Clinical trial results:
Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease

Summary

EudraCT number	2017-002713-58
Trial protocol	DE IT
Global end of trial date	17 February 2021

Results information

Result version number	v1 (current)
This version publication date	25 December 2021
First version publication date	25 December 2021

Trial information

Trial identification

Sponsor protocol code	HZNP-TEP-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03461211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	1 Horizon Way, Deerfield, IL , United States, 60015
Public contact	Senior Medical Director, Horizon Pharma USA, Inc., 001 866-479-6742, clinicaltrials@horizontherapeutics.com
Scientific contact	Senior Medical Director, Horizon Pharma USA, Inc., 001 866-479-6742, clinicaltrials@horizontherapeutics.com

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	17 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of teprotumumab on the proptosis responder rate (i.e., the percentage of subjects with a ≥ 2 mm reduction from Baseline in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at the EOT Visit.

Protection of trial subjects:

The Investigators will ensure that this study is conducted in a manner that fully conforms with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Conference of Harmonization (ICH) Tripartite Guideline or with local law if it affords greater protection to the subject.

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The Investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2018
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	Germany: 16
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	51
EEA total number of subjects	26

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)	43
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were eligible for enrollment in this study (OPTIC-X) if they completed the 24-week double-masked Treatment Period in Study HZNP-TEP-301 (NCT03298867; OPTIC) and were proptosis non-responders or were proptosis responders at Week 24 but met the criteria for re-treatment due to relapse during the Follow-Up Period of HZNP-TEP-301.

Pre-assignment

Screening details:

The Baseline (Day 1) Visit of this extension study occurred within 14 days after the final visit of Study HZNPTEP-301, which was Week 24 for proptosis non-responders and up to Week 72 for participants who relapsed. The study treatment previously administered in HZNP-TEP-301 (teprotumumab or placebo) remained masked
throughout this extension study

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study treatment previously administered in HZNP-TEP-301 (teprotumumab or placebo) remained masked throughout this extension study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Teprotumumab (OPTIC Placebo)

Arm description:

Participants who received placebo in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.

Arm type	Experimental
Investigational medicinal product name	Teprotumumab
Investigational medicinal product code	HZN-001
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All study drug dosing was performed at the clinic under the supervision of clinic staff.

Arm title	Teprotumumab (OPTIC Teprotumumab)

Arm description:

Participants who received teprotumumab in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.

Arm type	Experimental
Investigational medicinal product name	Teprotumumab
Investigational medicinal product code	HZN-001
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All study drug dosing was performed at the clinic under the supervision of clinic staff.

Number of subjects in period 1	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)
Started	37	14
Proptosis Non- Responders in OPTIC	36	5 [1]
Relapsed During OPTIC Follow-Up Period	1 [2]	9 [3]
Completed	36	12
Not completed	1	2
Adverse event	1	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone categories are correctly defined.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone categories are correctly defined.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone categories are correctly defined.

Baseline characteristics

Reporting groups	
Reporting group title	Teprotumumab (OPTIC Placebo)
Reporting group description:	
Participants who received placebo in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.	
Reporting group title	Teprotumumab (OPTIC Teprotumumab)
Reporting group description:	
Participants who received teprotumumab in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.	

Reporting group values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)	Total
Number of subjects	37	14	51
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48.5	56.1	
standard deviation	± 13.49	± 11.52	-
Gender categorical			
Units: Subjects			
Female	27	11	38
Male	10	3	13
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	36	14	50
Race			
Units: Subjects			
Asian	1	2	3
Black or African American	1	1	2
White	33	11	44
Other, Not Specified	2	0	2

End points

End points reporting groups

Reporting group title	Teprotumumab (OPTIC Placebo)
Reporting group description:	
Participants who received placebo in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.	
Reporting group title	Teprotumumab (OPTIC Teprotumumab)
Reporting group description:	
Participants who received teprotumumab in OPTIC received 8 infusions of open-label teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.	

Primary: Percentage of Participants With a ≥ 2 mm Reduction From Baseline in the Study Eye Without Deterioration of Proptosis in the Fellow Eye at Week 24

End point title	Percentage of Participants With a ≥ 2 mm Reduction From Baseline in the Study Eye Without Deterioration of Proptosis in the Fellow Eye at Week 24[1]
End point description:	
Proptosis responders were defined as participants with a ≥ 2 mm reduction from study baseline in proptosis in the study eye, without deterioration (≥ 2 mm increase) of proptosis in the fellow eye at Week 24. Participants missing Week 24 values were considered non-responders, aside from those with missing data related to the COVID-19 pandemic. Intent-to-Treat Population: all participants enrolled in the study. Participants missing Week 24 values were considered non-responders, aside from those with missing data related to the COVID-19 pandemic. One participant in the Teprotumumab (OPTIC Teprotumumab) arm was excluded from all Week 24 summaries due to COVID-19 (visit delayed).	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

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: Descriptive statistics are presented per protocol.

End point values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	13		
Units: percentage of participants				
number (not applicable)	89.2	53.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a European Group on Graves'

Ophthalmopathy (EUGOGO) Amended Clinical Activity Score (CAS) Total Score of 0 or 1 in the Study Eye at Week 24

End point title	Percentage of Participants With a European Group on Graves' Ophthalmopathy (EUGOGO) Amended Clinical Activity Score (CAS) Total Score of 0 or 1 in the Study Eye at Week 24

End point description:

CAS responders were defined as participants with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) as a categorical response variable at Week 24.

The 7-item CAS assigns 1 point for each of the following items present in the study eye: spontaneous orbital pain; gaze evoked orbital pain; eyelid swelling that is considered to be due to active (inflammatory phase) thyroid eye disease/Graves' ophthalmopathy (TED/GO); eyelid erythema; conjunctival redness that is considered to be due to active (inflammatory phase) TED/GO (ignore "equivocal" redness); chemosis; inflammation of caruncle or plica. The sum of these points is the total score (0 to 7), with higher scores indicating worse symptoms.

ITT Population: all participants enrolled in the study. Participants with CAS > 1 at Study Baseline. Per the statistical analysis plan, participants missing Week 24 values were considered non-responders, aside from those with missing data related to the COVID-19 pandemic.

End point type	Secondary

End point timeframe:

Week 24

End point values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[2]	11[3]		
Units: percentage of participants				
number (not applicable)	65.6	36.4		

Notes:

[2] - Participants with CAS > 1 at Study Baseline.

[3] - Participants with CAS > 1 at Study Baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Proptosis From Baseline to Week 24

End point title	Change in Proptosis From Baseline to Week 24

End point description:

Mean change from study baseline to Week 24 in proptosis measurement (mm) in the study eye at Week 24.

Intent-to-Treat Population: all participants enrolled in the study. Participants with both baseline and Week 24 measurements. One participant in the Teprotumumab (OPTIC Teprotumumab) arm was excluded from all Week 24 summaries due to COVID-19 (visit delayed).

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	11		
Units: mm				
arithmetic mean (standard deviation)	-3.47 (± 1.732)	-1.77 (± 1.126)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Diplopia Responders at Week 24

End point title	Percentage of Participants Who Were Diplopia Responders at Week 24

End point description:

Diplopia responders were defined as participants with 1 grade or greater reduction in diplopia score in the study eye without worsening by at least 1 grade in the fellow eye at Week 24.

The subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position) was recorded for each eye. A participant was considered to have diplopia if a score > 0 is observed in the study eye at study baseline.

Intent-to-Treat Population: all participants enrolled in the study. Participants with diplopia at Study Baseline. Per the statistical analysis plan, participants missing Week 24 values were considered non-responders, aside from those with missing data related to the COVID-19 pandemic. One participant in the Teprotumumab (OPTIC Teprotumumab) arm was excluded from all Week 24 summaries due to COVID-19.

End point type	Secondary

End point timeframe:

Week 24

End point values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	4		
Units: percentage of participants				
number (not applicable)	60.9	75.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) Questionnaire Overall Score

End point title	Mean Change From Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) Questionnaire Overall Score

End point description:

The GO-QoL is a 16-item self-administered questionnaire divided into 2 subsets and used to assess the perceived effects of TED by the participants on (i) their daily physical activity as it relates to visual function, and (ii) psychosocial functioning. The sum of the scores from each set of 8 questions was calculated and transformed to a scale from 0 (worst) to 100 (best) – one for visual function (VF), one for appearance (A) and one for the overall combined (VF + A) score. Scores were transformed as follows: Transformed score = [(sum of each score – number of completed items) / (2 * number of completed items)] * 100. The "overall combined (VF + A) score" is also 0 to 100, with higher scores indicating a better outcome.

Intent-to-Treat Population: all participants enrolled in the study. Participants with both baseline and Week 24 measurements. One participants in the Teprotumumab (OPTIC Teprotumumab) arm was excluded from the Week 24 summary due to COVID-19 (visit delayed).

End point type	Secondary

End point timeframe:

Study Baseline, Week 24

End point values	Teprotumumab (OPTIC Placebo)	Teprotumumab (OPTIC Teprotumumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	11		
Units: score on a scale				
arithmetic mean (standard deviation)	13.39 (± 17.890)	14.73 (± 11.777)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and serious adverse events (AEs): from informed consent through 30 days after study discontinuation. Mean days on study was 332.9 and 218.8 for Placebo (OPTIC Placebo) and Teprotumumab (OPTIC Teprotumumab) arms, respectively.

Adverse event reporting additional description:

Non-serious AEs: from first dose of study drug through last dose of study drug + 3 weeks (Treatment Period; mean 168.1 and 170.9 days for Placebo and Teprotumumab arms, respectively) or from Week 24 up to Week 48 in the Follow-Up Period (mean 170.1 and 165.0 days for Placebo [OPTIC Placebo] and Teprotumumab [OPTIC Teprotumumab] arms, respectively).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Treatment Period: Teprotumumab (OPTIC Placebo)

Reporting group description:

Participants who received placebo in OPTIC received 8 infusions of teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.

Reporting group title	Treatment Period: Teprotumumab (OPTIC Teprotumumab)

Reporting group description:

Participants who received teprotumumab in OPTIC received 8 infusions of teprotumumab every 3 weeks (q3W) for a total of 21 weeks: teprotumumab 10 mg/kg administered on Day 1 and teprotumumab 20 mg/kg administered q3W for the remaining 7 infusions.

Reporting group title	Follow-Up Period: No Treatment (OPTIC Placebo)

Reporting group description:

Participants who received placebo in OPTIC and were proptosis non-responders. Participants received 8 infusions of teprotumumab q3W for a total of 21 weeks in OPTIC-X and entered a 24-week Follow-up Period; no trial drug was administered.

Reporting group title	Follow-Up Period: No Treatment (OPTIC Teprotumumab)

Reporting group description:

Participants who received teprotumumab in OPTIC and were proptosis non-responders. Participants received 8 infusions of teprotumumab q3W for a total of 21 weeks in OPTIC-X and entered a 24-week Follow-up Period; no trial drug was administered.

Serious adverse events	Treatment Period: Teprotumumab (OPTIC Placebo)	Treatment Period: Teprotumumab (OPTIC Teprotumumab)	Follow-Up Period: No Treatment (OPTIC Placebo)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Follow-Up Period: No Treatment (OPTIC Teprotumumab)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment Period: Teprotumumab (OPTIC Placebo)	Treatment Period: Teprotumumab (OPTIC Teprotumumab)	Follow-Up Period: No Treatment (OPTIC Placebo)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 37 (86.49%)	11 / 14 (78.57%)	16 / 36 (44.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of skin			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic keratosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Hypotension			

subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Jugular vein distension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	4 / 37 (10.81%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
Influenza like illness			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Erectile dysfunction			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vaginal discharge			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vaginal haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0

Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Nasal discomfort			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	0 / 37 (0.00%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Paranasal sinus discomfort			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Sneezing			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Nightmare			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Tension			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Investigations			

Blood glucose increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Post procedural contusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Procedural headache			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Aphasia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Balance disorder			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
Dizziness			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	4 / 37 (10.81%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	10	0	0
Headache			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
Hypogeusia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Hyposmia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Visual field defect			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
White matter lesion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Autophony			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Deafness Neurosensory			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Ear discomfort			
subjects affected / exposed	3 / 37 (8.11%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
Hypoacusis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Tinnitus			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	2 / 37 (5.41%)	1 / 14 (7.14%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
Eye irritation			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Eye pain			

subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Keratitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Lenticular opacities			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Ocular discomfort			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Punctate keratitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Pupillary reflex impaired			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Strabismus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2

Diarrhoea			
subjects affected / exposed	5 / 37 (13.51%)	1 / 14 (7.14%)	1 / 36 (2.78%)
occurrences (all)	6	1	1
Dry mouth			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Gingival pain			
subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Gingival recession			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Noninfective gingivitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Tongue ulceration			
subjects affected / exposed	1 / 37 (2.70%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 37 (10.81%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	4	2	0
Diffuse alopecia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Dry skin			

subjects affected / exposed	4 / 37 (10.81%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	4	2	0
Eczema			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Ingrowing nail			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Madarosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Onychoclasis			
subjects affected / exposed	4 / 37 (10.81%)	0 / 14 (0.00%)	4 / 36 (11.11%)
occurrences (all)	4	0	4
Petechiae			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Pruritus generalised			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 37 (5.41%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
Rash pruritic			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Urticaria			

subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Polyuria			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 37 (0.00%)	2 / 14 (14.29%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Bursitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Exostosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	18 / 37 (48.65%)	4 / 14 (28.57%)	3 / 36 (8.33%)
occurrences (all)	24	8	3
Musculoskeletal stiffness			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			

subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	4	0	1
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	4	0	0
Localised infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 14 (7.14%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	1
Sinusitis bacterial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	3 / 37 (8.11%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 37 (2.70%)	0 / 14 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Follow-Up Period: No Treatment (OPTIC Teprotumumab)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of skin			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Seborrhoeic keratosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Jugular vein distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Thirst			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Erectile dysfunction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vaginal discharge			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vaginal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasal discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasal dryness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Paranasal sinus discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nightmare			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tension			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood pressure increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Post procedural contusion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Procedural headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rib fracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Disturbance in attention			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypogeusia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyposmia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Visual field defect			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
White matter lesion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Autophony			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Deafness Neurosensory			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dry eye			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Keratitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lenticular opacities			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ocular discomfort			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Punctate keratitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pupillary reflex impaired			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Dry mouth subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Gingival pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Gingival recession subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Glossodynia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Nausea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Noninfective gingivitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Tongue ulceration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0			
Skin and subcutaneous tissue disorders Alopecia				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Diffuse alopecia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Eczema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Ingrowing nail				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Madarosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Nail disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Onychoclasis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Petechiae				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Pruritus generalised				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences (all)	0			
Rash				

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Bursitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Exostosis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Muscle spasms			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinusitis bacterial			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gout			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Glucose tolerance impaired			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Polydipsia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2018	• Added inclusion criterion #11 clarifying subjects should not receive treatment for TED between Week 24 of OPTIC and entry into OPTIC-X. • Added language clarifying lack of efficacy/disease progression withdrawal criteria. • Amended and clarified restrictions on previous and planned use of corticosteroids for the treatment of TED and non-TED conditions. • Added restrictions on the use of non-steroid eye drops during the trial. • Added systemic administration of potential ototoxic medications that may be reasonable to avoid, such as aminoglycosides and platinum-based chemotherapy. • Added that medications that may cause muscle spasm/cramps should be avoided during the trial and added donepezil, neostigmine and vincristine to the list of restricted medications. • Defined end of the trial (the last visit date of the last subject in the trial).
31 January 2019	• Added diplopia responder rate (defined as the percentage of subjects with baseline diplopia >0 in study eye who had a reduction of ≥1 grade with no corresponding deterioration [≥1 grade worsening] in the fellow eye at Week 24) as a secondary endpoint. • Added evaluation of PK parameters of teprotumumab to estimate exposure and understand the PK-PD relationships as an exploratory endpoint. • Changed the number of teprotumumab doses administered from "up to 8 infusions based on Investigator judgment" to "8 infusions." • Specified the End-of-Treatment Visit as Week 24. • Added 2 additional follow-up contacts (telephone or email) at 6 and 12 months after the last visit to assess any additional TED treatment received since last trial contact. For subjects who were proptosis non-responders after completion of the Treatment Period in OPTIC, the last clinic visit was Month 12, with the follow-up contacts at Month 18 and 24. For subjects who relapsed during the Follow-up Period of OPTIC, the last clinic visit was Week 24, with the follow-up contacts at Month 12 and 18. • Clarified that female subjects of childbearing potential who were sexually active with a non vasectomized male partner must agree to use 2 reliable forms of contraception, one of which was recommended to be hormonal, during the trial and for 180 days after the last dose of trial drug. • Clarified that male subjects who were sexually active with a female partner of childbearing potential must agree to use a barrier contraceptive method from Baseline through 180 days after the last dose of trial drug. • Clarified that CAS criteria for determining relapse refers only to the study eye.
31 January 2019	(continued) • Amended the CAS relapse criterion to include an increase in CAS of ≥2 points since Week 24 with an absolute CAS ≥4 following the Week 24 Visit of OPTIC. • Specified the minimum duration of trial drug infusions. • Clarified that the weight obtained at Week 12 could be used for the calculation of trial drug dose beginning at Week 12 or Week 15. • Added PK sampling pre- and post-infusion on Day 1, Week 3 and Week 9 of the Treatment Period, with single samples collected at Weeks 1, 4 and 24. • Changed the definition of the end of the trial to date of the last subject contact at Month 24.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported