

**Clinical trial results:****A Multicenter, Randomized, Double-Masked, Placebo-Controlled, Efficacy and Safety Study of RV 001, an Insulin-Like Growth Factor-1 Receptor (IGF-1R) Antagonist Antibody (Fully Human), Administered Every 3 Weeks (q3W) by Intravenous (IV) Infusion in Patients Suffering From Active Thyroid Eye Disease (TED)****Summary**

EudraCT number	2014-000113-31
Trial protocol	DE IT GB NL
Global end of trial date	22 February 2017

Results information

Result version number	v2 (current)
This version publication date	13 May 2018
First version publication date	10 March 2018
Version creation reason	• Correction of full data set Update information to align with CT.gov.

Trial information**Trial identification**

Sponsor protocol code	TED01RV
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01868997
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	150 S. Saunders Road, Lake Forest, Illinois, United States, 60045
Public contact	Julie Ball, Horizon Pharma USA, Inc., clinicaltrials@horizonpharma.com
Scientific contact	Raymond Douglas, MD, PhD, Cedars-Sinai Medical Center, Raymond.Douglas@cshs.org

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	22 February 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to investigate the efficacy, safety, and tolerability of RV 001 (teprotumumab), a fully human anti-IGF1R antibody, administered q3W for 6 months, in comparison to placebo, in the treatment of participants suffering from active TED.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with legal and regulatory requirements including Guidance for Good Clinical Practice (International Conference on Harmonization [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008). Written informed consent was to be obtained from the subject's legally acceptable representative and assent by the minor subject, as applicable, before screening or baseline assessments. Instructions were given to the subject's legally acceptable representative in case of emergency or other questions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	87
EEA total number of subjects	35

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	88 ^[1]
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Number of subjects completed	87
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	randomized, not treated: 1
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Notes:

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

Justification: A total of 88 subjects were randomized; 1 subject was never dosed and early terminated.

Period 1

Period 1 title	Overall Study (overall period)
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Double blind
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Roles blinded	Investigator, Subject
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Blinding implementation details:

The pharmacists responsible for preparing the teprotumumab solution or placebo solution for IV use will not be masked. The investigator and all other study site personnel will be masked to the treatment being administered.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description:

A placebo infusion (normal saline) was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions.

Arm type	Placebo
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Investigational medicinal product name	sterile normal saline 0.9%
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Solution for infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

Placebo will be administered q3W by IV infusion over 6 months

Arm title	Teprotumumab
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Arm description:

Teprotumumab administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All participants started treatment at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and kept constant for the remainder of the study.

Arm type	Experimental
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Investigational medicinal product name	Teprotumumab
Investigational medicinal product code	RV 001
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Teprotumumab will be administered q3W by IV infusion over 6 months

Number of subjects in period 1	Placebo	Teprotumumab
Started	45	42
Completed	38	36
Not completed	7	6
Not specified	3	1
Adverse event	2	5
Lack of efficacy	2	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

A placebo infusion (normal saline) was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions.

Reporting group title	Teprotumumab
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Reporting group description:

Teprotumumab administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All participants started treatment at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and kept constant for the remainder of the study.

Reporting group values	Placebo	Teprotumumab	Total
Number of subjects	45	42	87
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	54.1 ± 12.87	51.7 ± 10.78	-
Gender categorical Units: Subjects			
Female	36	28	64
Male	9	14	23

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: A placebo infusion (normal saline) was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions.	
Reporting group title	Teprotumumab
Reporting group description: Teprotumumab administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All participants started treatment at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and kept constant for the remainder of the study.	

Primary: Responder Status at Week 24

End point title	Responder Status at Week 24
End point description: Number of subjects classified as responders and non-responders at Week 24. Responders were defined as subjects with a reduction in clinical activity score (CAS, see secondary endpoint 'Change From Baseline in CAS' description for details) of ≥ 2 points, and a reduction in proptosis (amount of protrusion of the eye from the orbital rim) of ≥ 2 mm in the study eye, and no deterioration (increase in CAS of ≥ 2 points or increase in proptosis of ≥ 2 mm) in the non-study eye. Subjects who had no assessment at 24 weeks were considered non-responders.	
Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo).	
End point type	Primary
End point timeframe: Week 24	

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: subjects				
Responder	9	29		
Non-Responder / Missing	36	13		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Teprotumumab v Placebo

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.293
upper limit	23.825

Notes:

[1] - Odds ratio, 95% confidence interval, and P-value are obtained from a logistic regression model with treatment and smoking status as covariates.

Secondary: Overall Average Change From Baseline in Graves' Ophthalmopathy Quality of Life (GO-QOL) Scale - Overall to Week 24 (Mixed-Model Repeated Measures [MMRM])

End point title	Overall Average Change From Baseline in Graves' Ophthalmopathy Quality of Life (GO-QOL) Scale - Overall to Week 24 (Mixed-Model Repeated Measures [MMRM])
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End point description:

The GO-QOL is a 16-item self-administered questionnaire used to assess the perceived effects of thyroid eye disorder (TED) by the subjects on their daily physical and psychosocial functioning. Two subscales of the 16-question GO-QOL have been defined: Visual Functioning and Appearance, with 8 questions comprising each subscale. The transformed overall score is the sum of scores from all 16 questions to a scale of 0 (worst health) to 100 (best health).

Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo). A change from baseline of zero was imputed at the first postbaseline visit for subjects with no postbaseline assessment.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: units on a scale				
least squares mean (standard error)	6.77 (± 2.251)	17.74 (± 2.423)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed-Model Repeated Measures
Parameter estimate	Difference in Least Squares Mean
Point estimate	10.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.561
upper limit	17.375
Variability estimate	Standard error of the mean
Dispersion value	3.221

Secondary: Overall Average Change From Baseline in Proptosis of the Study Eye to Week 24 (MMRM)

End point title	Overall Average Change From Baseline in Proptosis of the Study Eye to Week 24 (MMRM)
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End point description:

Proptosis is the amount of protrusion of the eye from the orbital rim. Measurements were recorded using the Hertel exophthalmometer. Subjects with a decrease ≥ 2 mm were considered improving, those with an increase or decrease < 2 mm were considered remaining stable, and those with an increase ≥ 2 mm were considered worsening.

Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo). A change from baseline of zero was imputed at the first postbaseline visit for subjects with no postbaseline assessment.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: mm				
least squares mean (standard error)	-0.15 (\pm 0.188)	-2.46 (\pm 0.200)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-Model Repeated Measures
Parameter estimate	Difference in Least Squares Mean
Point estimate	-2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.843
upper limit	-1.772
Variability estimate	Standard error of the mean
Dispersion value	0.269

Secondary: Overall Average Change From Baseline in CAS to Week 24 (MMRM)

End point title	Overall Average Change From Baseline in CAS to Week 24 (MMRM)
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End point description:

The 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS was used to evaluate clinical activity. For each of the following items, one point is given: spontaneous orbital pain, gaze evoked orbital pain, eyelid swelling that is considered to be due to active (inflammatory phase) Graves' ophthalmopathy (GO), eyelid erythema, conjunctival redness that is considered to be due to active (inflammatory phase) GO, chemosis, and inflammation of caruncle or plica. The sum of these points is the total score, with 0 indicating no clinical activity and 7 indicating the most severe clinical activity.

Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo). A change from baseline of zero was imputed at the first postbaseline visit for subjects with no postbaseline assessment.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: units on a scale				
least squares mean (standard error)	-1.85 (± 0.172)	-3.43 (± 0.181)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-Model Repeated Measures
Parameter estimate	Difference in Least Squares Mean
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.073
upper limit	-1.098
Variability estimate	Standard error of the mean
Dispersion value	0.245

Secondary: Overall Average Change From Baseline in GO-QOL Scale - Visual Functioning to Week 24 (MMRM)

End point title	Overall Average Change From Baseline in GO-QOL Scale - Visual Functioning to Week 24 (MMRM)
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End point description:

The GO-QOL is a 16-item self-administered questionnaire used to assess the perceived effects of TED by the subjects on their daily physical and psychosocial functioning. Two subscales of the 16-question GO-QOL have been defined: Visual Functioning and Appearance, with 8 questions comprising each subscale. Transformed Visual Functioning score is the sum of scores from following 8 questions to a scale of 0 (worst health) to 100 (best health): bicycling, driving, moving around the house, walking outdoors, reading, watching television (TV), hobby or pastime, feel hindered.

Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo). A change from baseline of zero was imputed at the first postbaseline visit for subjects with no postbaseline assessment.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: units on a scale				
least squares mean (standard error)	7.51 (\pm 2.646)	21.67 (\pm 2.891)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-Model Repeated Measures
Parameter estimate	Difference in Least Squares Mean
Point estimate	14.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.549
upper limit	21.773
Variability estimate	Standard error of the mean
Dispersion value	3.827

Secondary: Overall Average Change From Baseline in GO-QOL Scale - Appearance to Week 24 (MMRM)

End point title	Overall Average Change From Baseline in GO-QOL Scale - Appearance to Week 24 (MMRM)
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End point description:

The GO-QOL is a 16-item self-administered questionnaire used to assess the perceived effects of TED by the subjects on their daily physical and psychosocial functioning. Two subscales of the 16-question GO-QOL have been defined: Visual Functioning and Appearance, with 8 questions comprising each subscale. Transformed Appearance score is the sum of scores from the following 8 questions to a scale of 0 (worst health) to 100 (best health): feel appearance has changed, feel being stared at, feel people react unpleasantly, influence on self-confidence, feel socially isolated, influence on making friends, appear less often on photos, try to mask changes in appearance.

Intent to Treat Population: all subjects who were randomized to treatment and received at least 1 dose of medication (either teprotumumab or placebo). A change from baseline of zero was imputed at the first postbaseline visit for subjects with no postbaseline assessment.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Placebo	Teprotumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	42		
Units: units on a scale				
least squares mean (standard error)	6.60 (± 2.656)	12.92 (± 2.836)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Mixed-Model Repeated Measures
Parameter estimate	Difference in Least Squares Mean
Point estimate	6.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.255
upper limit	13.901
Variability estimate	Standard error of the mean
Dispersion value	3.81

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 72

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) are presented, defined as events with onset at the time of or following the start of treatment with study drug or an event starting before the start of treatment but increasing in severity following the start of treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Safety Population: Placebo
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Reporting group description:

A placebo infusion (normal saline) was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions.

Safety Population: subjects who received at least 1 dose of study treatment, grouped by treatment actually received.

Reporting group title	Safety Population: Teprotumumab
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Reporting group description:

Teprotumumab administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All participants started treatment at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and kept constant for the remainder of the study.

Safety Population: subjects who received at least 1 dose of study treatment, grouped by treatment actually received.

Serious adverse events	Safety Population: Placebo	Safety Population: Teprotumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	5 / 43 (11.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Hashimoto's encephalopathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Population: Placebo	Safety Population: Teprotumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 44 (47.73%)	25 / 43 (58.14%)	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 44 (9.09%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Dysgeusia			
subjects affected / exposed	0 / 44 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

Headache subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	3 / 43 (6.98%) 4	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	3 / 43 (6.98%) 3	
Somnolence subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 4	0 / 43 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6	3 / 43 (6.98%) 4	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2 4 / 44 (9.09%) 6	5 / 43 (11.63%) 8 8 / 43 (18.60%) 9	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2 0 / 44 (0.00%) 0 4 / 44 (9.09%) 5	3 / 43 (6.98%) 3 3 / 43 (6.98%) 3 3 / 43 (6.98%) 4	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	8 / 43 (18.60%) 25	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4	0 / 43 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	5 / 43 (11.63%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2013	Changed Inclusion Criteria #s 3, 4, and 5
17 December 2013	Added HgbA1c testing at screening
25 April 2014	Added text that contraception to continue for 3 months after last dose of study drug
10 June 2014	Added clarification about definition of women of childbearing potential
23 June 2014	Added HgbA1c testing at Weeks 24 and 36
27 August 2014	Added HgbA1c at Weeks 12 and 72 Added language in Section 9.1.1 to allow for dose interruption in subjects who developed hyperglycemia in order to be treated for the adverse event
28 September 2015	Primary endpoint definition changed and secondary endpoints limited. Changes were made in consultation with key opinion leaders not participating in TED01RV after results from recent and relevant TED clinical trials became available. The goal was to have a more rigorous and clinically meaningful primary outcome measure, and one that would potentially differentiate teprotumumab as a clear improvement over existing therapies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28467880>