Clinical trial results:
A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Active Thyroid Eye Disease (OPTIC Trial)

Summary

EudraCT number	2017-002763-18
Trial protocol	DE IT
Global end of trial date	30 November 2020

Results information

Result version number	v1 (current)
This version publication date	21 November 2021
First version publication date	21 November 2021

Trial information

Trial identification

Sponsor protocol code	HZNP-TEP-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03298867
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Horizon Pharma USA, Inc.
Sponsor organisation address	1 Horizon Way, Deerfield, Illinois, 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	30 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2020
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 versus placebo 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 Week 24.

Protection of trial subjects:

The Investigators ensured that the study was conducted in a manner that fully conformed with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in Guideline for Good Clinical Practice International Council for Harmonisation (ICH) Tripartite Guideline or with local law if it afforded greater protection to the subject.

It was 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 the study after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The Investigator or designee also explained that subjects were 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	04 November 2017
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	Germany: 22
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	83
EEA total number of subjects	39

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)	70
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening for this study was performed 42 to 14 days prior to Day 1 of the Treatment Period.

Period 1

Period 1 title	24-Week Double-Masked Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The pharmacists or designees responsible for preparing the teprotumumab or placebo solutions for IV administration were not masked to the identity of the study drug. Pharmacists/designees provided study drug in infusion bags (fully diluted for administration) to investigative site personnel with appropriate masked labels. The subject, Investigator and all other investigative site personnel were masked to the treatment administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo consisted of a normal saline (0.9% sodium chloride) solution and was administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.

Arm title	Teprotumumab 20 mg/kg

Arm description:

Eight infusions of teprotumumab every 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 solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prior to administration, each vial containing 500 mg teprotumumab freeze-dried powder was reconstituted with 10 mL of water for injection (approximate concentration of 50 mg/mL). Reconstituted teprotumumab solution was further diluted in 0.9% (weight/volume) sodium chloride prior to administration. Doses up to 1800 mg were administered in a total infusion volume of 100 mL, and those above 1800 mg were administered in a total infusion volume of 250 mL.

Number of subjects in period 1	Placebo	Teprotumumab 20 mg/kg
Started	42	41
Completed	40	39
Not completed	2	2
Consent withdrawn by subject	1	1
Adverse event	1	1

Period 2	
Period 2 title	48-Week Follow-Up Period (Weeks 24-72)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Teprotumumab 20 mg/kg

Arm description:

Eight infusions of teprotumumab every 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	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Placebo	Teprotumumab 20 mg/kg
Started	4	36
Completed	3	20
Not completed	1	16
Physician decision	-	1
Consent withdrawn by subject	-	2
Relapsed/Entered OPTIC-X	1	9
Other, not specified	-	1
Misclassified as responders	-	2
Relapsed/Did Not Enter OPTIC-X	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 36 non-responders in the placebo arm and 5 non-responders in the teprotumumab arm did not enter the 48-week follow up period, but enrolled in the OPTIC-X open-label extension study (2017-002713-58; NCT03461211).

Period 3

Period 3 title	48-Week Follow-Up Contact (Weeks 96-120)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Teprotumumab 20 mg/kg

Arm description:

Eight infusions of teprotumumab every 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	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Placebo	Teprotumumab 20 mg/kg
Started	3	20
Completed	3	19
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.	
Reporting group title	Teprotumumab 20 mg/kg
Reporting group description:	
Eight infusions of teprotumumab every 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	Placebo	Teprotumumab 20 mg/kg	Total
Number of subjects	42	41	83
Age categorical Units: Subjects			
<65 years	38	32	70
≥65 years	4	9	13
Age continuous Units: years			
arithmetic mean	48.9	51.6	
standard deviation	± 12.96	± 12.63	-
Gender categorical Units: Subjects			
Female	31	29	60
Male	11	12	23
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	41	39	80
Race Units: Subjects			
Asian	1	2	3
Black or African American	2	4	6
White	37	35	72
More Than 1 Race	2	0	2
Tobacco use status - as randomized Units: Subjects			
Non-User	33	32	65
User	9	9	18
Tobacco use status - actual			
Actual tobacco use status reflects the status as reported on the substance use case report form. One participant was randomized in error to the tobacco user stratum as this subject was reported as a non-user (former tobacco use status) on the substance use case report form.			
Units: Subjects			
Non-User	34	32	66
User	8	9	17

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.	
Reporting group title	Teprotumumab 20 mg/kg
Reporting group description:	
Eight infusions of teprotumumab every 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	Placebo
Reporting group description:	
Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.	
Reporting group title	Teprotumumab 20 mg/kg
Reporting group description:	
Eight infusions of teprotumumab every 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	Placebo
Reporting group description:	
Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.	
Reporting group title	Teprotumumab 20 mg/kg
Reporting group description:	
Eight infusions of teprotumumab every 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 Who Were Proptosis Responders at Week 24

End point title	Percentage of Participants Who Were Proptosis Responders at Week 24
End point description:	
Proptosis responders were defined as participants with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration (≥2 mm increase) of proptosis in the fellow eye at Week 24. Intent-to-treat population: all randomized participants.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: percentage of participants				
number (not applicable)	9.5	82.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified difference (teprotumumab - placebo) is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with Cochran-Mantel-Haenszel (CMH) weights.

Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	73.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.89
upper limit	88.01
Variability estimate	Standard error of the mean
Dispersion value	7.43

Notes:

[1] - Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

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

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

End point description:

Overall responders were defined as participants with a ≥2 mm reduction in proptosis AND a ≥2 point reduction in Clinical Activity Score (CAS) from Baseline in the study eye, without deterioration (≥2 mm increase in proptosis or ≥2 point increase in CAS) in the fellow eye at Week 24.
The CAS is a 7-item description of clinical activity, including: 1. Spontaneous orbital pain; 2. Gaze evoked orbital pain; 3. Eyelid swelling that is considered to be due to active (inflammatory phase) thyroid eye disease/ Graves' Ophthalmopathy or Orbitopathy (TED/GO); 4. Eyelid erythema; 5. Conjunctival redness that is considered to be due to active (inflammatory phase) TED/GO (ignore "equivocal" redness); 6. Chemosis; 7. Inflammation of caruncle or plica. Each item is scored (1=present; 0=absent) and scores for each item are summed for total score of 0 (no clinical activity) to 7 (most clinical activity).

Intent-to-treat population: all randomized participants.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: percentage of participants				
number (not applicable)	7.1	78.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified difference (teprotumumab - placebo) is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights.

Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	70.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.89
upper limit	85.75
Variability estimate	Standard error of the mean
Dispersion value	7.62

Notes:

[2] - Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

Secondary: Percentage of Participants Who Were CAS Categorical Responders at Week 24 (Study Eye)

End point title	Percentage of Participants Who Were CAS Categorical Responders at Week 24 (Study Eye)

End point description:

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

The CAS is a 7-item description of clinical activity, including: 1. Spontaneous orbital pain; 2. Gaze evoked orbital pain; 3. Eyelid swelling that is considered to be due to active (inflammatory phase) thyroid eye disease/ Graves' Ophthalmopathy or Orbitopathy (TED/GO); 4. Eyelid erythema; 5. Conjunctival redness that is considered to be due to active (inflammatory phase) TED/GO (ignore "equivocal" redness); 6. Chemosis; 7. Inflammation of caruncle or plica. Each item is scored (1=present; 0=absent) and scores for each item are summed for total score of 0 (no inflammatory symptoms) to 7 (most inflammatory symptoms).

Intent-to-treat population: all randomized participants.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: percentage of participants				
number (not applicable)	21.4	58.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified difference (teprotumumab - placebo) is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights.

Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	36.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.39
upper limit	54.67
Variability estimate	Standard error of the mean
Dispersion value	9.51

Notes:

[3] - Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

Secondary: Change From Baseline in Proptosis to Week 24 (Study Eye)

End point title	Change From Baseline in Proptosis to Week 24 (Study Eye)

End point description:

Intent-to-treat population: all randomized participants.

End point type	Secondary

End point timeframe:

Baseline, up to Week 24

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: mm				
least squares mean (standard error)	-0.54 (± 0.192)	-2.82 (± 0.191)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	MMRM
Parameter estimate	Difference in LS mean
Point estimate	-2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.77
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	0.244

Notes:

[4] - Results obtained from a mixed model repeated-measures (MMRM) with an unstructured covariance matrix including the following terms: Baseline value, tobacco use status, treatment group, visit, visit-by-treatment interaction and visit-by-Baseline-value

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 Baseline diplopia Subjective Diplopia Score grade >0 in the study eye who had a reduction of ≥1 grade with no corresponding deterioration (≥1 grade worsening) in the fellow eye at Week 24. Denominator is the number of subjects with diplopia at Baseline.
The Subjective Diplopia Score is a clinical measure of diplopia severity on a grade scale of 0 to 3: 0=no diplopia; 1=intermittent (diplopia in primary position of gaze, when tired or when first awakening); 2=inconstant (diplopia at extremes of gaze); 3=constant (continuous diplopia in primary or reading position).

Intent-to-treat population: all randomized participants with diplopia at baseline in the study eye.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: percentage of participants				
number (not applicable)	28.6	67.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified difference is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights.

Test statistic=3.244, calculated by dividing the stratified difference by the SE.

Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	39.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.55
upper limit	63.02
Variability estimate	Standard error of the mean
Dispersion value	12.11

Notes:

[5] - Two-sided p-value calculated assuming the test statistic was distributed as a standard normal random variable.

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

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

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 subjects on (i) their daily physical activity as it relates to visual function, and (ii) psychosocial functioning. The range of the GO-QoL overall transformed scores is 0 to 100, where higher values correspond to better quality of life.

Intent-to-treat population: all randomized participants.

End point type	Secondary

End point timeframe:

Baseline, up to Week 24

End point values	Placebo	Teprotumumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: score on a scale				
least squares mean (standard error)	4.43 (± 2.102)	13.79 (± 2.074)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Teprotumumab 20 mg/kg
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	9.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.08
upper limit	14.64
Variability estimate	Standard error of the mean
Dispersion value	2.651

Notes:

[6] - Results obtained from an MMRM with an unstructured covariance matrix including the following terms: Baseline value, tobacco use status, treatment group, visit, visit-bytreatment interaction and visit-by-Baseline-value interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through the end of the Double-Masked Treatment Period (up to 24 weeks) plus 3 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Eight infusions of placebo every 3 weeks (q3W) for a total of 21 weeks.

Reporting group title	Teprotumumab 20 mg/kg

Reporting group description:

Eight infusions of teprotumumab every 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.

Serious adverse events	Placebo	Teprotumumab 20 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)	2 / 41 (4.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Visual field defect			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
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	Placebo	Teprotumumab 20 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 42 (69.05%)	37 / 41 (90.24%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 42 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Dysgeusia			
subjects affected / exposed	0 / 42 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Headache			
subjects affected / exposed	4 / 42 (9.52%)	4 / 41 (9.76%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 42 (2.38%)	5 / 41 (12.20%)	
occurrences (all)	1	6	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Diarrhoea			
subjects affected / exposed	5 / 42 (11.90%)	5 / 41 (12.20%)	
occurrences (all)	6	6	
Nausea			
subjects affected / exposed	4 / 42 (9.52%)	6 / 41 (14.63%)	
occurrences (all)	5	14	
Stomatitis			
subjects affected / exposed	1 / 42 (2.38%)	3 / 41 (7.32%)	
occurrences (all)	1	3	

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 42 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 42 (11.90%)	10 / 41 (24.39%)	
occurrences (all)	5	13	
Dry skin			
subjects affected / exposed	0 / 42 (0.00%)	5 / 41 (12.20%)	
occurrences (all)	0	5	
Madarosis			
subjects affected / exposed	0 / 42 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	4 / 42 (9.52%)	14 / 41 (34.15%)	
occurrences (all)	4	28	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2017	1. Updated the SAE reporting procedure to enter the information into the eCRF and email/fax the information only if the site was unable to access the eCRF to ensure the Sponsor had access to the information; 2. Added efficacy evaluations (CAS and Clinical Measures of Severity [including proptosis]) to Weeks 36, 48 and 60 in order to identify relapsed subjects at earlier time points in the study; 3. Added pregnancy tests to Week 48 for women of childbearing potential, and increased the contraception requirement and the pregnancy reporting period (for both men and women) from 90 days to 180 days due to the teratogenic effects of teprotumumab noted in a monkey embryo-fetal development toxicity study. Based on the Week 24 plasma exposures demonstrated in a previous study (TED01RV), the 6-month waiting period would allow sufficient time for plasma concentrations to decrease to levels that would reduce the risk of teratogenicity; 4. Specified that any planned corrective surgery/irradiation over the course of the study was not allowed (Inclusion Criterion #7) in order not to interfere with interpretation of the efficacy results; 5. Added post-infusion vital signs to Week 3 (second infusion of study drug) as an added safety precaution; 6. Clarified/updated AEs requiring permanent discontinuation from the study: • Subjects with any drug-related anaphylactic reaction were to be discontinued from the study; • Provided a laboratory cutoff value for hyperglycemia; • Added diagnosed or suspected inflammatory bowel disease (diagnosed or suspected inflammatory bowel disease was already an exclusion criterion), as exacerbation of underlying inflammatory bowel disease by teprotumumab could not be excluded at that time; 7. Clarified the definition of an overdose to be 5% or more than the assigned dose;
24 October 2017	(continued) 8. Added Bioclinica eClinical Solutions IWRS contacts prior to dosing for each scheduled infusion (Weeks 3, 6, 9, 12, 15, 18 and 21) in addition to Day 1, as Bioclinica was also responsible for clinical supply inventory management. Also added IWRS contacts at Screening and the Week 24 Visit to register the Screening and End-of-Treatment Visits; 9. Clarified that the volume of study drug to be administered was determined by the IWRS and not the site pharmacist; 10. Added that any subject testing positive for ADA (after confirmatory and reactive titer testing) was tested for NAb. Subjects positive for NAb (not those positive for ADA) were to be followed until levels either reverted to Baseline or the subject's value decreased or remained stable; and 11. Other minor typographical errors, omissions and clarifications.

16 April 2018	1. Incorporated the changes of Protocol Version 1.1; 2. Updated the contract research organization name (from INC Research to Syneos Health) and address; 3. Increased the upper age limit from 75 to 80 years; 4. Clarified that the exclusionary changes in proptosis and CAS between Screening and Baseline refers only to the study eye; 5. Amended and clarified restrictions on previous and planned use of corticosteroids for the treatment of TED and non-TED conditions; 6. Excluded subjects with human immunodeficiency virus, hepatitis C, or hepatitis B infections; 7. Added restrictions on the use of non-steroid eye drops during the study; 8. Added 'or designee' to the unmasked pharmacist role in the study where allowed by institutional policy and local regulations; 9. Clarified that used and partially used drug vials were to be retained at the investigative site only if permitted by site policy; and 10. Updated the status of the Investigator's Brochure from in progress to completed.
31 January 2019	1. Added diplopia responder rate (defined as the percentage of subjects with Baseline diplopia >0 in study eye who have a reduction of ≥1 grade with no corresponding deterioration [≥1 grade worsening] in the fellow eye at Week 24) as a secondary endpoint; 2. Added 2 additional follow-up contacts (telephone or email) at 6 and 12 months after the Week 72 Visit to assess any additional TED treatment received since last study contact; 3. Clarified that female subjects of childbearing potential who were sexually active with a non-vasectomized male partner must have agreed 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 study drug; 4. Clarified that male subjects who were sexually active with a female partner of childbearing potential must have agreed to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug; 5. Changed the number of teprotumumab doses administered in the open-label extension study (HZNP-TEP-302) from "up to 8" to '8'. 6. Clarified that the CAS criteria for determining relapse refers only to the study eye; 7. 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; 8. Specified the minimum duration of study drug infusions; 9. Clarified that the weight obtained at Week 12 could be used for the calculation of study drug dose beginning at Week 12 or Week 15; 10. Removed the specified temperature collection methods (oral or tympanic); 11. Corrected that the urine sample collected at Week 15 was for pregnancy testing only; 12. Changed the definition of the end of the trial to date of the last subject contact at Week 120; 13. Updated statistical analysis methods; 14. Updated Sponsor Representative title; and 15. Corrected minor typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported