core Period	TV-1106 - Extension Period
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Endocrine disorders			
Pituitary haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo - Core Period	TV-1106 - Core Period	TV-1106 - Extension Period
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 6 (50.00%)	4 / 8 (50.00%)	1 / 2 (50.00%)
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 8 (12.50%) 1	0 / 2 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all) Carpal tunnel syndrome subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2 0 / 6 (0.00%) 0	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all) Injection site swelling subjects affected / exposed occurrences (all) Injection site rash subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	2 / 8 (25.00%) 2 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	0 / 2 (0.00%) 0 1 / 2 (50.00%) 2 1 / 2 (50.00%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 8 (12.50%) 1	0 / 2 (0.00%) 0
Musculoskeletal and connective tissue disorders Joint swelling subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 8 (0.00%) 0	0 / 2 (0.00%) 0
Rhinovirus infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 8 (12.50%) 1	0 / 2 (0.00%) 0

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; 14 patients enrolled. Limited efficacy analyses were completed; as only 2 patients (1 in each treatment group) completed the core phase of the study, no efficacy conclusions were reached.

Notes: