# 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 | v1 |
| This version publication date | 10 March 2018 |
| First version publication date | 10 March 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TED01RV |

**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] |
| Number of subjects completed | 87 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | randomized, not treated: 1 |

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) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

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 |
| **Arm title** | Placebo |

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 |
| Investigational medicinal product name | sterile normal saline 0.9% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo will be administered q3W by IV infusion over 6 months

| | |
|---|---|
| **Arm title** | Teprotumumab |

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 |

| | |
|---|---|
| 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 |
| 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. | |

| Reporting group values | Placebo | Teprotumumab | Total |
|---|---|---|---|
| Number of subjects | 45 | 42 | 87 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.1 | 51.7 | |
| standard deviation | ± 12.87 | ± 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.<br><br>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]) |

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) |

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 |

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 (± 0.188) | -2.46 (± 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) |

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 |

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) |

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 |

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 (± 2.646) | 21.67 (± 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) |

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 |

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.

No evidence of rebound was observed in the off-treatment follow-up period.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety Population: 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.

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

| | |
|---|---|
| Reporting group title | Safety Population: 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.

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

| | | | |
|---|---|---|---|
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all) | 2 / 44 (4.55%)<br>2 | 8 / 43 (18.60%)<br>25 | |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 44 (9.09%)<br>4 | 0 / 43 (0.00%)<br>0 | |
| Metabolism and nutrition disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 44 (4.55%)<br>2 | 5 / 43 (11.63%)<br>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<br>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