



**CLINICAL STUDY PROTOCOL
FOR TEPROTUMUMAB (HZN-001)**

IND: 112952

Protocol Number: HZNP-TEP-301

EudraCT No.: 2017-002763-18

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

Short Title: PTIC™

**Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in a
Randomized, Placebo-Controlled, Clinical Study**

Date: 31 January 2019

Version 4.0, incorporating Amendment 3

**Sponsor:
Horizon Pharma USA, Inc.
150 S. Saunders Road
Lake Forest, IL 60045**

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CONFIDENTIAL

PROTOCOL

1 TITLE PAGE

Study Title: 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)

Protocol Number: HZNP-TEP-301

Version: 4.0 incorporating Amendment 3

Investigational Product: Teprotumumab (HZN-001)

Indication: Thyroid Eye Disease (TED) (also called Graves' Ophthalmopathy or Orbitopathy [GO] and Thyroid-Associated Ophthalmopathy [TAO]).

Sponsor: Horizon Pharma USA, Inc.
150 S. Saunders Road
Lake Forest, IL 60045

Development Phase: 3

Sponsor's Responsible Medical Officer: [REDACTED]
Horizon Pharma USA, Inc.
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Lake Forest, IL 60045

Sponsor Signatory: [REDACTED]
Horizon Pharma USA, Inc.

Approval Date: 31 January 2019

CONTACT IN THE EVENT OF AN EMERGENCY

Any death, life threatening event, or other Serious Adverse Event experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contact numbers provided below.

Fax: [REDACTED]

Email: [REDACTED]

Horizon Pharma USA, Inc.
Date: 31 January 2019

Teprotumumab (HZN-001) IND: 112952
Protocol: HZNP-TEP-301
Version 4.0, Incorporating Amendment 3

SPONSOR SIGNATURE PAGE

Protocol Number: HZNP-TEP-301
Version: 4.0, incorporating Amendment 3
Protocol Title: 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)
Version Date: 31 January 2019
Approved by:

[Redacted Signature]

06 FEB 2019
Date

Horizon Pharma USA, Inc.
[Redacted Signature]

2-6-19
Date

[Redacted Signature]

2.2.19
Date

[Redacted Signature]

06 FEB 2019
Date

Feb 6, 2019
Date

Horizon Pharma USA, Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-TEP-301
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I agree to conduct the study according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a subject.

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the study drug supplied by the Sponsor will be used only as described in the protocol named above.

Signature:

Name
Study Center
Address
City State Country

Date

SUMMARY OF CHANGES
Protocol HZNP-TEP-301
Version 4.0, incorporating Amendment 3

Version 3.0 of the protocol, which was approved 16 April 2018, has been amended to incorporate the changes of Amendment 3.

- Add 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.
- Add 2 additional follow-up contacts (telephone or email) at 6 and 12 months after the Week 72 Visit to assess any additional thyroid eye disease (TED) treatment received since last study contact.
- Clarify that female subjects of childbearing potential who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception, one of which is recommended to be hormonal, during the trial and for 180 days after the last dose of study drug.
- Clarify that male subjects who are sexually active with a female partner of childbearing potential must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.
- Change the number of teprotumumab doses that will be administered in the open-label extension study (HZNP-TEP-302) from “up to 8” to ‘8’.
- Clarify that Clinical Activity Score (CAS) criteria for determining relapse refers only to the study eye.
- Amend 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.
- Specify the minimum duration of study drug infusions.
- Clarify that the weight obtained at Week 12 can be used for the calculation of study drug dose beginning at Week 12 or Week 15.
- Remove the specified temperature collection methods (oral or tympanic).
- Correct that the urine sample collected at Week 15 is for pregnancy testing only.
- Change the definition of the end of the trial to date of the last subject contact at Week 120.
- Update statistical analysis methods.
- Update Sponsor Representative title.
- Correct minor typographical errors (changes are not detailed below).

The following sections of the protocol are affected: 2, 2.1, 7.1.3.4.5.5.1, 8.2, 9.1, Figure 9.1, 9.3.1, 9.3.4, 9.4.1, 9.4.6.2, 9.4.6.3.1, 9.4.6.3.2, 9.5.1, 9.5.5.4, 9.5.5.5, 9.5.7.1, 9.5.7.2, 9.5.7.6, 9.5.7.8, 9.5.7.9, 9.5.7.10, 9.5.7.12, 9.5.7.13, 9.5.7.14, 9.5.7.15, 9.5.7.16, 9.5.7.17, 9.5.7.18,

9.5.7.19, 9.6.1.2, 9.6.3, 9.6.4.2, and 17.1. Additional text is marked in red, underlined, and bolded; deleted text is marked as strikethrough text.

2 SYNOPSIS

Objectives:

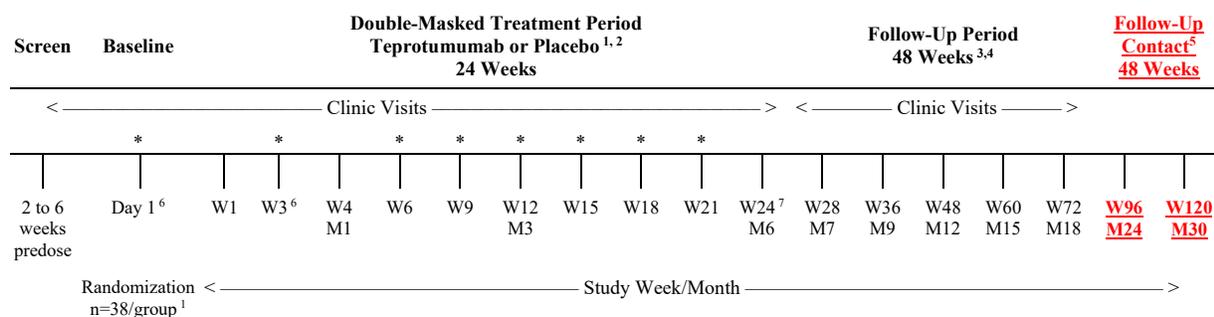
Secondary Objectives (analyzed hierarchically)

- 4. Evaluate the effect of teprotumumab versus placebo on the diplopia responder rate (i.e., 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.**
- 5.4.** Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

Study Design:

At the end of the double-masked Treatment Period (Week 24), subjects who are proptosis non-responders (study eye has < 2 mm decrease in proptosis) will be eligible to enter an open-label extension study (HZNP-TEP-302) in which subjects may receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion.

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.



* Infusion of study drug.

1. Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive:
 - a. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
 - b. Placebo (placebo q3W for all 8 infusions).
2. Visit windows are ± 1 day for Weeks 1 and 4, ± 3 days for Weeks 3, 6, 9, 12, 15, 18, and 21, and ± 7 days for Week 24.
3. Subjects who are **proptosis** responders or non-responders who do not elect to participate in the open-label extension study will enter a 48-week Follow-Up Period. Subjects who are responders at Week 24 but relapse during the Follow-Up Period may enter the open-label study and receive ~~up to~~ 8 infusions if they meet specified criteria.
4. Visit windows of ± 7 days.
5. **Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.**
6. Subjects will be contacted by phone/email the day following the first and second infusions for safety and tolerability assessments; phone/email contacts will also occur the day after any clinic visit where a subject experiences an infusion-related adverse event.
7. Subjects who are **proptosis** non-responders at Week 24 of the double-masked Treatment Period will be offered the option to enter an open-label extension study and receive ~~up to~~ 8 ~~additional~~ infusions of teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions ~~all subsequent doses~~).

Inclusion Criteria:

10. Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through Week 48 of the Follow-Up Period); subjects **who are sexually active with a non-vasectomized male partner** must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, includes implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.
11. Male subjects must be surgically sterile or, **if sexually active with a female partner of childbearing potential**, must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.

Dose Regimen/Route of Administration:

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). The first and second infusions will be administered over **approximately 90 minutes (but not less than 80 minutes)**. Subsequent infusions will be

administered over a **approximately 60 minutes (but not less than 50 minutes), period** providing there are no significant infusion-associated events.

Duration of Treatment and Follow-up:

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.

Criteria for Evaluation:

Efficacy will be assessed by proptosis (measured as exophthalmos evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CAS (7-item scale), **diplopia (measured as part of the Clinical Measures of Severity)**, and Clinical Measures of Severity (including motility restriction assessments).

Statistical Analyses

Secondary Efficacy Endpoints (analyzed hierarchically):

- 4. The effect of teprotumumab versus placebo on the diplopia responder rate (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.**
- 5.4.** The effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire overall score.

Statistical Analysis of Efficacy Parameters:

The primary analyses will be conducted in the Intent-to-Treat (ITT) population. The analysis of the primary proptosis responder endpoint will **assess risk difference (difference in response rates) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference.** ~~be a logistic regression with treatment group as the model effect.~~ Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the primary analysis. **Further, subjects who prematurely discontinue study drug dosing prior to Week 21 during the double-masked Treatment Period will be considered to be treatment failures (non-responders), unless an assessment at Week 24 is available. Stratification for the analysis will use the same factor as was used to stratify randomization, tobacco use (non-user, user).** ~~Since tobacco use status (non-user vs. user) is used to stratify the randomization, it will be included as a categorical covariate.~~ **The difference in response rates, comparing teprotumumab to placebo, will be estimated** ~~Odds ratio comparing teprotumumab to placebo will be estimated along with the corresponding 95% confidence interval (CI) and p-value.~~

An analysis of risk difference with stratification by tobacco use (non-user vs. user) ~~Logistic regression~~ will also be used to analyze the **32** secondary categorical endpoints (overall responder rate, CAS [value of 0 or 1] **and diplopia responder rate**). For the analysis of proptosis as a continuous secondary endpoint and GO-QoL, a Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline

scores **for the study eve**, with terms in the model being the baseline score, tobacco use status, treatment group, visit, and the visit-by-treatment and visit-by-baseline-score interactions. The main focus of the analysis will be to test the treatment differences at Week 24, with the main results consisting of the Week 24 estimated Least Square (LS) means and their differences with 95% CIs and p-values.

To control the overall Type 1 error rate of the study, taking into consideration the one primary and 54 secondary outcome measures, the outcome measures will be tested in a hierarchical stepwise fashion. For each outcome measure, teprotumumab will be tested against placebo at the 0.05 level only if teprotumumab was statistically significant for the outcome measure preceding it in the hierarchical order.

2.1 Schedule of Assessments

	Screening ¹	Treatment Period ²											Follow-Up Period ³					Follow-Up Contact ⁴	
Study Visit	S1/S2/S3	1	2	3	4	5	6	7	8	9	10	11/ PW1 ^{5,4}	12	13	14	15	16/ PW2 ^{6,5}	17	18
Week (W)/ Month (M)	-42 to -14 days	Day 1 ^{7,6}	W1	W3	W4/ M1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M42	W120/ M66
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
Informed Consent	X																		
Review inc/exc criteria	X	X																	
Demographics	X																		
Medical History ^{8,7}	X ^{9,8}	X																	
Weight ^{10,9}	X							X				X		X	X	X	X		
Randomization ^{11,9}		X ^{7,6}																	
Study drug infusion		X	X		X	X	X	X	X	X	X								
Phone (email) contact for safety 24 hours postdose ^{12,†}		X	X																
Efficacy assessments																			
CAS ^{13,‡}	X	X ^{14,‡}				X		X		X		X	X	X	X	X	X		
Clinical Measures of Severity - includes proptosis, diplopia and motility restriction	X	X ^{15,‡}				X		X		X		X	X	X	X	X	X		
Safety assessments																			
Pregnancy Test ^{16,‡}	X	X		X		X	X	X	X	X	X	X	X	X	X		X ^{17,‡}		
Physical exam ^{18,‡}	X ^{19,‡}	X ^{18,‡}	X			X		X		X		X ^{18,‡}			X		X ^{18,‡}		
Ophthalmic exam ^{20,49}	X ^{21,9}	X	X			X		X		X		X			X		X		
Vital Signs ^{22,‡}	X	X ^{22,‡}	X	X ^{22,‡}	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X	X	X	X		X		X				X					X		
Clinical laboratory tests ^{23,‡}																			
Chemistry (excl. glucose)	X ^{24,‡}	X		X		X	X	X		X		X		X			X		
Thyroid (FT3, FT4, TSH) ^{25,-}	X	X		X		X	X	X		X		X		X			X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X		X			X		

	Screening ¹	Treatment Period ²											Follow-Up Period ³					Follow-Up Contact ⁴	
Study Visit	S1/S2/S3	1	2	3	4	5	6	7	8	9	10	11/ PW1 ^{5,4}	12	13	14	15	16/ PW2 ^{5,5}	17	18
Week (W)/ Month (M)	-42 to -14 days	Day 1 ^{2,6}	W1	W3	W4/ M1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M42	W120/ M66
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
Glucose ^{23,2}	X	X	X	X	X	X	X	X	X	X	X	X		X			X		
HbA1c ^{26,5}	X							X				X		X			X		
Urinalysis	X	X		X		X	X	X		X		X		X			X		
ADA/NAb samples ^{27,6}		X		X			X					X ^{28,9}		X			X		
AE, SAE assessment ^{29,7}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
GO-QoL Questionnaire		X				X		X				X	X		X		X		
Biomarker samples ^{30,28}		X						X				X							
PK samples ^{31,29}		X	X	X	X		X					X ^{28,29}							
Contact (phone/email) to assess additional TED treatment³²																		X	X

ADA=anti-drug antibody; AE=adverse event; CAS=Clinical Activity Score; ECG=electrocardiogram; FT3=free triiodothyronine; FT4=free thyroxine; FU=Follow-Up; GO-QoL=Graves' Ophthalmopathy Quality of Life Questionnaire; HbA1c=glycated hemoglobin; M=month; NAb=neutralizing antibody; PK=pharmacokinetic; PW=premature withdrawal; SAE=serious adverse event; TED=thyroid eye disease; TSH=thyroid stimulating hormone; W=week.

Footnotes:

- Screening procedures can take place over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window.
- Double-masked Treatment Period. Subjects who are proptosis non-responders at Week 24 are eligible to enroll in an open-label extension study in which all subjects will receive teprotumumab 20 mg/kg (10 mg/kg for the first infusion and 20 mg/kg for the remaining infusions).
- Proptosis responders and non-responders who choose not to enroll in the open-label extension study will participate in a 48-week Follow-Up Period.
- Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.**
- 5.4.** If a subject prematurely discontinues study drug during the Treatment Period, they will return for a clinic visit and undergo the Week 24 assessments, with the exception of the collection of blood samples for PK and ADA evaluations. Subjects will be encouraged to continue study participation in the Follow-Up Period.
- 6.5.** If a subject prematurely discontinues from the study during the Follow-Up Period, they will return for a clinic visit and undergo the Week 72 assessments prior to discharge.
- 7.6.** On Day 1 (Baseline), subjects will be randomized and receive the first dose of study drug; however, Baseline assessments will be performed prior to dosing.
- 8.7.** Medical history including tobacco use history and Graves' disease and treatment history.

- ~~9.8.~~ TED must be moderate to severe in intensity (non-sight threatening but appreciable impact on daily life) with an onset of symptoms (as determined by subject records) within 9 months prior to the Baseline Visit for study enrollment.
- ~~10.9.~~ Dosing will be adjusted if there is a change in weight during the Treatment Period. **The weight obtained at Week 12 can be used in dose calculations beginning at Week 12 or Week 15.**
- ~~11.40.~~ Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive either: a) teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) or b) placebo (q3W for all 8 infusions).
- ~~12.41.~~ Phone (or email) contact by research staff focusing on safety and tolerability aspects will be made the day after infusion for the first and second infusions, and thereafter as deemed appropriate. In addition, subjects who experience an infusion-associated event after any subsequent infusion will also be contacted by phone (or email) by research staff the day after the infusion, and thereafter as deemed appropriate.
- ~~13.42.~~ CAS must be ≥ 4 for enrollment and randomization.
- ~~14.43.~~ Subjects whose CAS score decreases 2 or more points in the study eye from Screening are not eligible for randomization.
- ~~15.44.~~ Subjects who have a ≥ 2 mm decrease in proptosis in the study eye from Screening are not eligible for randomization.
- ~~16.45.~~ Serum pregnancy test at Screening and urine pregnancy tests prior to dose at all other visits, as applicable. Perform for female subjects of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]).
- ~~17.46.~~ Pregnancy test only performed for female subjects of childbearing potential who enter the Follow-Up Period but discontinue study participation prior to Week 48.
- ~~18.47.~~ Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1 and Week 24 (or PW) of the Treatment Period and Week 72 (or PW) of the Follow-Up Period. If present, measurements of instep and calf will be taken.
- ~~19.48.~~ Height will be measured at Screening only.
- ~~20.49.~~ Ophthalmic exam: best corrected visual acuity, pupil exam, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure, and slit lamp exam. If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including APD, rise in intraocular pressure, development of corneal infiltrates or other abnormalities not here specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.
- ~~21.20.~~ Subjects who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) are not eligible for randomization.
- ~~22.21.~~ Vital signs (heart rate, blood pressure, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3, and pre-dose on all other infusion days. Additional vital signs will be monitored if infusion-associated AEs occur (see [Section 9.5.5.4](#) for details).
- ~~23.22.~~ Non-diabetic subjects should be fasting at Weeks 1 and 4 only. Diabetic subjects should be fasting at each visit blood glucose is evaluated.
- ~~24.23.~~ ALT/AST must be ≤ 3 x the upper limit of normal (ULN) and serum creatinine must be < 1.5 x the ULN according to age to be eligible for randomization.
- ~~25.24.~~ Subjects must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels $< 50\%$ above or below the normal limits). Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
- ~~26.25.~~ HbA1c must be $< 9.0\%$ for randomization. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 45 days until it returns to normal or baseline value.
- ~~27.26.~~ If a sample is positive in the ADA test, after confirmatory and reactive titer testing, the sample will then be tested for NAb. If the subject tests positive for NAb, he/she will be followed until levels either revert to Baseline or the subject's value decreases or remains stable. Any subject with a positive NAb test at Week 72 (or PW) during the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.
- 28. Not collected for subjects who prematurely discontinue from the Treatment Period.**

- ~~29.27.~~ Adverse events (AEs) that occur within 2 weeks prior to Day 1 and prior to dosing on Day 1 will be considered baseline signs/symptoms. Adverse events occurring or worsening after the dose on Day 1 through the end of the Treatment Period will be considered treatment-emergent AEs (TEAEs). Adverse events occurring or worsening during the Follow-Up Period will be considered postdose AEs. All SAEs that occur from the signing of informed consent through 30 days after study discontinuation will be recorded.
- ~~30.28.~~ Serum (two 5.0 mL samples) will be obtained on Day 1 and Weeks 12 and 24 of the Treatment Period for possible analysis of interleukin (IL)-4, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-1 β , sIL-1RA, INF γ , TGF β , TNF α , micRNA and TSH-R-Ab. Based on the results of the above assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms.
- ~~31.29.~~ PK samples will be collected prior to, and at the end of, the infusion on Day 1 and Weeks 3 and 9 of the Treatment Period; additional single samples will be collected at Weeks 1, 4, and 24.
- 32. If TED treatment has been received since last contact, the subject will be questioned regarding type of treatment and outcome/response.**
- ~~30.~~ Not collected for subjects who prematurely discontinue from the Treatment Period.

7.1.3.4.5.1 Overview and Precautions for AESIs

In general, the decision to keep a subject on study treatment with teprotumumab should take into consideration potential risks and benefits to the subject. Prior to all future infusions of teprotumumab, these subjects should be pre-medicated with IV diphenhydramine 1 to 1.25 mg/kg (maximum: 50 mg), IV ranitidine 50 mg, IV dexamethasone 0.4 mg/kg (maximum: 20 mg), and/or acetaminophen 500 mg. In addition, all future infusions should be administered over **approximately 90 minutes (but not less than 80 minutes)**. Vital signs should be taken every 15 minutes during the infusion.

8.2 Secondary Objectives

4. Evaluate the effect of teprotumumab versus placebo on the diplopia responder rate (i.e., 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.

5.4. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

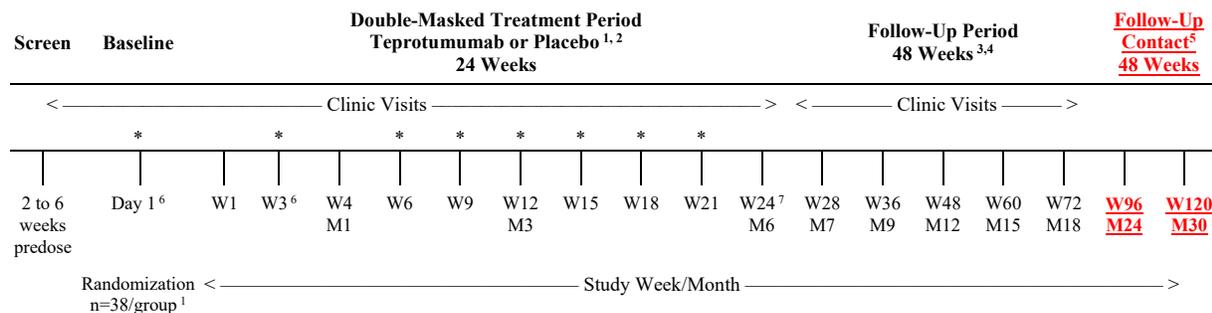
9.1 Overall Study Design and Plan

Study Design:

At the end of the double-masked Treatment Period (Week 24), subjects who are proptosis non-responders (study eye has < 2 mm decrease in proptosis) will be eligible to enter an open-label extension study (HZNP-TEP-302) in which subjects may receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion. Discussion of this option with the subject and informed consent presentation for HZNP-TEP-302 should be discussed at the Week 24 Visit given enrollment in HZNP-TEP-302 must occur within 2 weeks of the Week 24 Visit.

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

Figure 9.1 Schematic of Study Design



* Infusion of study drug.

1. Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive:
 - a. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
 - b. Placebo (placebo q3W for all 8 infusions).
2. Visit windows are ± 1 day for Weeks 1 and 4, ± 3 days for Weeks 3, 6, 9, 12, 15, 18, and 21, and ± 7 days for Week 24.
3. Subjects who are proptosis responders or non-responders who do not elect to participate in the open-label extension study will enter a 48-week Follow-Up Period. Subjects who are responders at Week 24 but relapse during the Follow-Up Period may enter the open-label study and receive up to 8 infusions if they meet the criteria defined in Section 9.3.4.
4. Visit windows of ± 7 days.
5. **Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.**
6. Subjects will be contacted by phone/email the day following the first and second infusions for safety and tolerability assessments; phone/email contacts will also occur the day after any clinic visit where a subject experiences an infusion-related AE.
7. Subjects who are proptosis non-responders at Week 24 of the double-masked Treatment Period will be offered the option to enter an open-label extension study and receive up to 8 additional infusions of teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions all subsequent doses).

9.3.1 Inclusion Criteria

10. Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through Week 48 of the Follow-Up Period); subjects **who are sexually active with a non-vasectomized male partner** must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, includes implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.
11. Male subjects must be surgically sterile or, **if sexually active with a female partner of childbearing potential**, must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.

9.3.4 Criteria for Responders Who Relapse

If subjects meet the response criteria at Week 24 but subsequently experience a disease relapse during the 48-week Follow-Up Period, they will have the option to enter the open-label study with teprotumumab (HZNP-TEP-302) and receive ~~up to~~ 8 infusions of teprotumumab. The criteria to determine relapse is the following:

- Increase in proptosis of ≥ 2 mm in the study eye since Week 24, or
- An **increase in CAS of ≥ 2 points since Week 24 with an** absolute CAS of ≥ 4 **in the study eye** following the Week 24 Visit.
- In addition to one of the bullet points above, the Investigator should also consider the subject's symptomology to ensure a relapse has occurred (e.g., new onset of double vision).

9.4.1 Treatments Administered

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability. The first and second infusions will be administered over **approximately** 90 minutes **(but not less than 80 minutes)**. Subsequent infusions will be administered over **approximately** 60 minutes **(but not less than 50 minutes)**, ~~period~~ providing there are no significant infusion-associated events.

9.4.6.2 Determination of Dose Volume

The volume of study drug to be administered will be determined by the interactive web response system (IWRS) and will be based on the subject's weight. The first dose will be 10 mg/kg, and subsequent doses will be 20 mg/kg. Weight will be measured at Screening and Weeks 12 and 24 during the Treatment Period. The dose on Day 1 of the double-masked Treatment Period will be based on the Screening weight. **The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15, as appropriate.** ~~and the dose may be adjusted at Week 12, as appropriate.~~

9.4.6.3.1 Preparation and Administration of Teprotumumab

The first and second IV infusions on Day 1 and Week 3 will be administered over **approximately** 90 minutes **(but not less than 80 minutes)** for all subjects; subsequent infusions may be administered over a shorter time period (**approximately** 60 minutes, **but not less than 50 minutes**) in the absence of any infusion-associated events. All subjects will be monitored for AEs from the start of infusion through 60 minutes after infusion completion for the first 3 doses; the monitoring period for subsequent doses may be reduced to 30 minutes after infusion completion for subjects who do not experience infusion-associated events.

9.4.6.3.2 Dose Modifications, Interruptions, and Delays

Following the appearance of either immediate or delayed infusion-associated events, subsequent doses may be pre-treated with diphenhydramine (1 to 1.25 mg/kg IV; maximum of 50 mg), ranitidine (50 mg IV), famotidine (0.5 mg/kg IV), dexamethasone (0.4 mg/kg IV; maximum of 20 mg), and/or acetaminophen (500 mg). All subsequent infusions will be administered over approximately 90 minutes (but not less than 80 minutes) period with vital signs monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion.

9.5.1 Efficacy Variables

Efficacy will be assessed by proptosis (measured as exophthalmos evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CAS (7-item scale), diplopia (measured as part of the Clinical Measures of Severity) and Clinical Measures of Severity (including motility restriction assessments).

9.5.5.4 Vital Signs

Vital signs (heart rate, blood pressure, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3, and predose on all other infusion days. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. Also, vital signs will be monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion for any subsequent infusions after the previous occurrence of immediate or delayed infusion-associated events.

Blood pressure and pulse measurements will be obtained with the subject's arm unconstrained by clothing or other material and while the subject is sitting up. When possible, the same arm will be used for measurements in all study visits. ~~Temperature will be obtained orally or via the ear.~~

9.5.5.5 Physical and Ophthalmic Examinations, Height, and Weight

Weight will be measured at Screening and every 12 weeks throughout the study (Weeks 12 and 24 [or PW] during the Treatment Period and Weeks 36, 48, 60, and 72 [or PW] of the Follow-Up Period). The dose on Day 1 of the double-masked Treatment Period will be based on the Screening weight. The weight obtained at Week 12 can be used in dose calculations beginning at Week 12 or Week 15, ~~and the dose may be adjusted at Week 12 as appropriate.~~

9.5.7.1 Screening

- Complete the efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

9.5.7.2 Day 1/Baseline

- Perform predose Baseline efficacy assessments (**CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction** ~~proptosis, CAS, Clinical Measures of Severity including motility restriction~~). Proptosis and CAS may not decrease ≥ 2 mm/points in the study eye from Screening to be eligible for enrollment.

9.5.7.6 Week 6

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).

9.5.7.8 Week 12

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).

9.5.7.9 Week 15

- Collect predose urine sample for ~~urinalysis and also~~ a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.

9.5.7.10 Week 18

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).

9.5.7.12 Week 24

- Perform ~~predose~~ efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).

Subjects who are proptosis non-responders will be offered the opportunity to receive ~~up to 8 additional~~ infusions of teprotumumab in an open-label extension study, HZNP-TEP-302.

9.5.7.13 Week 28

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).

9.5.7.14 Week 36

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia and motility restriction**).

9.5.7.15 Week 48

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

9.5.7.16 Week 60

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

9.5.7.17 Week 72

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

Subjects will be discharged from the study center after all of the procedures have been completed.

~~The end of the trial is defined as the date of the last visit of the last subject undergoing the trial.~~

9.5.7.18 Week 96 – Follow-Up Contact

Subjects who complete the Week 72 Visit will be contacted 6 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

9.5.7.19 Week 120 – Follow-Up Contact

Subjects who complete the Week 72 Visit will be contacted 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

The end of the trial is defined as the date of the last subject contact at Week 120.

9.6.1.2 Secondary Endpoints

Secondary Endpoints (analyzed hierarchically):

4. Diplopia responder rate (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.
- 5.4. Mean change from Baseline to Week 24 in the GO-QoL questionnaire overall score.

9.6.3 Primary and Secondary Endpoint Analysis

The primary analyses will be conducted in the ITT population. The analysis of the primary proptosis responder endpoint will **assess risk difference (difference in response rates) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference.** ~~be a logistic regression with treatment group as the model effect.~~ Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the primary analysis. **Further, subjects who prematurely discontinue study drug dosing prior to Week 21 during the double-masked Treatment Period will be considered to be treatment failures (non-responders), unless an assessment at Week 24 is available. Stratification for the analysis will use the same factor as was used to stratify randomization, tobacco use (non-user, user).** ~~Since tobacco use status (non-user vs. user) is used to stratify the randomization, it will be included as a categorical covariate. The difference in response rates, comparing teprotumumab to placebo, will be estimated~~ Odds ratio comparing teprotumumab to placebo will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

An analysis of risk difference with stratification by tobacco use (non-user vs. user) ~~Logistic regression~~ will also be used to analyze the ~~32~~-secondary categorical endpoints. For the analysis of proptosis and GO-QoL (see Section 9.6.4.4 for details) as continuous secondary endpoints, a Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline scores **for the study eye**, with terms in the model being the baseline score, tobacco use status, treatment group, visit, and the visit-by-treatment and visit-by-baseline-score interactions. The main focus of the analysis will be to test the treatment differences at Week 24, with the main results consisting of the Week 24 estimated Least Square (LS) means and their differences with 95% CIs and p-values.

To control the overall Type 1 error rate of the study, taking into consideration the one primary and ~~54~~-secondary outcome measures, the outcome measures will be tested in a hierarchical stepwise fashion. For each outcome measure, teprotumumab will be tested against placebo at the 0.05 level only if teprotumumab was statistically significant for the outcome measure preceding it in the hierarchical order.

9.6.4.2 Clinical Measures of Severity

The Clinical Measures of Severity results (see Table 9.3) for each item will be summarized at each designated visit for each eye with the number and percentage of subjects being classified as responders on each individual criterion. The proportions of responders will be analyzed using **the same risk difference method described for the primary endpoint** ~~a Chi-square test in~~ **Section 9.6.3.**

17.1 Administrative Appendix

Sponsor
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2 SYNOPSIS

Protocol Title: 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)	
Protocol Number: HZNP-TEP-301	Phase: 3
Protocol Version: 4.0	
Test Drug: Teprotumumab (HZN-001)	Indication: Active Thyroid Eye Disease (TED)
Number and Country of Study Sites: Up to 16 study centers in the United States and Europe.	
<p>Objectives: The overall objective is to investigate the efficacy, tolerability, and safety of teprotumumab (HZN-001, a fully human monoclonal antibody [mAb] inhibitor of the insulin-like growth factor-1 receptor [IGF-1R]) administered once every 3 weeks (q3W) for 24 weeks, in comparison to placebo, in the treatment of subjects with moderate-to-severe active TED.</p> <p><u>Primary Objective</u> The primary objective is to evaluate the effect of teprotumumab versus placebo on the <u>proptosis</u> 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.</p> <p><u>Secondary Objectives (analyzed hierarchically)</u></p> <ol style="list-style-type: none"> 1. Evaluate the effect of teprotumumab versus placebo on the <u>overall</u> responder rate (percentage of subjects with ≥ 2-point reduction in Clinical Activity Score [CAS] <u>AND</u> ≥ 2 mm reduction in proptosis from Baseline, provided there is no corresponding deterioration [≥ 2-point/mm increase] in CAS or proptosis in the fellow eye) at Week 24. 2. Evaluate the effect of teprotumumab versus placebo on the percentage of subjects with a CAS value of 0 or 1 at Week 24 in the study eye. 3. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in proptosis measurement in the study eye. 4. Evaluate the effect of teprotumumab versus placebo on the diplopia responder rate (i.e., 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. 5. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score. <p><u>Exploratory Objectives</u></p> <ol style="list-style-type: none"> 1. Evaluate the effect of teprotumumab versus placebo on the Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to Week 24. 2. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the CAS. 3. Evaluate the effect of teprotumumab versus placebo on the <u>overall</u> responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.4.3.1 for definitions). 4. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-pharmacodynamic (PD) relationships. 5. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores. 6. Evaluate the effect of teprotumumab on the mean change from Baseline to Week 24 in blood and serum biomarkers. 7. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity. 	

Study Design:

This is a randomized, double-masked, placebo-controlled, parallel-group, multicenter study. Subjects will be screened for the study within 2 to 6 weeks prior to the Baseline (Day 1) Visit. Approximately 76 subjects (38/group) who meet the study eligibility criteria will be randomized on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo q3W. All subjects will enter a 24-week double-masked Treatment Period, during which study drug will be infused on Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 (with a final visit at Week 24). All study drug dosing will be performed at the clinic under the supervision of clinic staff, and at any scheduled infusion, the infusion rate may be reduced or the dose may be interrupted or held based on decreased tolerability (see [Section 9.4.6.3.2](#) for details). On each dosing day, scheduled assessments (except for adverse event [AE] and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to study drug dosing. After each of the first 2 infusions, subjects will be contacted by phone/email the following day and will return to the clinic 1 week after the infusion (Weeks 1 and 4) for safety and tolerability assessments; additional phone/email contacts and clinic visits may also be conducted for any subject experiencing an infusion-associated event.

At the end of the double-masked Treatment Period (Week 24), subjects who are proptosis non-responders (study eye has < 2 mm decrease in proptosis) will be eligible to enter an open-label extension study (HZNP-TEP-302) in which subjects may receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion.

At Week 24, proptosis responders, as well as non-responders who choose not to enroll in the open-label extension study (HZNP-TEP-302), will enter a 48-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for Weeks 28, 36, 48, 60, and 72 (Months 7, 9, 12, 15, and 18). Subjects who are considered responders at Week 24 but who meet criteria for re-treatment due to relapse during the Follow-Up Period may enroll in the open-label extension study, HZNP-TEP-302 (see [Section 9.3.4](#)).

Subjects who prematurely discontinue study drug dosing prior to Week 21 of the Treatment Period will return to the clinic and undergo the scheduled Week 24 assessments and will be encouraged to participate in the Follow-Up Period unless they initiated another intervention due to lack of efficacy. Subjects who enter the Follow-Up Period but prematurely discontinue study participation prior to 48 weeks following the double-masked Treatment Period will return for a final visit and undergo the scheduled Week 72 assessments prior to study discharge.

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

An overview of the study design is presented in the schematic below, and details of study activities are provided in [Section 2.1, Schedule of Assessments](#).

Screen	Baseline	Double-Masked Treatment Period Teprotumumab or Placebo ^{1,2} 24 Weeks										Follow-Up Period 48 Weeks ^{3,4}				Follow-Up Contact ⁵ 48 Weeks			
		<----- Clinic Visits ----->										<----- Clinic Visits ----->							
		*		*		*	*	*	*	*	*								
2 to 6 weeks predose	Day 1 ⁶	W1	W3 ⁶	W4 M1	W6	W9	W12 M3	W15	W18	W21	W24 ⁷ M6	W28 M7	W36 M9	W48 M12	W60 M15	W72 M18	W96 M24	W120 M30	
		Randomization <----- Study Week/Month -----> n=38/group ¹																	
<p>* Infusion of study drug.</p> <ol style="list-style-type: none"> Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive: <ol style="list-style-type: none"> Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or Placebo (placebo q3W for all 8 infusions). Visit windows are ± 1 day for Weeks 1 and 4, ± 3 days for Weeks 3, 6, 9, 12, 15, 18, and 21, and ± 7 days for Week 24. Subjects who are <u>proptosis</u> responders or non-responders who do not elect to participate in the open-label extension study will enter a 48-week Follow-Up Period. Subjects who are responders at Week 24 but relapse during the Follow-Up Period may enter the open-label study and receive 8 infusions if they meet specified criteria. Visit windows of ± 7 days. Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. Subjects will be contacted by phone/email the day following the first and second infusions for safety and tolerability assessments; phone/email contacts will also occur the day after any clinic visit where a subject experiences an infusion-related adverse event. Subjects who are <u>proptosis</u> non-responders at Week 24 of the double-masked Treatment Period will be offered the option to enter an open-label extension study and receive 8 infusions of teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions). 																			
<p>Subject Population:</p> <p>Approximately 76 (38/group) male and non-pregnant female subjects between the ages of 18 and 80 years, inclusive, with a clinical diagnosis of Graves' disease associated with moderate-to-severe, active TED and a CAS ≥ 4 (using 7-item scale) for the most severely affected eye will be enrolled.</p>																			
<p>Inclusion Criteria:</p> <p>Eligible subjects must meet/provide all of the following criteria:</p> <ol style="list-style-type: none"> Written informed consent. Male or female subject between the ages of 18 and 80 years, inclusive, at Screening. Clinical diagnosis of Graves' disease associated with active TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia. Onset of active TED symptoms (as determined by subject records) within 9 months prior to Baseline. Subjects must be euthyroid with the baseline disease under control, or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels $< 50\%$ above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) or serum creatinine < 1.5 times the ULN according to age at Screening. 																			

9. Diabetic subjects must have well-controlled stable disease (defined as HbA1c < 9.0% with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening).
10. Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through Week 48 of the Follow-Up Period); subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, includes implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.
11. Male subjects must be surgically sterile or, if sexually active with a female partner of childbearing potential, must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.
12. Subject is willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

Exclusion Criteria:

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management.
3. Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline.
4. Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline.
5. Previous orbital irradiation or surgery for TED.
6. Any steroid use (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of < 1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to Screening.
7. Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed).
8. Selenium and biotin must be discontinued 3 weeks prior to Screening and must not be restarted during the clinical trial; however, taking a multivitamin that includes selenium and/or biotin is allowed.
9. Any previous treatment with rituximab (Rituxan[®] or MabThera[®]) or tocilizumab (Actemra[®] or Roactemra[®]). Use of any other non-steroid immunosuppressive agent within 3 months prior to Screening.
10. Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude study participation or complicate interpretation of study results.
12. Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin).
14. Pregnant or lactating women.

15. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
16. Biopsy-proven or clinically suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus, or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).
17. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to mAbs.
18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study.
19. Previous enrollment in this study or participation in a prior teprotumumab clinical trial.
20. HIV, hepatitis C or hepatitis B infections.

Dose Regimen/Route of Administration:

All study drug dosing will be performed at the clinic under the supervision of clinic staff. On Day 1 of the double-masked Treatment Period, subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive infusions of either:

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions),
or
2. Placebo (q3W for all 8 infusions).

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability (see [Section 9.4.6.3.2](#) for details). The first and second infusions will be administered over approximately 90 minutes (but not less than 80 minutes). Subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes), providing there are no significant infusion-associated events.

Dosage Form and Strength Formulation:

Teprotumumab 500 mg will be provided in single-dose 20 mL glass vials as a freeze-dried powder. Each vial of teprotumumab will be reconstituted with 10 mL of water for injection. The resulting solution will have an approximate concentration of 50 mg/mL teprotumumab. Reconstituted teprotumumab solution will be further diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration.

Doses up to 1800 mg will be administered in a total infusion volume of 100 mL, and those above 1800 mg will be administered in a total infusion volume of 250 mL. To maintain a constant volume in the infusion bags, a volume equal to the volume of teprotumumab to be placed into the infusion bag will be first removed from the infusion bag using a sterile syringe and needle. The appropriate volume of reconstituted drug product solution based on the subject's dose and body weight will be withdrawn and the teprotumumab reconstituted drug product solution will be diluted with normal saline (0.9% NaCl) in the infusion bag.

Placebo will consist of a normal saline (0.9% NaCl) solution and will be administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.

Duration of Treatment and Follow-Up:

The planned duration of the double-masked Treatment Period is 24 weeks (6 months). Subjects who are considered proptosis non-responders at Week 24 or subjects who were responders at Week 24 but who meet criteria for re-treatment due to relapse during the Follow-Up Period may enroll in the open-label extension study, HZNP-TEP-302 (see [Section 9.3.4](#)).

At Week 24, proptosis responders, as well as non-responders who choose not to enroll in the open-label extension study, will enter a 48-week Follow-Up Period.

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.

Criteria for Evaluation:

The most severely affected eye will be defined as the "study eye" at the Baseline (Day 1) Visit. If there is a discrepancy between CAS and proptosis in determining the study eye, this will be adjudicated always to the eye

with the most significant proptosis. If both eyes are affected equally, the Investigator will choose the “study eye”. Both eyes will be assessed for efficacy but the study eye will be used to assess the primary outcome measure.

Efficacy will be assessed by proptosis (measured as exophthalmos evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CAS (7-item scale), diplopia (measured as part of the Clinical Measures of Severity), and Clinical Measures of Severity (including motility restriction assessments).

Quality of life will be assessed using the GO-QoL questionnaire.

Blood samples for teprotumumab PK assessment will be collected prior to, and at the end of, the infusion on Day 1 and Weeks 3 and 9 during the Treatment Period; in addition, single samples will be collected at Weeks 1, 4, and 24. PK/PD relationships will be explored.

Serum samples may be analyzed for biomarkers (IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-1 β , sIL-1RA, INF γ , TGF β , TNF α , and micRNA) and possibly functional thyroid stimulating hormone receptor stimulating, blocking, and binding antibody (TSH-R-Ab) during the Treatment Period. Based on the results of the above assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms.

Safety will be assessed via AE and concomitant medication use monitoring, immunogenicity testing, physical and ophthalmic examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry (including thyroid panel and HbA1c), and urinalysis), pregnancy testing (if applicable), and electrocardiograms (ECG). The study will also be monitored by a Data Safety Monitoring Board (DSMB).

Statistical Analyses:

Primary Efficacy Endpoint

The primary outcome measure is the effect of teprotumumab versus placebo on the proptosis responder rate (percentage of subjects 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.

Secondary Efficacy Endpoints (analyzed hierarchically)

1. The effect of teprotumumab versus placebo on the overall responder rate (percentage of subjects with ≥ 2 -point reduction in CAS AND ≥ 2 mm reduction in proptosis from Baseline, provided there is no corresponding deterioration [≥ 2 -point/mm increase] in CAS or proptosis in the fellow eye) at Week 24.
2. The effect of teprotumumab versus placebo on the percentage of subjects with a CAS value of 0 or 1 at Week 24 in the study eye.
3. The effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in proptosis measurement in the study eye.
4. The effect of teprotumumab versus placebo on the diplopia responder rate (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.
5. The effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire overall score.

Exploratory Efficacy Endpoints

1. The effect of teprotumumab versus placebo on the Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to Week 24.
2. The effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the CAS.
3. The effect of teprotumumab versus placebo on the overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders).
4. To evaluate the PK parameters of teprotumumab to estimate exposure and understand the PK-PD relationships.

5. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire VF and A subscale scores.
6. To evaluate the effect of teprotumumab on the mean change from Baseline to Week 24 in blood and serum markers.
7. To evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.

Statistical Analysis on Efficacy Parameters

The primary analyses will be conducted in the Intent-to-Treat (ITT) population. The analysis of the primary proptosis responder endpoint will assess risk difference (difference in response rates) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the primary analysis. Further, subjects who prematurely discontinue study drug dosing prior to Week 21 during the double-masked Treatment Period will be considered to be treatment failures (non-responders), unless an assessment at Week 24 is available. Stratification for the analysis will use the same factor as was used to stratify randomization, tobacco use (non-user, user). The difference in response rates, comparing teprotumumab to placebo, will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

An analysis of risk difference with stratification by tobacco use (non-user vs. user) will also be used to analyze the 3 secondary categorical endpoints (overall responder rate, CAS [value of 0 or 1] and diplopia responder rate). For the analysis of proptosis as a continuous secondary endpoint and GO-QoL, a Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline scores for the study eye, with terms in the model being the baseline score, tobacco use status, treatment group, visit, and the visit-by-treatment and visit-by-baseline-score interactions. The main focus of the analysis will be to test the treatment differences at Week 24, with the main results consisting of the Week 24 estimated Least Square (LS) means and their differences with 95% CIs and p-values.

To control the overall Type 1 error rate of the study, taking into consideration the one primary and 5 secondary outcome measures, the outcome measures will be tested in a hierarchical stepwise fashion. For each outcome measure, teprotumumab will be tested against placebo at the 0.05 level only if teprotumumab was statistically significant for the outcome measure preceding it in the hierarchical order.

Sample Size Estimate:

In the prior TED01RV study, a 51% difference (71% vs 20%) in proptosis reduction of 2 mm or more between teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) and placebo was observed at Week 24 in favor of teprotumumab. A sample size of 38 subjects per group provides 90% power at the 2-sided alpha 0.05 level to detect a difference of 39% between teprotumumab and placebo; the sample size has been adjusted to allow for a 16% discontinuation rate.

2.1 Schedule of Assessments

	Screening ¹	Treatment Period ²											Follow-Up Period ³					Follow-Up Contact ⁴	
Study Visit	S1/S2/S3	1	2	3	4	5	6	7	8	9	10	11/ PW1 ⁵	12	13	14	15	16/ PW2 ⁶	17	18
Week (W)/ Month (M)	-42 to -14 days	Day 1 ⁷	W1	W3	W4/ M1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M42	W120/ M66
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
Informed Consent	X																		
Review inc/exc criteria	X	X																	
Demographics	X																		
Medical History ⁸	X ⁹	X																	
Weight ¹⁰	X							X				X		X	X	X	X		
Randomization ¹¹		X ⁷																	
Study drug infusion		X		X		X	X	X	X	X	X								
Phone (email) contact for safety 24 hours postdose ¹²		X		X															
Efficacy assessments																			
CAS ¹³	X	X ¹⁴				X		X		X		X	X	X	X	X	X		
Clinical Measures of Severity - includes proptosis, diplopia and motility restriction	X	X ¹⁵				X		X		X		X	X	X	X	X	X		
Safety assessments																			
Pregnancy Test ¹⁶	X	X		X		X	X	X	X	X	X	X	X	X	X		X ¹⁷		
Physical exam ¹⁸	X ¹⁹	X ¹⁸	X			X		X		X		X ¹⁸			X		X ¹⁸		
Ophthalmic exam ²⁰	X ²¹	X	X			X		X		X		X			X		X		
Vital Signs ²²	X	X ²²	X	X ²²	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X	X		X		X		X				X					X		
Clinical laboratory tests ²³																			
Chemistry (excl. glucose)	X ²⁴	X		X		X	X	X		X		X		X			X		
Thyroid (FT3, FT4, TSH) ²⁵	X	X		X		X	X	X		X		X		X			X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X		X			X		
Glucose ²³	X	X	X	X	X	X	X	X	X	X	X	X		X			X		

	Screening ¹	Treatment Period ²											Follow-Up Period ³					Follow-Up Contact ⁴	
Study Visit	S1/S2/S3	1	2	3	4	5	6	7	8	9	10	11/ PW1 ⁵	12	13	14	15	16/ PW2 ⁶	17	18
Week (W)/ Month (M)	-42 to -14 days	Day 1 ⁷	W1	W3	W4/ M1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M42	W120/ M66
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
HbA1c ²⁶	X							X				X		X			X		
Urinalysis	X	X		X		X	X	X		X		X		X			X		
ADA/NAb samples ²⁷		X		X			X					X ²⁸		X			X		
AE, SAE assessment ²⁹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
GO-QoL Questionnaire		X				X		X				X	X		X		X		
Biomarker samples ³⁰		X						X				X							
PK samples ³¹		X	X	X	X		X					X ²⁸							
Contact (phone/email) to assess additional TED treatment ³²																		X	X

ADA=anti-drug antibody; AE=adverse event; CAS=Clinical Activity Score; ECG=electrocardiogram; FT3=free triiodothyronine; FT4=free thyroxine; FU=Follow-Up; GO-QoL=Graves' Ophthalmopathy Quality of Life Questionnaire; HbA1c=glycated hemoglobin; M=month; NAb=neutralizing antibody; PK=pharmacokinetic; PW=premature withdrawal; SAE=serious adverse event; TED=thyroid eye disease; TSH=thyroid stimulating hormone; W=week.

Footnotes:

1. Screening procedures can take place over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window.
2. Double-masked Treatment Period. Subjects who are proptosis non-responders at Week 24 are eligible to enroll in an open-label extension study in which all subjects will receive teprotumumab 20 mg/kg (10 mg/kg for the first infusion and 20 mg/kg for the remaining infusions).
3. Proptosis responders and non-responders who choose not to enroll in the open-label extension study will participate in a 48-week Follow-Up Period.
4. Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.
5. If a subject prematurely discontinues study drug during the Treatment Period, they will return for a clinic visit and undergo the Week 24 assessments, with the exception of the collection of blood samples for PK and ADA evaluations. Subjects will be encouraged to continue study participation in the Follow-Up Period.
6. If a subject prematurely discontinues from the study during the Follow-Up Period, they will return for a clinic visit and undergo the Week 72 assessments prior to discharge.
7. On Day 1 (Baseline), subjects will be randomized and receive the first dose of study drug; however, Baseline assessments will be performed prior to dosing.
8. Medical history including tobacco use history and Graves' disease and treatment history.
9. TED must be moderate to severe in intensity (non-sight threatening but appreciable impact on daily life) with an onset of symptoms (as determined by subject records) within 9 months prior to the Baseline Visit for study enrollment.
10. Dosing will be adjusted if there is a change in weight during the Treatment Period. The weight obtained at Week 12 can be used in dose calculations beginning at Week 12 or Week 15.

11. Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive either: a) teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) or b) placebo (q3W for all 8 infusions).
12. Phone (or email) contact by research staff focusing on safety and tolerability aspects will be made the day after infusion for the first and second infusions, and thereafter as deemed appropriate. In addition, subjects who experience an infusion-associated event after any subsequent infusion will also be contacted by phone (or email) by research staff the day after the infusion, and thereafter as deemed appropriate.
13. CAS must be ≥ 4 for enrollment and randomization.
14. Subjects whose CAS score decreases 2 or more points in the study eye from Screening are not eligible for randomization.
15. Subjects who have a ≥ 2 mm decrease in proptosis in the study eye from Screening are not eligible for randomization.
16. Serum pregnancy test at Screening and urine pregnancy tests prior to dose at all other visits, as applicable. Perform for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]).
17. Pregnancy test only performed for female subjects of childbearing potential who enter the Follow-Up Period but discontinue study participation prior to Week 48.
18. Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1 and Week 24 (or PW) of the Treatment Period and Week 72 (or PW) of the Follow-Up Period. If present, measurements of instep and calf will be taken.
19. Height will be measured at Screening only.
20. Ophthalmic exam: best corrected visual acuity, pupil exam, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure, and slit lamp exam. If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including APD, rise in intraocular pressure, development of corneal infiltrates or other abnormalities not here specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.
21. Subjects who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) are not eligible for randomization.
22. Vital signs (heart rate, blood pressure, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3, and pre-dose on all other infusion days. Additional vital signs will be monitored if infusion-associated AEs occur (see [Section 9.5.5.4](#) for details).
23. Non-diabetic subjects should be fasting at Weeks 1 and 4 only. Diabetic subjects should be fasting at each visit blood glucose is evaluated.
24. ALT/AST must be ≤ 3 x the upper limit of normal (ULN) and serum creatinine must be <1.5 x the ULN according to age to be eligible for randomization.
25. Subjects must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels $< 50\%$ above or below the normal limits). Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
26. HbA1c must be $< 9.0\%$ for randomization. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 45 days until it returns to normal or baseline value.
27. If a sample is positive in the ADA test, after confirmatory and reactive titer testing, the sample will then be tested for NAb. If the subject tests positive for NAb, he/she will be followed until levels either revert to Baseline or the subject's value decreases or remains stable. Any subject with a positive NAb test at Week 72 (or PW) during the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.
28. Not collected for subjects who prematurely discontinue from the Treatment Period.
29. Adverse events (AEs) that occur within 2 weeks prior to Day 1 and prior to dosing on Day 1 will be considered baseline signs/symptoms. Adverse events occurring or worsening after the dose on Day 1 through the end of the Treatment Period will be considered treatment-emergent AEs (TEAEs). Adverse events occurring or worsening during the Follow-Up Period will be considered postdose AEs. All SAEs that occur from the signing of informed consent through 30 days after study discontinuation will be recorded.

30. Serum (two 5.0 mL samples) will be obtained on Day 1 and Weeks 12 and 24 of the Treatment Period for possible analysis of interleukin (IL)-4, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-1 β , sIL-1RA, INF γ , TGF β , TNF α , micRNA and TSH-R-Ab. Based on the results of the above assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms.
31. PK samples will be collected prior to, and at the end of, the infusion on Day 1 and Weeks 3 and 9 of the Treatment Period; additional single samples will be collected at Weeks 1, 4, and 24.
32. If TED treatment has been received since last contact, the subject will be questioned regarding type of treatment and outcome/response.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
A subscale	Appearance subscale of GO-QoL
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APD	Afferent pupillary defect
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CAS	Clinical activity score
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
C _{max}	Maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CPI	Coordinating principal investigator
CRO	Contract research organization
CS	Clinically significant
C _{trough}	Trough concentration
CV	Coefficient of variance
DSMB	Data safety monitoring board
EAA	European Economic Area
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
EUGOGO	European Group on Graves' Ophthalmopathy
FDA	Food and Drug Administration
FT ₃	Free triiodothyronine
FT ₄	Free thyroxine
GCP	Good Clinical Practice
GD-IgG	Graves' disease immunoglobulin G

Abbreviation	Definition
GO	Graves' ophthalmopathy or orbitopathy
GO-QoL	Graves' Ophthalmopathy Quality of Life
HbA1c	Glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HZN-001	Teprotumumab (previously RV 001)
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICD	Intercanthal distance
ICF	Informed consent form
ICH	International Conference of Harmonization
IEC	Independent ethics committee
IGF-1R	Insulin-like growth factor-1 receptor
IL	Interleukin
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
LR	Light reflex
LS	Least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
MMRM	Mixed-Model Repeated-Measures
NAb	Neutralizing antibody
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population pharmacokinetics

Abbreviation	Definition
PP	Per-protocol
PVC	Polyvinyl chloride
PW	Premature withdrawal
q3W	Once every 3 weeks
QoL	Quality of life
qW	Once per week
SAE	Serious adverse event
SAP	Statistical analysis plan
SST	Serum separator tube
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to observed maximum concentration
TAO	Thyroid-associated ophthalmopathy
TEAE	Treatment-emergent adverse event
TED	Thyroid eye disease
TSH	Thyroid stimulating hormone
TSHR	Thyroid-stimulating-hormone receptor
TSH-R-Ab	TSH-Receptor stimulating, blocking and binding antibody
ULN	Upper limit of normal
VF subscale	Visual functioning subscale of GO-QoL
V_{ss}	Volume of distribution at steady-state
WHODrug	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or Contract Research Organization (CRO) authorized by the Sponsor will submit this protocol, any protocol modifications, and the Informed Consent Form (ICF) and all applicable study documentation to be used in this study to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval/favorable opinion. A letter confirming the IRB/IEC approval/favorable opinion of the protocol the subject ICF and applicable study documentation, a list of the IRB/IEC members involved in the vote as well as a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the Sponsor or its designee **prior to** the enrollment of subjects into the study. A copy of the approved ICF will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the study will be made to the IRB/IEC and the Sponsor or its designee by the Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

5.2 Ethical Conduct of the Study

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. For studies conducted in the European Union/European Economic Area (EU/EEA) countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US Investigational New Drug (IND), the Investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”.

In other countries where a “Guideline for Good Clinical Practice” exists, the Sponsor and the Investigators will strictly ensure adherence to the stated provisions.

5.3 Subject Information and Consent

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.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written ICF. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IRB/IEC's approval/favorable opinion in advance of use.

All signed ICFs are to remain in the Investigator's site file or, if locally required, in the subjects' notes/files of the medical institution.

The electronic case report forms (eCRFs) for this study contain a section for documenting all subject informed consents, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

5.4 Compensation for Health Damage of Subjects/Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

5.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Pharma USA, Inc. (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see [Section 17.1](#) for details). The Sponsor's regulatory representative will be responsible for timely reporting of serious

adverse events (SAEs) to regulatory authorities as required. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators as required.

The study will be conducted at up to 16 study centers in the United States and Europe, and the Coordinating Principal Investigators (CPIs) will be [REDACTED] at the [REDACTED] in the US and [REDACTED] in the EU (Table 6.1). Prior to initiation of the study, each Principal Investigator will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators listed on the Form 1572. It is the responsibility of the Investigators or sub-investigators to advise the Sponsor of any change in the relevant financial interests that occur during the study and the one-year period following its completion.

The study will be monitored by a Data Safety Monitoring Board (DSMB), which will advise the Sponsor regarding the continuing safety of study subjects and potential subjects as well as continuing validity and scientific merit of the trial. Table 6.1 lists other organizations that are critical to the conduct of the study, with a brief description of their roles:

Table 6.1 Table of Non-Sponsor Study Responsibilities

Study Responsibility	Organization
Coordinating Principal Investigator (CPI)	[REDACTED]
Contract research organization (CRO) (monitoring, data management, statistical analysis, and pharmacokinetic [PK] analysis)	[REDACTED]
Interactive Web Response System (IWRS)	[REDACTED]

Study Responsibility	Organization
Clinical drug supply and distribution	[REDACTED]
Immunogenicity and PK Laboratory	[REDACTED]
Central safety laboratory	[REDACTED]
Biomarker analysis laboratory	[REDACTED]
Data Safety Monitoring Board Managing Organization	[REDACTED]

7 INTRODUCTION

7.1 Background

7.1.1 Thyroid Eye Disease

Thyroid eye disease (TED), also termed Graves' ophthalmopathy/orbitopathy (GO) and thyroid-associated ophthalmopathy (TAO), is an autoimmune condition commonly associated with Graves' hyperthyroidism/disease, but also occurs in a proportion of patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis. TED is divided by severity into mild, moderate, and severe disease, with moderate-to-severe disease representing 25-50% of cases [Bartley, 1994; Noth et al, 2001; Tanda et al, 2013]. In terms of time course, TED can be

considered as 2 distinct conditions: “active TED,” which is an autoimmune inflammatory response targeting orbital soft tissues; and “inactive TED,” which is the name given to the expanded and fibrotic tissues that are the sequelae of the active disease. Active TED typically lasts 1 to 3 years, and then the inflammation spontaneously subsides to leave the permanent pathology of inactive TED [Burch et al, 1993].

The annual incidence rate of TED in the US has been estimated to be 16 cases per 100,000 people for women and 2.9 cases per 100,000 people for men [Bartley, 1994]. The incidence appears to be comparable in Europe [Abraham-Nordling et al, 2011; Mostbeck et al, 1998; Noth et al, 2001; Tanda et al, 2013]. Patients aged between 30 and 50 years are most frequently affected, with severe cases more frequent in those older than 50 years [Dickinson, 2010]. The occurrence and severity of TED is associated with smoking [Prummel et al, 1993].

A mounting body of evidence in the scientific literature indicates that the pathophysiology of active TED involves the autoimmune activation and proliferation of orbital fibroblasts [Bahn, 2010; Boschi et al, 2005; Smith, 2010]. The activation of fibroblasts triggers release of inflammatory cytokines, infiltration of immune cells into orbital soft tissues (muscle, interstitial and adipose), excessive synthesis of extracellular matrix, and tissue expansion and remodeling (*ibid*). Clinical features of moderate-to-severe TED include orbital pain, swelling, dry eye, redness and discomfort of the lids and ocular surface, thickening and retraction of the eyelids, and proptosis (exophthalmos) due to the expansion of tissue behind the eye [Bahn, 2010; Burch et al, 1993; Dickinson, 2010; Mallika et al, 2009].

In its moderate-to-severe form, TED has high morbidity [Bartalena et al, 2008; Bartley, 1994; Dickinson, 2010; Gerding et al, 1997]. Morbidity takes the form of orbital pain, together with a number of serious, sight-threatening conditions, including diplopia (due to inability to correctly align the eyes), corneal ulceration (due to inability to close lids), and dysthyroid optic neuropathy (due to proptosis, tissue crowding, and stress on the optic nerve). These combine to produce marked reductions in quality of life (QoL) (e.g., physical functioning, role functioning, social functioning, mental health, health perceptions, and pain) [Gerding et al, 1997; C. Terwee et al, 2002]. TED can also produce profound psychosocial problems, in particular anxiety and depression, due to the alarming and disfiguring changes in appearance [Bartley et al, 1996; Coulter et al, 2007; G. J. Kahaly et al, 2005]. Taken together, these data show that moderate-to-severe active TED is a physically and emotionally debilitating condition (Figure 7.1).

[REDACTED]

[REDACTED]

[REDACTED]

For mild active TED, “watchful waiting” is considered appropriate for a proportion of patients, especially those with a satisfactory QoL [Bartalena et al, 2000]. In the mild condition, signs and symptoms can resolve leaving minor or no clinically relevant sequelae as inactive TED. In contrast, moderate-to-severe active TED often requires prompt treatment [Burch et al, 1993; G.J. Kahaly, 2010]. There are no approved therapies. Currently, the most commonly used medical therapies for moderate-to-severe active TED are high-dose corticosteroids [Bartalena et al, 2012; G.J. Kahaly, 2010], and in recent years rituximab [Salvi et al, 2015; Silkiss et al, 2010], neither of which is approved for treatment of TED. The most common nonmedical methods for treating moderate-to-severe active TED are orbital radiation and emergency decompression surgeries [Baril et al, 2014; Prummel et al, 2004]. All treatments for moderate-to-severe active TED are viewed as suboptimal due to inadequate efficacy and significant tolerability issues and safety concerns [Bartalena et al, 2012; Gasinska et al, 2012; Gorman et al, 2001; Melamud et al, 2014; Perez et al, 2014; Poetker et al, 2010; Stan et al, 2015; Zang et al, 2011]. Inactive TED is treated by rehabilitative and cosmetic surgeries, with the goal to reduce proptosis, correct strabismus, minimize eyelid retraction, and address disfiguration [Baldeschi, 2010]. Surgical treatment of inactive TED is essentially an attempt to repair the damage done by the active disease once it has run its course.

It is widely stated in the literature that there is significant unmet medical need in TED, and specifically that novel pharmacotherapies with improved efficacy and better tolerability are needed to treat active disease [Bahn, 2012; Bartalena, 2013; Bartalena et al, 2000; Coulter et al, 2007; Naik et al, 2010; Stan et al, 2015; C. Terwee et al, 2002].

Teprotumumab has the potential to meet these requirements by specifically blocking the autoimmune pathophysiology thought to underlie active TED.

7.1.2 Insulin-like Growth Factor-1 Receptor (IGF-1R)

The key underlying mechanism in Graves' hyperthyroidism is the generation of auto-antibodies (Graves' Disease immunoglobulin G; GD-IgGs) that act on the thyroid to produce hyperthyroidism [Akamizu, 2001]. The primary molecular mechanism through which GD-IgGs produce hyperthyroidism is believed to be activation of thyroid stimulating hormone receptors (TSHR) in thyroid follicular cells [Akamizu, 2001]. TED also has an autoimmune basis, but in this case, the primary cellular target appears to be orbital fibroblasts. GD-IgGs stimulate orbital fibroblasts to proliferate, release cytokines, initiate an inflammatory response, differentiate into adipocytes and myofibroblasts, and to secrete excessive amounts of extracellular matrix (e.g., hyaluronan), which in turn results in fibrosis and edema [Smith, 2010]. It was initially assumed that, as with Graves' hyperthyroidism, GD-IgGs produced TED through activation of TSHR. However, the data for this has never been definitive and a number of lines of evidence argue against there being a single, common molecular target for the 2 conditions. For example, it is not uncommon for there to be longitudinal misalignments in the time courses of Graves' hyperthyroidism and TED; approximately 10% of TED patients never become hyperthyroid and some TED patients experience unilateral eye symptoms. Moreover, there is disagreement in the literature about whether the levels of TSHR expressed in orbital tissues are alone sufficient to trigger and drive TED (e.g., [Bahn, 2010; Boschi et al, 2005; Smith et al, 2004]).

There are no well-established animal models for TED, and this has hampered both the study of mechanism and the discovery of novel therapeutics. Nevertheless, evidence is now accumulating that TSHR may not be the only autoantigen that is involved in regulating TED pathology. Specifically, a substantial body of data has been generated arguing that the insulin-like growth factor-1 receptor (IGF-1R) plays an important role in regulating the pathophysiological responses produced in orbital immune cells by GD-IgGs. Key nonclinical data supporting the involvement of IGF-1R in the mechanism of active TED are:

1. IGF-1R is localized on orbital fibroblasts and binding of IGF to fibroblasts can be displaced by GD-IgGs [Weightman et al, 1993].
2. IGF-1R is up-regulated in cultured orbital fibroblasts from patients with TED, while TSHR is only expressed at low levels [Tsui et al, 2008].
3. Stimulation of IGF-1R by GD-IgGs in orbital fibroblasts from patients with TED causes increased release of the T-cell attracting cytokines IL-16 and RANTES [Pritchard et al, 2003]. Importantly, this effect of GD-IgGs is fully reversed by a monoclonal antibody (mAb) antagonist specific for IGF-1R.
4. IGF-1 and GD-IgGs increase hyaluronan synthesis in orbital fibroblasts from patients with TED, but not in orbital fibroblasts from control subjects or dermal fibroblasts [Smith et al, 2004]. Again, this effect of GD-IgGs is blocked by a selective IGF-1R antagonist antibody. Interestingly, in these studies thyroid stimulating hormone (TSH) failed to stimulate hyaluronan synthesis in orbital fibroblasts from patients with TED.

5. IGF-1R expression is increased on both T-cells and B-cells from patients with TED, providing additional, immune-based mechanisms through which GD-IgGs acting on IGF-1R would promote an inflammatory response [Douglas et al, 2007; Douglas et al, 2008].
6. A recent microarray genomics study, using orbital fat samples from TED patients, showed that active disease has a marked dysregulation of genes in the IGF/IGF-1R signaling pathway [Ezra et al, 2011].
7. Experiments with human orbital fibroblasts and thyrocytes suggest that IGF-1R is physically associated with TSHR. Moreover, inhibiting IGF-1R with an antagonist antibody also has the effect of reducing signaling through TSHR [Tsui et al, 2008]. Remarkably, this work suggests that the 2 major autoantigens implicated in TED are physically and functionally coupled.

7.1.3 Teprotumumab

Teprotumumab (HZN-001) is a fully human immunoglobulin G1 (IgG₁) mAb directed against human IGF-1R. The IGF-1R is a tyrosine kinase cell surface receptor that shares ~50% overall homology with the insulin receptor [Ullrich et al, 1986]. Teprotumumab binds with high affinity and selectivity to the extracellular domain of IGF-1R and prevents its activation by the endogenous ligands, IGF-1 and IGF-2. Teprotumumab has no partial agonist activity at IGF-1R, as assessed by activation of the canonical signaling pathway (phosphoinositide 3 kinase/Akt), and has no affinity for the insulin receptor. In addition, teprotumumab causes direct inactivation of IGF-1R through antibody-induced cellular internalization and degradation. Binding of teprotumumab has been shown to inhibit canonical signal transduction and cellular proliferation and survival functions mediated by IGF-1R in cancer cells. Teprotumumab does not induce antibody-dependent cellular cytotoxicity.

Teprotumumab was originally developed by F. Hoffman-La Roche, Ltd., for the treatment of subjects with advanced solid tumors, including sarcoma. *In vitro* and *in vivo* studies suggest that IGFs play important roles in the development and progression of cancer. Details of the development of the compound (previously identified as RO4858696 or R1507) in the oncology indication are provided in the Horizon Investigator's Brochure (IB) [*Investigator's Brochure*, Edition 7.0, 07 July 2017]. Roche is no longer pursuing development of teprotumumab in oncology indications. Development was terminated due to inadequate efficacy in cancer indications, not to any observed side effects or safety issues.

River Vision Development Corporation licensed teprotumumab for development in the orphan indication of TED. Horizon Pharma acquired River Vision Development Corporation in May of 2017 and will continue the development of teprotumumab for TED.

7.1.3.1 Physiochemical Properties

[REDACTED]

[REDACTED]

[REDACTED]

7.1.3.2 Safety Pharmacology

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] tal

7.1.3.3 Non-Clinical Pharmacokinetics

[REDACTED]

7.1.3.4 Clinical Experience

7.1.3.4.1 Introduction

Teprotumumab was originally developed by F. Hoffman-La Roche Ltd. for the treatment of subjects with advanced solid tumors, including sarcoma. Development for this indication was discontinued based on insufficient clinical efficacy and was not based on any observed safety issues in the more than 700 subjects treated in the oncology program.

Teprotumumab is currently being developed by Horizon for subjects with moderate-to-severe active TED (also known as Graves' Ophthalmopathy or Orbitopathy [GO] and Thyroid-Associated Ophthalmopathy [TAO]).

The pharmacokinetics (PK) of teprotumumab were characterized by Roche. A biomarker to assess target interaction – increases in serum IGF-1 – was also identified. PK/PD modeling indicated that concentrations of 20 µg/mL resulted in > 90% IGF-1R receptor occupancy, and that doses that produced teprotumumab trough blood concentrations of 20 µg/mL were well tolerated.

The clinical safety database of teprotumumab in oncology was likely confounded by the comorbidity of late stage cancer and concomitant administration of other treatments. The oncology studies, however, did identify a number of potential AEs of special interest (AESIs: infusion-associated events, thrombocytopenia, hyperglycemia, and anemia) and these events were monitored carefully in the initial study in TED subjects, TED01RV.

TED01RV was the first study in which non-oncology subjects received teprotumumab. This study enrolled 87 subjects (43 teprotumumab; 44 placebo) between the ages of 18 and 75 years with recent onset (≤ 9 months from diagnosis) moderate-to-severe active TED. The primary efficacy endpoint was the overall responder rate (decreases from Baseline of ≥ 2 points in overall Clinical Activity Score [CAS] and ≥ 2 mm in proptosis, provided that there was no deterioration [i.e., increases of ≥ 2 points in CAS or ≥ 2 mm in proptosis] in the non-study eye) at the end of the 24-week treatment phase. In this study, the responder rate was significantly greater with teprotumumab treatment compared to placebo (69% versus 20%; $p < 0.001$) at Week 24. Therapeutic effects were rapid, with increased responder rates in the teprotumumab group relative to placebo detected at Weeks 6, 12, and 18 (all $p < 0.001$). The secondary endpoints (QoL, proptosis, and CAS as continuous variables) all supported the primary analysis conclusion that teprotumumab was superior to placebo in the treatment of TED. Population PK modeling in TED01RV confirmed that trough concentrations were consistently above the 20 µg/mL threshold, which had been previously determined by Roche PK/PD modeling as resulting in > 90% IGF-1R occupancy in the tissues. Results of the TED01RV study were published in the New England Journal of Medicine [Smith et al, 2017].

Of the AESIs identified in the oncology studies (i.e., infusion-associated events, thrombocytopenia, hyperglycemia, and anemia), the only one that emerged in the initial trial in subjects with TED was hyperglycemia. Among subjects treated with teprotumumab, hyperglycemia was uniformly mild in non-diabetic subjects and adequately controlled by

adjusting standard anti-diabetic therapy in diabetic subjects. Importantly, hyperglycemia in all teprotumumab-treated subjects was at Baseline levels after the end of the Treatment Period.

7.1.3.4.2 Efficacy

The TED01RV study demonstrated that subjects with active moderate-to-severe TED experienced statistically significant and clinically meaningful results in the proportion of responders at Week 24 in the teprotumumab group relative to placebo (69% [29/42 subjects] versus 20% [9/43 subjects], respectively; $p < 0.001$). Therapeutic effects were rapid, with responder rates in the teprotumumab group significantly greater than those in the placebo group at Weeks 6, 12, and 18 (all $p < 0.001$). Specifically, the proptosis component of the responder analysis showed a mean (standard error) reduction of 2.46 mm (0.20) in the teprotumumab group compared to 0.15 mm (0.19) in the placebo group at Week 24 ($p < 0.001$).

The secondary endpoints (QoL, proptosis, and CAS as continuous variables) supported the primary analysis conclusion that teprotumumab was superior to placebo in the treatment of this population.

In conclusion, for subjects with active ophthalmopathy, teprotumumab was more effective than placebo in reducing proptosis and the CAS.

7.1.3.4.3 Pharmacokinetics

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.1.3.4.4 Pharmacodynamic Markers

[REDACTED]

7.1.3.4.5 Safety

7.1.3.4.5.1 River Vision TED01RV Study

Treatment-emergent AEs (TEAEs) in TED01RV that were reported for at least 5% of the subjects in the teprotumumab group and had a greater frequency than that in the placebo group are shown in [Table 7.2](#). The majority of AEs were mild, required no treatment, and resolved while subjects remained on drug. Hyperglycemia, which was monitored by assessing blood glucose and HbA1c, was the only AE clearly identified as related to study drug.

Table 7.2 Summary of TEAEs Reported in at Least 5% of Subjects in Teprotumumab Treatment Group and % is Greater Than Placebo

TEAEs	Placebo N=44 n (%)	Teprotumumab N=43 n (%)	Summary Details for TEAEs in Teprotumumab Group
Any TEAE	32 (72.7)	32 (74.4)	
Nausea	4 (9.1)	8 (18.6)	Generally mild and reported after first/second infusions
Muscle spasms	2 (4.5)	8 (18.6)	Intermittent, 2/8 cases experienced for >1 week and treated with muscle relaxants
Diarrhea	2 (4.5)	6 (14.0)	Treatment required in 2/6 cases, 1 designated an SAE (see below)
Hyperglycemia	2 (4.5)	5 (11.6)	Mechanism-based AE
Alopecia	2 (4.5)	3 (7.0)	All mild and no treatment required
Dry skin	0	3 (7.0)	All mild, one case used topical dry skin cream
Dysgeusia	0	3 (7.0)	For 2/3 cases a transient “metallic” taste on Days 1-2
Headache	2 (4.5)	3 (7.0)	Generally mild, one subject took paracetamol
Paresthesia	0	3 (7.0)	“Tingling” reported in nose, feet or chest; variable onset and in 2/3 cases occurred on 1 day
Hearing impaired	0	3 (7.0)	Disparate symptoms, onset and duration (i.e., one unilateral with onset 16 weeks after end of therapy, one mild bilateral that resolved, one intermittent in a subject with positive history of tinnitus)
Weight loss	0	3 (7.0)	Variable timing; decreases range from 5-9 lb.

No deaths occurred in TED01RV, and early terminations were comparable in each treatment group (6/group). SAEs occurred in 5/43 (11.6%) of the subjects in the teprotumumab group and 1/45 (2.2%) of the subjects in the placebo group (Table 7.3). Two SAEs in the teprotumumab group were categorized by the Investigators as “possibly related” (diarrhea and mental confusion, which had a provisional diagnosis of Hashimoto’s encephalopathy); the remaining were categorized as “unrelated”. In the teprotumumab group, 4 discontinuations for SAEs occurred after the following number of infusions: diarrhea after 6 infusions; inflammatory bowel disease (IBD) after 7 infusions; *Escherichia coli* sepsis after 3 infusions; and Hashimoto’s encephalopathy after 6 infusions.

Clinically relevant levels of ADAs were not detected in any subject.

In the Phase 2 study, three non-serious adverse events (AEs) involving hearing impairment occurred in the teprotumumab group. A 59-year-old subject experienced acute bilateral hearing abnormality approximately 12 weeks following the 1st infusion of teprotumumab with resolution several months following the last infusion. A second 43-year-old subject with eustachian tube dysfunction experienced hearing loss nearly 4 months following discontinuation of teprotumumab. A third 60-year-old subject with a history of tinnitus experienced hearing loss following loud noise exposure. While a causal relationship between teprotumumab and the event

of hearing impairment is considered doubtful, it may be reasonable to avoid ototoxic drugs while receiving teprotumumab, if possible.

Table 7.3 Summary of SAEs Reported in Either Treatment Group by Preferred Term

SAE	Placebo N=44 n (%)	Teprotumumab N=43 n (%)	Summary Details for SAEs in Teprotumumab Group
Any SAE	1 (2.3)	5 (11.6)	
Optic neuropathy	1 (2.3)	0	
Diarrhea	0	1 (2.3)	Severe diarrhea in one subject with 6-month history of ulcerative colitis – hospitalized
IBD	0	1 (2.3)	Subject with recent diagnosis of ileitis and colitis, diagnosed and treated for IBD while on therapy – hospitalized
Escherichia sepsis	0	1 (2.3)	<i>E. coli</i> infection of unknown origin, treated with IV antibiotics – hospitalized
Suspected Hashimoto's encephalopathy	0	1 (2.3)	Provisional diagnosis for episodic mental confusion with no other neurological symptoms – hospitalized
Urinary retention	0	1 (2.3)	Occurred following an inguinal herniorrhaphy – hospitalized

AEs Previously Identified as Special Interest

AESIs identified in the oncology studies (infusion-associated events, hyperglycemia, thrombocytopenia, and anemia; see [Section 7.1.3.4.5.5](#)) were examined in TED01RV.

Infusion-associated AEs were reported for 1 teprotumumab-treated subject (facial flushing and warmth with concomitant elevated heart rate and blood pressure at the end of the 90-minute observation period after the second infusion). At the third infusion visit, the subject was pre-medicated with diphenhydramine, dexamethasone, famotidine and Tylenol and had a similar reaction prior to the study drug infusion.

Among non-diabetic subjects, hyperglycemia occurred at comparable rates in both treatment groups and was uniformly Grade 1 and intermittent. Among diabetic subjects, Grade 2 or 3 hyperglycemia occurred in some teprotumumab-treated subjects; this was well-controlled after diabetes medication adjustment. Glycemic control, as assessed by HbA1c, was at baseline levels following the treatment phase for all subjects in the teprotumumab group.

No subjects experienced thrombocytopenia as an AE. There were small differences in the population means of platelet values in the teprotumumab group compared to placebo that were not considered clinically significant and, importantly, diminished with continued dosing.

No subjects experienced anemia as an AE.

7.1.3.4.5.2 Safety Data Oncology Studies

In the oncology program, over 700 subjects were treated with teprotumumab at dose levels ranging from 1 to 27 mg/kg q3W or 1 to 9 kg/mg qW. The safety profile of teprotumumab in these studies was confounded by the poor health of the enrolled subjects (most had late-stage cancers) and the administration of combination therapy (teprotumumab in conjunction with other cytotoxic agents) in some subjects.

7.1.3.4.5.3 Teprotumumab Material Safety Profile

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.1.3.4.5.5 AEs of Special Interest

Following a comprehensive review of the safety data from the oncology studies and that from the TED01RV study, the following AESIs have been identified for the current study:

- Infusion reactions
- Hyperglycemia
- Muscle spasms
- Diarrhea

7.1.3.4.5.5.1 Overview and Precautions for AESIs

Infusion-Associated Events

Infusion-associated AEs were reported for 1 teprotumumab-treated subject (mild facial flushing and warmth with concomitant elevated heart rate and blood pressure and moderate hypertension and tachycardia at the end of the 90-minute observation period after the second infusion). At the third infusion visit, the subject was pre-medicated with diphenhydramine, dexamethasone, famotidine and Tylenol and had a similar reaction prior to the study drug infusion.

Monoclonal antibodies may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea and/or vomiting. Such reactions typically occur during or shortly after the infusion of mAbs and are usually associated with the first infusion. Their incidence and severity typically decrease with subsequent infusion. Severe infusion-associated reactions might be clinically indistinguishable from anaphylactic reactions.

Infusion-associated AEs observed with teprotumumab to date have not been anaphylactic in nature. However, because of the protein nature of teprotumumab and the potential for infusion-associated reactions and hypersensitivity reactions, teprotumumab should be administered in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to emergencies. For the first 3 infusions, subjects should be monitored for any AEs during infusion and for 60 minutes after completion of infusion. For subsequent infusions (the fourth dose and beyond), subjects who have not previously experienced an infusion reaction should be monitored during the infusion and for at least 30 minutes after the infusion.

Subjects who exhibit immediate hypersensitivity reactions or infusion-associated reactions during an infusion of teprotumumab should have the infusion interrupted or the infusion rate slowed. Symptomatic treatment (e.g., antipyretics, antihistamines and/or corticosteroids, oxygen, beta-agonists, and IV fluids) should be administered to the subject. Following an immediate hypersensitivity reaction or infusion-associated reaction, vital signs (temperature, blood pressure, pulse, and respiratory rate) should be determined every 5 minutes until stable, and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms except in the case of subjects who experience an anaphylactic reaction; these subjects should be removed from the study.

In general, the decision to keep a subject on study treatment with teprotumumab should take into consideration potential risks and benefits to the subject. Prior to all future infusions of teprotumumab, these subjects should be pre-medicated with IV diphenhydramine 1 to 1.25 mg/kg (maximum: 50 mg), IV ranitidine 50 mg, IV dexamethasone 0.4 mg/kg (maximum: 20 mg), and/or acetaminophen 500 mg. In addition, all future infusions should be administered over approximately 90 minutes (but not less than 80 minutes). Vital signs should be taken every 15 minutes during the infusion.

Subjects who experience delayed-type hypersensitivity reactions (e.g., skin rash) may remain in the study at the discretion of the Investigator, and prior to all future infusions of teprotumumab, should be pre-medicated with the above medications (diphenhydramine, ranitidine, dexamethasone, and/or acetaminophen). Subjects who experience a worsening delayed-type hypersensitivity reaction following repeated infusions of teprotumumab or who have other signs of serum-sickness (e.g., delayed fever, myalgias, arthralgias) may be removed from the study after discussion with the Investigator and Sponsor.

Hyperglycemia

In preclinical studies, there was no *in vitro* cross-reactivity of teprotumumab with the insulin receptor. During TED01RV, among non-diabetic subjects, hyperglycemia occurred at comparable rates in both treatment groups and was uniformly Grade 1 and intermittent. Among diabetic subjects, Grade 2 or 3 hyperglycemia occurred in some teprotumumab-treated subjects; this was well-controlled after diabetes medication adjustment. Glycemic control, as assessed by HbA1c, was at baseline levels following the treatment phase for all subjects in the teprotumumab group.

Subjects with known controlled diabetes mellitus are allowed to participate in studies with teprotumumab. HbA1c levels should be monitored regularly in these subjects. Investigators are strongly encouraged to adjust their subjects' diabetes management to maintain subjects' HbA1c levels at $\leq 7\%$. In the event a subject's HbA1c level rises to $> 7\%$ while in the study, the Investigator must determine the risk versus benefit for each subject to remain in the study.

Fasting glucose levels (after at least an 8-hour fast) should be tested at Baseline. Hyperglycemia should be promptly investigated and managed. Subjects with recurrent hyperglycemia, defined as a fasting glucose level of moderate intensity (glucose $>160 - 250$ mg/dL), will require evaluation for diabetes mellitus (e.g., fasting glucose, glucose tolerance, and HbA1c tests) and appropriate medical management at the discretion of the Investigator.

Muscle Spasms

During the TED01RV study, muscle spasms were identified in 19% of the subjects receiving teprotumumab versus 5% of those receiving placebo. In the teprotumumab group, 8 subjects had muscle spasms (6 had Grade 1 and 2 had Grade 2); only 2 subjects experienced the event for longer than one week and were treated with muscle relaxants. If possible, avoid medications known to cause muscle spasms or muscle toxicity such as diuretics or statins and evaluate for other causes of muscle spasm such as electrolyte abnormalities and dehydration.

Diarrhea

In the TED01RV study, diarrhea occurred in 14% of subjects receiving teprotumumab versus 5% of those receiving placebo. In the teprotumumab group, 8 subjects had diarrhea (5 had Grade 1, 2 had Grade 2, and 1 had a Grade 3 [severe]), with 2 subjects requiring treatment. The severe diarrhea (Grade 3) occurred in a subject with a history of colitis and was considered possibly related to study drug. This subject was subsequently diagnosed with ulcerative colitis and required colectomy leading to discontinuation from the study. Additionally, another subject was diagnosed with IBD during the course of the study.

Both subjects likely had IBD as a pre-existing condition, prior to study start. However, given the temporal sequence, exacerbation of underlying IBD by teprotumumab cannot be excluded at this time. Therefore, diarrhea that is progressive and persistent, or has features of IBD such as bloody stools or abdominal pain, should undergo prompt evaluation to exclude IBD or other serious conditions. If possible, avoid medications known to cause diarrhea such as laxatives and magnesium.

7.2 Rationale for this Study

Multiple lines of evidence indicate that IGF-1R plays a critical role in regulating the autoimmune response that underlies TED. Teprotumumab is a mAb with low nanomolar affinity for human IGF-1R. Binding of teprotumumab to IGF-1R blocks receptor activation by agonists, IGF1 and IGF2, and also causes direct inactivation of the receptor through antibody-induced internalization. Teprotumumab has no agonist activity for canonical IGF-1R signaling pathways and is highly selective; in particular, it does not recognize the insulin receptor. Teprotumumab is well-tolerated in humans at doses that produce > 90% IGF-1R occupancy. Systemic administration of teprotumumab to subjects with moderate-to-severe active TED should, therefore, attenuate all disease symptoms that are dependent on IGF-1R activation. This argument holds whether IGF-1R is being activated by GD-IgG or endogenous ligands IGF-1 and IGF2, or whether the receptor is expressed on fibroblasts, progenitor fibrocytes, adipocytes, or lymphocytes. Moreover, inhibition of IGF-1R receptor function with an antibody may also attenuate signaling through the TSHR, an autoantigen that has been implicated in TED, because IGF-1R and TSHR are physically and functionally coupled. Teprotumumab, therefore, has the potential to treat TED at multiple different molecular and cellular levels.

Administering teprotumumab early in active TED is designed to reduce the intensity and duration of the active disease, minimize the sequelae that are carried over to constitute inactive TED, and thereby have a beneficial effect on long-term outcome, reducing the need for corrective surgeries. Previous preclinical and clinical experience indicates that, at doses that are pharmacologically relevant for blocking IGF-1R, teprotumumab has an acceptable safety profile following IV infusion and is, therefore, a suitable drug candidate to be investigated in the TED indication.

7.3 Rationale for Dose Selection

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8 STUDY OBJECTIVES

The overall objective is to investigate the efficacy, tolerability, and safety of teprotumumab (HZN-001, a fully human mAb inhibitor of IGF-1R) administered q3W for 24 weeks, in comparison to placebo, in the treatment of subjects with moderate-to-severe active TED.

8.1 Primary Objective

The primary objective is to evaluate the effect of teprotumumab versus placebo on the proptosis responder rate (i.e., percentage of subjects 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.

8.2 Secondary Objectives

The secondary objectives (analyzed hierarchically) are:

1. Evaluate the effect of teprotumumab versus placebo on the overall responder rate (percentage of subjects with ≥ 2 -point reduction in CAS AND ≥ 2 mm reduction in proptosis from Baseline, provided there is no corresponding deterioration [≥ 2 point/mm increase] in CAS or proptosis in the fellow eye) at Week 24.
2. Evaluate the effect of teprotumumab versus placebo on the percentage of subjects with a CAS value of 0 or 1 at Week 24 in the study eye.
3. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in proptosis measurement in the study eye.
4. Evaluate the effect of teprotumumab versus placebo on the diplopia responder rate (i.e., 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.
5. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

8.3 Exploratory Objectives

The exploratory objectives are:

1. Evaluate the effect of teprotumumab versus placebo on the Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to Week 24.
2. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the CAS.
3. Evaluate the effect of teprotumumab versus placebo on the overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see [Section 9.6.4.3.1](#) for definitions).
4. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.
5. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Evaluate the effect of teprotumumab on the mean change from Baseline to Week 24 in blood and serum biomarkers.
7. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be conducted at up to 16 sites in the United States and Europe.

This is a randomized, double-masked, placebo-controlled, parallel-group, multicenter study. Subjects will be screened for the study within 2 to 6 weeks prior to the Baseline (Day 1) Visit. Approximately 76 subjects (38/group) who meet the study eligibility criteria will be randomized on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo every 3 weeks (q3W). All subjects will enter a 24-week double-masked Treatment Period, during which study drug will be infused on Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 (with a final visit at Week 24). All study drug dosing will be performed at the clinic under the supervision of clinic staff, and at any scheduled infusion, the infusion rate may be reduced or the dose may be interrupted or held based on decreased tolerability (see [Section 9.4.6.3.2](#) for details). On each dosing day, scheduled assessments (except for AE and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to study drug dosing. After each of the first 2 infusions, subjects will be contacted by phone/email the following day and will return to the clinic 1 week after the infusion (Weeks 1 and 4) for safety and tolerability assessments; additional phone/email contacts and clinic visits may also be conducted for any subject experiencing an infusion-associated event.

At the end of the double-masked Treatment Period (Week 24), subjects who are proptosis non-responders (study eye has < 2 mm decrease in proptosis) will be eligible to enter an open-label extension study (HZNP-TEP-302) in which subjects may receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion. Discussion of this option with the subject and informed consent presentation for HZNP-TEP-302 should be discussed at the Week 24 Visit given enrollment in HZNP-TEP-302 must occur within 2 weeks of the Week 24 Visit.

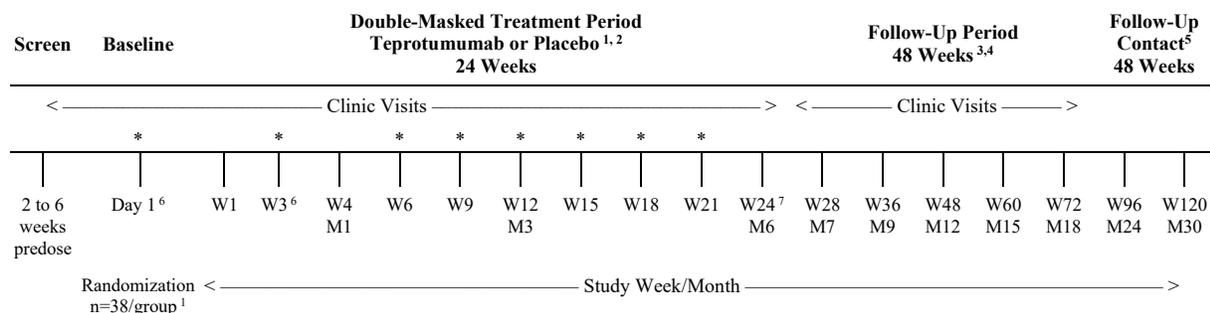
At Week 24, proptosis responders, as well as non-responders who choose not to enroll in the open-label extension study (HZNP-TEP-302), will enter a 48-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for Weeks 28, 36, 48, 60, and 72 (Months 7, 9, 12, 15, and 18). Subjects who are responders at Week 24 but who meet the criteria for re-treatment due to a relapse during the Follow-Up Period may enroll in the open-label extension study, HZNP-TEP-302 (see [Section 9.3.4](#) for details).

Subjects who prematurely discontinue study drug dosing prior to Week 21 of the Treatment Period will return to the clinic and undergo the scheduled Week 24 assessments and will be encouraged to participate in the Follow-Up Period unless they initiated another intervention due to lack of efficacy. Subjects who enter the Follow-Up Period but prematurely discontinue study participation prior to 48 weeks following the double-masked Treatment Period will return for a final visit and undergo the scheduled Week 72 assessments prior to study discharge.

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

An overview of the study design is presented in [Figure 9.1](#), and details of study activities were previously presented in [Section 2.1, Schedule of Assessments](#).

Figure 9.1 Schematic of Study Design



* Infusion of study drug.

- Subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive:
 - Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
 - Placebo (placebo q3W for all 8 infusions).
- Visit windows are ± 1 day for Weeks 1 and 4, ± 3 days for Weeks 3, 6, 9, 12, 15, 18, and 21, and ± 7 days for Week 24.
- Subjects who are proptosis responders or non-responders who do not elect to participate in the open-label extension study will enter a 48-week Follow-Up Period. Subjects who are responders at Week 24 but relapse during the Follow-Up Period may enter the open-label study and receive 8 infusions if they meet the criteria defined in [Section 9.3.4](#).
- Visit windows of ± 7 days.
- Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.
- Subjects will be contacted by phone/email the day following the first and second infusions for safety and tolerability assessments; phone/email contacts will also occur the day after any clinic visit where a subject experiences an infusion-related AE.
- Subjects who are proptosis non-responders at Week 24 of the double-masked Treatment Period will be offered the option to enter an open-label extension study and receive 8 infusions of teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions).

9.2 Discussion of Study Design

This study is a randomized, double-masked, placebo-controlled, parallel-group, multi-center study designed according to standard principles for adequate and well-controlled studies. The study population is well-defined and is consistent with the expected target population for whom teprotumumab will be indicated (adult subjects with Graves' disease and moderate-to-severe active TED).

The measurements used in this study for the primary and secondary endpoints (proptosis, CAS, and GO-QoL questionnaire) are established and well-validated endpoints that have been shown to correlate significantly with TED.

The sample size for this study was based on the data from the TED01RV study. A sample size of 38 subjects per group provides 90% power at the 2-sided alpha 0.05 level to detect a difference of 39% between teprotumumab and placebo in the proptosis responder rate; this sample size has been adjusted for a 16% dropout rate.

Given the teratogenic effects of teprotumumab noted in a monkey embryo-fetal development toxicity study (see [Section 7.1.3.2](#) for details) and pharmacokinetic profile of teprotumumab (see [Section 7.1.3.4.3](#)), all subjects (men and women) are required to use adequate contraception and report any pregnancies for at least 6 months after the last dose of study drug. Six months after the last dose, the estimated plasma concentration (0.2 µg/mL) is considered reasonably safe with a low risk of teratogenicity. Furthermore, a 6-month waiting period is in line with recommendations given for other teratogens, such as cytostatic chemotherapy.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Eligible subjects must meet all of the following criteria:

1. Written informed consent.
2. Male or female subject between the ages of 18 and 80 years, inclusive, at Screening.
3. Clinical diagnosis of Graves' disease associated with active TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline.
4. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia.
5. Onset of active TED symptoms (as determined by subject records) within 9 months prior to Baseline.
6. Subjects must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels $< 50\%$ above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study.
8. Alanine aminotransferase (ALT) or AST ≤ 3 times the upper limit of normal (ULN) or serum creatinine < 1.5 times the ULN according to age at Screening.
9. Diabetic subjects must have well-controlled stable disease (defined as HbA1c $< 9.0\%$ with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening).
10. Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening,

or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through Week 48 of the Follow-Up Period); subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, includes implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.

11. Male subjects must be surgically sterile or, if sexually active with a female partner of childbearing potential, must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug.
12. Subject is willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

9.3.2 Exclusion Criteria

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management.
3. Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline.
4. Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline.
5. Previous orbital irradiation or surgery for TED.
6. Any steroid use (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to Screening.
7. Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed).
8. Selenium and biotin must be discontinued 3 weeks prior to Screening and must not be restarted during the clinical trial; however, taking a multivitamin that includes selenium and/or biotin is allowed.

9. Any previous treatment with rituximab (Rituxan[®] or MabThera[®]) or tocilizumab (Actemra[®] or Roactemra[®]). Use of any other non-steroid immunosuppressive agent within 3 months prior to Screening.
10. Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude study participation or complicate interpretation of study results.
12. Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin).
14. Pregnant or lactating women.
15. Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
16. Biopsy-proven or clinically suspected IBD (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus, or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).
17. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to mAbs.
18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study.
19. Previous enrollment in this study or participation in a prior teprotumumab clinical trial.
20. HIV, hepatitis C or hepatitis B infections.

9.3.3 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from study participation at any time, for any reason, and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from the study at any time. The primary reason for discontinuation from the study and/or study drug should be recorded on the eCRF using one of the following categories:

- Adverse Event. The subject experiences an AE that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of an AE. AEs requiring permanent study drug discontinuation per the protocol include:

- A drug-related anaphylactic reaction.
 - A persistently severe drug-related AE that does not abate to mild or moderate intensity at least 2 weeks prior to the next scheduled dose.
 - Severe drug-related hyperglycemia (e.g., blood glucose > 250 mg/dL) that does not abate to mild or moderate intensity with anti-diabetic treatment (dose may be skipped up to 2 times prior to permanently discontinuing study drug; see [Section 9.4.6.3.2](#) for details).
 - Diagnosed or suspected IBD (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus, or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis.
- Lack of Efficacy. Removal of a subject from the study is at the discretion of the Investigator and may occur if the Investigator determines that study drug administration is not benefitting the subject and eye symptoms linked to progressing disease worsen posing an unacceptable risk to the subject. The specific care of the subject is best determined by the Investigator and managing physician(s) involved in the subject's care and may require removal from the study. All subjects are free to withdraw from study participation at any time, for any reason, allowing them to receive any specific treatment for TED that is considered necessary per their treating physician and local standard of care.
 - Non-Compliance with Study Drug/Other/Protocol Deviations. The subject has a significant protocol deviation, does not comply with study drug administration schedule, or fails to adhere to other study requirements as stated in the protocol.
 - Lost to Follow-Up. The subject does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the subject.
 - Withdrawal by Subject/Guardian. The subject wishes to withdraw from the study. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF; if the underlying reason is documented as an AE or lack of efficacy, the category of withdrawal should be marked in the corresponding category and not as voluntary withdrawal.
 - Study Terminated by Sponsor. The Sponsor, IRB/IEC, or regulatory agency terminates the study.
 - Pregnancy.

Subjects who prematurely discontinue study drug dosing prior to Week 21 of the Treatment Period will return to the clinic and undergo the scheduled Week 24 assessments and will be encouraged to participate in the Follow-Up Period unless they initiated another intervention due to lack of efficacy. Subjects who enter the Follow-Up Period but prematurely discontinue study participation prior to 48 weeks following the Treatment Period will return for a final visit and undergo the scheduled Week 72 assessments prior to study discharge. Subjects who discontinue

due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained.

9.3.4 Criteria for Responders Who Relapse

If subjects meet the response criteria at Week 24 but subsequently experience a disease relapse during the 48-week Follow-Up Period, they will have the option to enter the open-label study with teprotumumab (HZNP-TEP-302) and receive 8 infusions of teprotumumab. The criteria to determine relapse is the following:

- Increase in proptosis of ≥ 2 mm in the study eye since Week 24, or
- An increase in CAS ≥ 2 points since Week 24 with an absolute CAS of ≥ 4 in the study eye following the Week 24 Visit.
- In addition to one of the bullet points above, the Investigator should also consider the subject's symptomology to ensure a relapse has occurred (e.g., new onset of double vision).

9.3.5 Replacement Policy

9.3.5.1 Subjects

No subject prematurely discontinued from the study for any reason will be replaced.

9.3.5.2 Centers

A center may be closed and/or replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.

9.3.5.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that they can satisfy all of the eligibility criteria. Based on the TED01RV study, the expected screen failure rate is 20 – 25% [Smith et al, 2017].

9.4 Treatments

9.4.1 Treatments Administered

All study drug dosing will be performed at the clinic under the supervision of clinic staff. On Day 1 of the double-masked Treatment Period, subjects will be randomized in a 1:1 ratio (stratified by tobacco use status) to receive infusions of either:

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions), or
2. Placebo (q3W for all 8 infusions).

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability. The first and second infusions will be administered over approximately 90 minutes (but not less than 80 minutes). Subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes), providing there are no significant infusion-associated events.

9.4.2 Identity of Investigational Products

9.4.2.1 Teprotumumab

Teprotumumab (HZN-001) is a fully human anti-IGF-1R mAb. The physiochemical properties were previously presented in [Section 7.1.3.1](#). Teprotumumab will be provided in single-dose 20 mL glass vials as a freeze-dried powder containing, in addition to the drug substance, 20 mmol/L histidine-histidine chloride, 250 mmol/L trehalose, and 0.01% polysorbate 20 (w/w).

Prior to administration, each vial containing 500 mg teprotumumab freeze-dried powder will be reconstituted with 10 mL of water for injection. The resulting solution has an approximate concentration of 50 mg/mL teprotumumab. The reconstituted teprotumumab solution must be further diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration (see [Section 9.4.6.3](#) for details).

9.4.2.2 Placebo

Placebo will consist of a normal saline (0.9% NaCl) solution and will be administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.

9.4.3 Labeling

Study drug packaging will be in compliance with Sponsor/CRO standard procedures and will meet all local requirements.

Upon arrival of investigational products at the site, the investigational pharmacist or site personnel not assigned to the study should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor/Sponsor upon discovery.

9.4.4 Storage

Recommended storage conditions for the freeze-dried teprotumumab drug product are between 2°C to 8°C (36°F to 46°F), protected from light. Storage at ambient temperature of the reconstituted teprotumumab solution should be limited to 4 hours. For batch-specific information on shelf-life, see the packaging.

The IV infusion should be administered at room temperature (20°C to 24°C [68°F to 75°F]). The diluted product should be used within 4 hours of preparation. However, if not used within 4 hours, and if dilution has taken place under controlled and validated aseptic conditions, the infusion solution can be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F). An Investigational Pharmacy Manual will be provided to all sites and further describe these processes in detail.

At the clinic, all study medications must be stored in a secure area with limited access, and a daily temperature log of the drug storage area will be maintained every working day; deviations from the specified temperature range will be reported as protocol deviations.

9.4.5 Drug Accountability

The Principal Investigator at each site is responsible for the control of all study medication and delegating infusion bag preparation and drug accountability responsibilities to an unmasked pharmacist (or designee in accordance with institutional policies and local regulations), who must maintain adequate records of the receipt and disposition of all study medication shipped to the study center. Records will include receipt dates, condition at time of receipt, quantities received, quantities dispensed, quantities returned or destroyed, and the identification numbers of the subjects who received study medication.

As permitted by site policy, all empty, partially empty, and full vials of study drug must be retained by the study center under locked storage until drug accountability has been completed. Periodically throughout the study and at the conclusion of the study, inventory checks and accountability of study materials will be conducted by an unmasked representative of the Sponsor. Once accountability is completed, the Sponsor's representative will authorize the return of study medication (all used, partially used, and unused vials) to the 3rd party vendor (see [Table 6.1](#)). The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the unmasked CRO manager. The Investigator's copy of the Drug Accountability and Drug Return/Destruction Record(s) must document accurately the return of all study drug supplies and be maintained by the unmasked pharmacist or designee until the study is complete and the database is locked. Records will also include disposition dates and quantities returned to the designated facility.

9.4.6 Study Drug Administration and Timing of Dose for each Subject

9.4.6.1 Description of Clinical Supplies

██████████ will supply study drug to clinical sites. Ancillary supplies for dosing will be provided by the study site (i.e., infusion bags containing normal saline, infusion administration sets, syringes, needles, alcohol swabs, gauze pads, bandages, and biohazard containers for safe storage of used needles and syringes).

9.4.6.2 Determination of Dose Volume

The volume of study drug to be administered will be determined by the interactive web response system (IWRS) and will be based on the subject's weight. The first dose will be 10 mg/kg, and subsequent doses will be 20 mg/kg. Weight will be measured at Screening and Weeks 12 and 24 during the Treatment Period. The dose on Day 1 of the double-masked Treatment Period will be based on the Screening weight. The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15, as appropriate.

9.4.6.3 Details Concerning Timing and Dose Administration

9.4.6.3.1 Preparation and Administration of Teprotumumab

Teprotumumab will be prepared by the site pharmacist (or designee in accordance with institutional policies and local regulations), who is not masked to the identity of the study medication. Each vial of teprotumumab will be reconstituted with 10 mL of water for injection. The resulting solution will have an approximate concentration of 50 mg/mL teprotumumab antibody. Reconstituted teprotumumab solution will be further diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration by the site pharmacist or designee.

Doses up to 1800 mg will be administered in a total infusion volume of 100 mL, and those above 1800 mg will be administered in a total infusion volume of 250 mL. To maintain a constant volume in the infusion bags, a volume equal to the volume of teprotumumab to be placed into the infusion bag will be first removed from the infusion bag using a sterile syringe and needle. The appropriate volume of reconstituted drug product solution based on the subject's dose and body weight will be withdrawn and the teprotumumab drug product solution will be diluted with normal saline (0.9% NaCl) in the infusion bag.

The IV infusion is to be administered at room temperature (20°C to 24°C [68°F to 75°F]). The diluted product should be used within 4 hours. However, if not used within 4 hours, and if dilution has taken place under controlled and aseptic conditions, the infusion solution can be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).

No incompatibilities have been observed with:

- administration sets with product contact surface of polyethylene, polyvinyl chloride (PVC), or polyurethane
- inline filters with product contact surface of polyether sulphone
- IV bags (0.9% sodium chloride) with product contact surface of polyolefin or PVC.

In-line filters are not required, but if a hospital is routinely using them, in-line filters with a 0.2 µm pore size should be utilized.

Exposure of the solution to direct sunlight should be avoided.

All parenteral products should be visually inspected for particulates before administration.

Partially used vials should not be re-used.

The first and second IV infusions on Day 1 and Week 3 will be administered over approximately 90 minutes (but not less than 80 minutes) for all subjects; subsequent infusions may be administered over a shorter time period (approximately 60 minutes, but not less than 50 minutes) in the absence of any infusion-associated events. All subjects will be monitored for AEs from the start of infusion through 60 minutes after infusion completion for the first 3 doses; the

monitoring period for subsequent doses may be reduced to 30 minutes after infusion completion for subjects who do not experience infusion-associated events.

9.4.6.3.2 Dose Modifications, Interruptions, and Delays

All dosing instructions are applicable for teprotumumab and placebo administration.

Subjects will be monitored for immediate infusion-associated events (e.g., nausea, vomiting, facial flushing, warmth, dyspnea, dizziness, hypertension, hypotension, pruritus) and delayed infusion-associated events (e.g., rash). If immediate infusion-associated events are noted, the infusion rate will be slowed or interrupted, symptomatic treatment (e.g., antipyretics, antihistamines, beta-agonists, oxygen, IV fluid) will be administered, and vital signs (temperature, blood pressure, pulse, and respiratory rate) will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms; however, study drug dosing will be permanently discontinued if the event is an anaphylactic reaction.

If delayed infusion-associated events are noted, subjects may continue dosing at the Investigator's discretion; however, if a rash worsens following repeated dosing or other signs of serum sickness (e.g., delayed fever, myalgias, arthralgias) are present, study drug dosing will be permanently discontinued.

Following the appearance of either immediate or delayed infusion-associated events, subsequent doses may be pre-treated with diphenhydramine (1 to 1.25 mg/kg IV; maximum of 50 mg), ranitidine (50 mg IV), famotidine (0.5 mg/kg IV), dexamethasone (0.4 mg/kg IV; maximum of 20 mg), and/or acetaminophen (500 mg). All subsequent infusions will be administered over approximately 90 minutes (but not less than 80 minutes) with vital signs monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion.

In general, the decision to continue dosing should take into consideration the potential benefit and risk to a subject.

Any severe drug-related AE must revert to mild or moderate in intensity at least 2 weeks prior to the next scheduled dose in order for the dose to be administered; if the AE remains severe in intensity within 2 weeks of the next scheduled dose, the subject will be withdrawn from treatment.

Increase in blood glucose is a known AE observed in previous clinical trials with teprotumumab and other IGF-1R antagonists and is known to respond to treatment. Since a referral for treatment of hyperglycemia may take some time, if the Investigator considers it appropriate to continue the subject in the study, the next scheduled infusion visit may be skipped to allow modified anti-diabetic treatment to show its activity and hyperglycemia to return to mild/moderate level before dosing. The subject would then be dosed at the next scheduled visit (i.e., 6 weeks after the previous infusion). Fasting blood glucose levels must return to mild/moderate severity before the next scheduled infusion. The above process of withholding a scheduled infusion will be permitted only twice during the study.

Any changes to the scheduled dosing interval (q3W) or adjustments in the infusion rate should be reported to the Sponsor/CRO.

9.4.7 Method of Assigning Subjects to Treatment Groups

A randomization schedule will be generated by the CRO prior to shipment of any study drug to the clinical sites. On Day 1 of the double-masked Treatment Period, once all Baseline procedures other than administration of drug have been completed, the masked site personnel will use the IWRS to randomize the subject. The unmasked pharmacist or designee will then use the IWRS to obtain dosing information, and dispense the appropriate study drug.

9.4.8 Masking and Unmasking

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

During the phase 2 TED01RV trial, hyperglycemia was the only laboratory finding and adverse event clearly identified by the Investigators as being related to teprotumumab. Furthermore, hyperglycemia was observed in both treatment groups, placebo and teprotumumab. Given the occurrence of this event in both treatment groups, it is not possible to determine the identity of the masked study product based on the occurrence of this particular event.

The study mask should be broken only if the safety of a subject is at risk and the treatment plan depends on which medication he or she received. Unless the subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor or Sponsor's designee before unmasking the subject's data. If a subject's data are unmasked without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented.

The Sponsor's Pharmacovigilance department or designee will unmask the identity of the study medication for an unexpected, drug-related SAE for submission to health authorities and IRB/IEC according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at study sites. Details of subjects who are unmasked during the study will be included in the Clinical Study Report.

Unmasking for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

All investigative site staff directly involved in this study will remain masked from Screening through analysis of the Follow-Up data and all site close-out visits. The Sponsor and its designees will be unmasked after the database lock following completion of all subjects in the double-masked treatment phase.

9.4.9 Concomitant Therapy and Restricted Medications

Local supportive measures for TED, simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies), and medications/supplements for conditions other than TED are permitted during the study. Topical corticosteroids for conditions other than TED are allowed; however, oral corticosteroid use during the study is restricted to subjects who experience infusion-associated AEs.

Symptomatic treatment (e.g., antipyretics, antihistamines, beta-agonists, oxygen, IV fluid) may be administered to subjects who experience immediate infusion-associated AEs. Following the appearance of either immediate or delayed infusion-associated events, subsequent dosing of study drug may be pre-treated with diphenhydramine (1 to 1.25 mg/kg IV; maximum of 50 mg), ranitidine (50 mg IV), famotidine (0.5 mg/kg IV), dexamethasone (0.4 mg/kg IV; maximum of 20 mg), and/or acetaminophen (500 mg).

9.4.9.1 Restricted Therapy and Medications

Subjects with a previous orbital irradiation or surgery for TED or who have a planned orbital irradiation or surgery for TED over the course of this study are not eligible for study enrollment. In addition, oral corticosteroids, selenium, biotin, immunosuppressive agents, investigational agents, and illicit drug/alcohol use are restricted as shown in [Table 9.1](#).

Table 9.1 Restricted Medications and Therapies

Medication/Therapy	Restricted Dose or Time Period
Orbital irradiation for TED	Any history or planned procedure during entire study duration (Screening through Week 72 of Follow-Up Period).
Eye surgery for TED	Any history or planned procedure during entire study duration (Screening through Week 72 of Follow-Up Period).
Steroids for treatment of TED	Any history of steroid use (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED is excluded. Previous steroid use (IV or oral) with a cumulative dose < 1 g methylprednisolone or equivalent for the treatment of TED is allowed if the corticosteroid was discontinued at least 4 weeks prior to Screening. Steroid eye drops must be discontinued at least 4 weeks prior to screening. Steroids (IV or oral) for treatment of TED and steroid eye drops are not allowed during the entire study duration.
Steroids for conditions <u>other than TED</u>	Previous steroid use for conditions other than TED is allowed but must be discontinued at least 4 weeks prior to Screening. Topical steroids for dermatological conditions and inhaled steroids are allowed during the study. IV dexamethasone for infusion-associated AEs is allowed (see Section 9.4.9 for details).
Non-steroid eye drops	Vasoconstrictor eye drops are not allowed during the study. Other non-steroid drops such as saline or methylcellulose are allowed but should not be used on the day of a clinic visit.
Selenium or biotin for TED	3 weeks prior to Screening through study completion. A multivitamin containing selenium and/or biotin is allowed.
Rituximab (Rituxan [®] or MabThera [®]) or tocilizumab (Actemra [®] or Roactemra [®])	Any previous use or anticipated use during the study.
Non-steroid immunosuppressive agent (other than rituximab or tocilizumab)	3 months prior to Screening through study completion.
Investigational agent	60 days prior to Screening through study completion.
Illicit drug/alcohol use	History of abuse within the past 2 years or abuse during study.

Hearing loss and/or ototoxicity is not considered to be an adverse event causally associated with the use of teprotumumab. However, it may be reasonable to avoid ototoxic medications such as systemic administration of aminoglycoside and platinum-based chemotherapy during the study.

The following medications may cause muscle spasm/cramps and should be avoided during the study: donepezil, neostigmine, and vincristine.

All concomitant treatment (for TED and other conditions) in the Treatment Period and the Follow-Up Period must be documented in the eCRF.

9.4.10 Treatment Compliance

The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

All infusions of study medication will be administered at the clinic under the supervision of clinic staff. Infusion volumes, and start and stop times of the infusions will be recorded in the eCRF.

An inventory of the study medication supplies will be performed by the site or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

9.5 Efficacy, Quality-of-Life, Pharmacokinetic, and Safety Variables

The Schedule of Assessments was previously provided in [Section 2.1](#).

9.5.1 Efficacy Variables

Efficacy assessments will be performed for both eyes at each assessment time point. The most severely affected eye will be defined as the "study eye" at the Baseline (Day 1) Visit. If there is a discrepancy between CAS and proptosis in determining the study eye, this will be adjudicated always to the eye with the most significant proptosis. If both eyes are affected equally, the Investigator will choose the "study eye". Both eyes will be assessed for efficacy but the study eye will be used to assess the primary outcome measure.

Efficacy will be assessed by proptosis (measured as exophthalmos evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CAS (7-item scale), diplopia (measured as part of the Clinical Measures of Severity) and Clinical Measures of Severity (including motility restriction assessments).

9.5.1.1 Proptosis (Exophthalmos)

The most severely affected eye will be defined as the "study eye" at the Baseline (Day 1) Visit. Proptosis assessments will be performed using a Hertel exophthalmometer provided by the Sponsor for consistency in measurement, and (except when strictly unavoidable) the same Hertel instrument and same observer should be used at each evaluation for the full duration of the study. Additionally, the same intercanthal distance (ICD) must be used on each occasion. Instructions for the measurement of proptosis are included in [Section 17.2](#).

Proptosis will be measured for each eye at Screening, Day 1 and Weeks 6, 12, 18, and 24 (or premature withdrawal [PW]) during the Treatment Period, and at Weeks 28, 36, 48, 60, and 72

(or PW) during the Follow-Up Period. Subjects who have a ≥ 2 mm decrease in proptosis from Screening to Baseline in the study eye are not eligible for randomization. Measurements will be recorded on the Clinical Measures of Severity eCRF under exophthalmos. The Baseline value will also be recorded.

9.5.1.2 Clinical Activity Score (CAS)

The CAS will be completed at Screening, Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and at Weeks 28, 36, 48, 60, and 72 (or PW) during the Follow-Up Period using the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS [Mourits et al, 1989] (Table 9.2).

The CAS must be ≥ 4 for enrollment and randomization. Subjects whose CAS score decreases 2 or more points from Screening to Baseline are not eligible for randomization.

Table 9.2 Clinical Activity Score (CAS) Assessment

Item ¹	Description
1.	Spontaneous orbital pain.
2.	Gaze evoked orbital pain.
3.	Eyelid swelling that is considered to be due to active (inflammatory phase) 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.

¹ Each item is scored (1=present; 0=absent) and scores for each item are summed for total score.

To promote consistency in data collection across clinical trial sites, all Investigators will be provided with training and copies of the Clinical Manifestations chapter in *Graves' Orbitopathy: A Multidisciplinary Approach – Questions and Answers* [Dickinson, 2010]. Except when strictly unavoidable, the same observer should conduct each CAS evaluation for the full duration of the study.

9.5.1.3 Clinical Measures of Severity

Based on the EUGOGO Consensus Statement [Bartalena et al, 2008; Wiersinga et al, 2006], the following items will be assessed at Screening, Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and Weeks 28, 36, 48, 60, and 72 (or PW) during the Follow-Up Period (Table 9.3). Except when strictly unavoidable, the same observer should conduct each evaluation of severity measure for the full duration of the study.

Table 9.3 Clinical Measures of Severity

Item and Assessment Scale	Minimum change required for classifying overall response
Exophthalmos (measured in mm using the same Hertel exophthalmometer provided by the Sponsor for consistency in measurement and same intercanthal distance for each individual patient)	Decrease \geq 2 mm
Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation)	Decrease \geq 2 mm
Swelling of the eyelids (absent, mild, moderate, severe)	Decrease \geq One grade
Redness of the eyelids (absent, present)	Decrease \geq One grade
Redness of the conjunctiva (absent, present)	Decrease \geq One grade
Conjunctival edema (absent, present)	Decrease \geq One grade
Inflammation of the caruncle or plica (absent, present)	Decrease \geq One grade
Subjective diplopia score 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)	Decrease \geq One grade
Eye muscle involvement (ductions in degrees)	Increase \geq 8° in at least one direction of gaze
Corneal involvement (absent/punctate keratopathy/ulcer) Optic nerve involvement Best corrected visual acuity Color vision Optic disc Relative afferent pupillary defect (APD) (absent/present) Visual fields if optic nerve compression is suspected.	Decrease \geq One grade Change of best corrected visual acuity by \geq 2 lines on Snellen chart, or substantial color vision change, or significant change of visual fields, or significant change in optic disc appearance, or (Dis-) appearance of relative afferent pupillary defect

9.5.1.3.1 Motility Restriction – Details for Measurement

Motility is examiner assessed by estimating the degrees of restriction in eye movements. It will be assessed at the same time points as the Clinical Measures of Severity.

Monocular excursions in horizontal and vertical directions of gaze are recorded using the light reflex (LR) test [Dolman et al, 2012].

The clinician will shine a pen light in line with the eye being examined in ambient room light and observe the subject's eye along the light's axis. The subject will be asked to look in the 4 cardinal directions and the position of the light reflex is viewed on the surface of the cornea. If the light touches the limbus, the eye is assessed to be turned 45 degrees, if half way between the limbus and pupil edge, the eye is assessed at 30 degrees, and if it is at the pupil edge, it was

assessed at 15 degrees. Intermediate ductions are judged by estimating the light position between these points to the nearest 5 degrees.

The monocular ductions of each eye (degrees) will be recorded for adduction, abduction, supraduction and infraduction.

Except when strictly unavoidable, the same observer should conduct each duction evaluation for the full duration of the study.

9.5.2 Quality-of-Life Assessment

The GO-QoL questionnaire [C. B. Terwee et al, 1998] will be completed at Baseline, Weeks 6, 12, and 24 (or PW) during the Treatment Period, and at Weeks 28, 48, and 72 (or PW) during the Follow-Up Period.

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 English version of the questionnaire is included in [Section 17.3](#).

9.5.3 Pharmacokinetic Measurements

Blood samples will be collected in 5 mL serum separator tube (SST) collection tubes to evaluate PK at the following time points: pre- and post-infusion on Day 1 and Weeks 3 and 9 of the Treatment Period; single samples will also be collected at Weeks 1, 4, and 24 (but not PW) of the Treatment Period. Samples will be collected, processed, and stored at $\geq -70^{\circ}\text{C}$ at the site until shipment to the central laboratory (████████████████████). ██████████ will store the samples at $\geq -70^{\circ}\text{C}$ until shipment to ██████████ for PK testing (see [Table 6.1](#)).

Instructions for processing, handling, storing and shipping of PK samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation. A central laboratory will be used for PK sample analysis.

9.5.4 Biomarker Assessments

Blood samples will be collected in two 5.0 mL SST collection tubes prior to dosing on Day 1 and Weeks 12 and 24 (or PW) for possible analysis of interleukin (IL)-4, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-1 β , sIL-1RA, INF γ , TGF β , TNF α , micRNA and possibly functional thyroid stimulating hormone receptor stimulating, blocking, and binding antibody (TSH-R-Ab). Samples will be collected, processed, and stored at $\geq -70^{\circ}\text{C}$ at the site until shipment to the central laboratory (████████████████████). ██████████ will store the samples at $\geq -70^{\circ}\text{C}$ until shipment to the appropriate laboratory for testing (see [Table 6.1](#)). Based on the results of the above assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms. Blood samples collected for analysis of biomarkers may be used for future testing should there be new information about the disease however the samples will be stored for no more than 5 years after the study is completed. All samples will be destroyed after all potential biomarkers have been tested or 5 years after the study is complete, whichever comes first.

Instructions for processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.5 Safety Variables

Safety will be assessed via AE and concomitant medication use monitoring, immunogenicity testing, physical and ophthalmic examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry [including thyroid panel and HbA1c], and urinalysis), pregnancy testing (if applicable), and ECGs. The study will also be monitored by a DSMB.

9.5.5.1 Adverse Events

9.5.5.1.1 Definitions

9.5.5.1.1.1 Adverse Event Definition

According to ICH, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Pre-existing conditions that worsen during a study are to be reported as AEs. New findings reported from the on-study ophthalmic examinations will not be reported as AEs if according to the Investigator the abnormalities are related to TED and not considered related to the investigational product.

Unchanged, chronic conditions are **NOT** considered AEs and should not be recorded on the AE pages of the eCRF unless there is a clear exacerbation of a chronic condition.

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied (i.e., TED). It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of worsening proptosis may be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug.

9.5.5.1.1.2 Serious Adverse Event Definition

A TEAE, baseline event, or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drug (e.g., car accidents).

- Life-threatening adverse experience. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- Congenital anomaly or birth defect.
- Other medically important event which, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Elective surgeries that require hospitalization and treatment received at an emergency room or similar facility will not be considered as SAEs unless one of the definitions of an SAE listed above is met.

In addition, hospitalizations for planned procedures are not considered an AE unless they are prolonged hospitalizations, and emergency room visits less than 24 hours in duration are not considered hospitalizations.

9.5.5.1.1.3 Non-Serious Adverse Event Definition

A non-serious AE includes any AE that is not described in the previous SAE category.

9.5.5.1.1.4 Unexpected Adverse Event Definition

An AE or suspected adverse reaction is considered unexpected if it is not listed in the Reference Safety Information section of the IB or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.5.5.1.1.5 Adverse Events of Special Interest

Based on previous clinical experience in TED, the following AESIs are identified for this study (See [Section 7.1.3.4.5.5](#) for further information):

- Infusion reactions (e.g., nausea, vomiting, facial flushing, warmth, dyspnea, dizziness, hypertension, hypotension, pruritus)
- Hyperglycemia
- Muscle spasms
- Diarrhea

9.5.5.1.2 Documentation of Adverse Events

Adverse events that occur within 2 weeks prior to Day 1 and prior to dosing on Day 1 will be considered baseline signs/symptoms. The TEAE reporting period begins with administration of the first dose of study medication on Day 1 and continues until 3 weeks after the last dose of study drug, and the Follow-Up AE reporting period begins 3 weeks after the last dose of study drug through completion of the Follow-Up Period (Week 72 or PW). All baseline signs/symptoms, TEAEs, and AEs during the Follow-Up Period must be recorded in the source documents and on the subject's eCRF.

If the Investigator observes an SAE after study completion that he/she believes was possibly caused by the study medication, the Investigator will report this SAE using the procedures described in [Section 9.5.5.1.5](#).

Detailed information regarding all SAEs must also be recorded on the Serious Adverse Event Reporting Form. Whenever possible, the Investigator should group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as "upper respiratory infection" if the Investigator is confident of the diagnosis.

9.5.5.1.3 Intensity of Adverse Events

All clinical AEs encountered during the clinical study will be reported on the AE form of the CRF. Intensity of AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, death) and reported in detail on the eCRF.

Intensity	Definition	Corresponding NCI Grade
Mild	discomfort noticed but no disruption of normal daily activity	1
Moderate	discomfort sufficient to reduce or affect daily activity	2
Severe	inability to work or perform normal daily activity	3
Life-Threatening	represents an immediate threat to life	4
Fatal	results in death	5

9.5.5.1.4 Relationship to Study Drug

The relationship of the study drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions:

- No reasonable causal relationship (probably not related): There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.

- Yes, reasonable causal relationship (possibly related): There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply:
 - There is a reasonable pharmacological relationship (or known class effect)
 - There is no other more plausible explanation
 - There is a positive de-challenge (without active treatment of the event)
 - There is a positive re-challenge
 - There is a distinguishable dose effect

Within the reporting requirement under 21 CFR 312.32(c)(1)(i), the FDA provides the following examples of types of evidence that would suggest a causal relationship between the drug and the AE.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.5.5.1.5 Reporting and Documenting SAEs

All SAEs beginning with the time of signing of the ICF and continuing until 30 days after study discharge must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to the study medication:

1. Report the SAE to the Sponsor by entering the information into the eCRF **within 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to [REDACTED], fax, or telephone **within 24 hours** after becoming aware that a subject has experienced an SAE (see [Appendix 17.1](#) for contact information).

2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the Sponsor's representative.
3. Respond in a timely manner to any queries from Sponsor regarding the SAE.
4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator.
5. Review each SAE report and evaluate the relationship of the SAE to study treatment. The Sponsor will determine whether the SAE is unexpected in nature.
6. The Investigator must report all AEs or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB/IEC.

9.5.5.1.6 Follow-Up of Adverse Events

Any ongoing study drug-related AE present at the time of study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

In the event of unexplained, treatment-emergent, clinically significant abnormal laboratory test results or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed until the values have returned to within the reference range or to Baseline for that subject.

9.5.5.1.7 Medication Error and Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to, or by a study subject, at a dose > 5% above that which is assigned to that individual subject according to the study protocol.

All cases of medication errors and overdose (with or without associated AEs) will be documented on the eCRF in order to capture this important safety information consistently in the database. AEs associated with an overdose and SAEs of overdose are to be reported according to the procedures outlined in [Sections 9.5.5.1.2](#) and [9.5.5.1.5](#), respectively.

In the event of drug overdose, the subject is to be treated with symptomatic and supportive care as required.

9.5.5.1.8 Review of Adverse Events and Emerging New Safety Information

The Sponsor will perform an ongoing review of all AEs and all other emerging new information relevant to the safety of the drug, including periodic review and analyses of their entire safety database.

9.5.5.1.9 Reporting of IND Safety Reports

The Sponsor will notify the US FDA and all Investigators on any new serious risks associated with the drug.

9.5.5.1.10 Reporting of Suspected Unexpected Serious Adverse Reactions in the EU

The Sponsor or designee will report all Suspected Unexpected Serious Adverse Reactions (SUSARs), to the competent authorities and the concerned ethics committee according to applicable law. Investigators will also be informed according to local requirements.

9.5.5.1.11 Development Safety Update Reports

The Sponsor will prepare and submit annual safety reports to competent authorities and concerned ethics committees.

9.5.5.2 Pregnancy Reporting

Pregnancy testing will be performed for women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) at Screening, Baseline, prior to dosing during the Treatment Period (Weeks, 3, 6, 9, 12, 15, and 21), the end of the Treatment Period (Week 24 or PW), and at Weeks 28, 36, and 48 during the Follow-Up Period; if a subject discontinues study participation during the Follow-Up Period prior to the Week 48 Visit, a pregnancy test will be performed at the PW assessment. A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to dose at all other visits, as applicable; the serum sample will be analyzed at a central study laboratory and the urinary pregnancy tests will be performed locally.

If a female subject becomes pregnant during the Treatment Period, she should immediately notify the Investigator, and teprotumumab dosing should be permanently discontinued.

Pregnancy occurring in the partner of a male subject participating in the study should be reported to the Investigator and the Sponsor. Monitoring of the partner should continue until conclusion of the pregnancy.

Pregnancies occurring up to 180 days after the last dose must also be reported to the Investigator.

The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form by email to [REDACTED] fax, or telephone within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see [Appendix 17.1](#) for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues, monitoring should also continue to the conclusion of the pregnancy.

Subjects should be instructed to continue contraception for 180 days after their last dose of study drug.

9.5.5.3 Medical History

Medical history, including tobacco use history and Graves' disease and treatment history, will be conducted at Screening. TED must be moderate to severe in intensity (non-sight threatening but appreciable impact on daily life) with an onset of ophthalmic symptoms (as determined by subject records) within 9 months prior to the Baseline Visit for study enrollment.

9.5.5.4 Vital Signs

Vital signs (heart rate, blood pressure, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3, and predose on all other infusion days. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. Also, vital signs will be monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion for any subsequent infusions after the previous occurrence of immediate or delayed infusion-associated events.

Blood pressure and pulse measurements will be obtained with the subject's arm unconstrained by clothing or other material and while the subject is sitting up. When possible, the same arm will be used for measurements in all study visits.

9.5.5.5 Physical and Ophthalmic Examinations, Height, and Weight

A physical examination, including complete undilated ophthalmic examination, will be performed at Screening, Baseline (Day 1) and thereafter at Weeks 1, 6, 12, 18, and 24 (or PW) during the Treatment Period and at Weeks 48 and 72 (or PW) of the Follow-Up Period.

The ophthalmic exam should include best-corrected visual acuity, pupil exam, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure and slit lamp exam. If significant abnormalities are noted compared with previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including afferent pupillary defect (APD), rise in intraocular pressure, development of corneal infiltrates or other abnormalities not here specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.

Subjects who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) at Screening are not eligible for enrollment.

New findings reported from on-study ophthalmic examinations will not be reported as AEs if, according to the Investigator, the abnormalities are related to TED and not related to the study drug.

Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1, Week 24 (or PW) of the Treatment Period, and Week 72 (or PW) of the Follow-Up Period. If

present, measurements of instep and calf will be taken. Height will be measured at Screening only.

Weight will be measured at Screening and every 12 weeks throughout the study (Weeks 12 and 24 [or PW] during the Treatment Period and Weeks 36, 48, 60, and 72 [or PW] of the Follow-Up Period). The dose on Day 1 of the double-masked Treatment Period will be based on the Screening weight. The weight obtained at Week 12 can be used in dose calculations beginning at Week 12 or Week 15.

9.5.5.6 ECGs

12-lead ECGs will be performed at Screening, Baseline, Weeks 3, 6, 12, and 24 (or PW) of the Treatment Period, and Week 72 (or PW) of the Follow-Up Period. At infusion visits, the ECG will be performed prior to the infusion. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as clinically (CS) or not clinically significant (NCS) by the Investigator. A copy of the ECG tracing will remain with the source documents.

9.5.5.7 Clinical Laboratory Safety Tests

With the exception of urine pregnancy tests, a central study laboratory will be used for all protocol-specified clinical laboratory parameters. Urine pregnancy tests will be performed locally (see [Section 9.5.5.2](#) for details). Details concerning the collection of these samples are presented in [Table 9.4](#).

Table 9.4 Schedule of Clinical Laboratory Safety Tests, Including Thyroid Panel and Hyperglycemia Monitoring

Analysis Panel	SCR	Treatment Period											Follow-Up Period				
		BL	W1	W3	W4 M1	W6	W9	W12 M3	W15	W18	W21	W24 M6	W28 M7	W36 M9	W48 M12	W60 M15	W72 M18
Chemistry (excl. glucose)	X ¹	X		X		X	X	X		X		X		X			X
Thyroid (FT3, FT4, TSH) ²	X	X		X		X	X	X		X		X		X			X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X		X			X
Glucose ³	X	X	X	X	X	X	X	X	X	X	X	X		X			X
HbA1c ⁴	X							X						X			X
Urinalysis	X	X		X		X	X	X		X		X		X			X
Serum pregnancy ⁵	X																
Urine pregnancy ⁵		X		X		X	X	X	X	X	X	X	X	X	X		X ⁶

BL=Baseline; FT3=free triiodothyronine; FT4=free thyroxine; HbA1c=glycated hemoglobin; M=Month; SCR=Screening; TSH=thyroid stimulating hormone; W=Week.

1. ALT/AST must be ≤ 3 x the ULN and serum creatinine must be < 1.5 x the ULN according to age for randomization.
2. Subjects must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as FT4 and FT3 levels $< 50\%$ above or below the normal limits). Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
3. Non-diabetic subjects will fast at Weeks 1 and 4 only. Diabetic subjects will fast for each blood glucose evaluation. NOTE: Subjects with severe hyperglycemia that does not abate to mild or moderate intensity with anti-diabetic treatment (dose may be skipped up to 2 times prior to permanently discontinuing study drug, see Section 9.4.6.3.2 for details) will be permanently discontinued from study drug.
4. HbA1c must be $< 9.0\%$ for randomization. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 45 days until it returns to normal or baseline value.
5. Perform for female subjects of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]).
6. Perform for female subjects of childbearing potential who enter the Follow-Up Period but discontinue study participation prior to Week 48.

Instructions for the collection, handling and analysis of clinical laboratory samples will be provided to the site prior to study site initiation.

9.5.5.8 Immunogenicity Testing

Blood samples will be collected in a 5 mL SST collection tube for immunogenicity testing (ADA and possibly Neutralizing Antibodies [NAb]) from all subjects prior to dosing on Day 1, prior to dosing on Weeks 3 and 9, and at Week 24 (or PW) of the Treatment Period, and Weeks 36 and 72 (or PW) of the Follow-Up Period. Samples will be collected, processed, and stored at $\geq -70^{\circ}\text{C}$ at the site until shipment to the central laboratory [REDACTED]. [REDACTED] will store the samples at $\geq -70^{\circ}\text{C}$ until shipment to [REDACTED] for immunogenicity testing (see Table 6.1). If a subject tests positive for ADA after confirmatory and reactive titer testing, the sample will then be tested for NAb. If the subject tests positive for NAb, he/she will be followed until levels either revert to Baseline or the subject's value decreases or remains stable. Any

subject with a positive NAb test at Week 72 (or PW) of the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.

Instructions for processing, handling, storing, and shipping of immunogenicity samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.5.9 Data Safety Monitoring Board

The study will be monitored by a DSMB, which will advise the Sponsor regarding the continuing safety of study subjects and potential subjects as well as continuing validity and scientific merit of the trial. The details regarding frequency of meetings, members, and the safety review criteria will be outlined in a separate DSMB Charter. ACI Clinical will manage the logistics of the DSMB (Table 6.1).

9.5.6 Appropriateness of Measurements

This study, which is a randomized, double-masked, placebo-controlled, parallel-group, multi-center study, is designed according to standard principles for adequate and well-controlled studies. The study population is well-defined and is consistent with the expected target population for whom teprotumumab will be indicated (adult subjects previously diagnosed with Graves' hyperthyroidism and with moderate-to-severe active TED).

9.5.7 Study Procedures

Subjects who provide informed consent and who meet all the entry criteria for participation in this study will be randomized to treatment.

9.5.7.1 Screening

Due to the large number of screening assessments, the Screening Visit may be completed in more than one day. During the Screening Visit, potential study subjects will be informed fully regarding the nature of the study and possible AEs, and will receive a copy of the ICF for review. Potential study subjects must read the ICF and sign the document after the Investigator has answered all questions to the study candidate's satisfaction. Further procedures can begin only after the ICF has been signed. The original signed ICF will be retained by the Investigator and a copy will be given to the study subject.

Study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Section 9.3). The Investigator will evaluate the results of all examinations, including clinical laboratory tests, and will determine each candidate's suitability for the study. The Investigator must review the results of all Screening tests before determining that a candidate is eligible for study drug treatment. The serum pregnancy test performed at Screening on all female candidates of childbearing potential must be negative for those subjects to be eligible for initiation of treatment. All screening procedures must be completed within 42 to 14 days prior to Study Day 1 (i.e., the first day of administration of study drug). The following procedures will be performed during Screening to establish each candidate's general health and eligibility for enrollment into the study:

- Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act [HIPAA]). Refusal to provide this permission excludes an individual from eligibility for study participation. Record date informed consent was given and who conducted the process on the appropriate source documentation.
- Collect medical history, including tobacco use history and Graves' disease and treatment history. Ensure active TED is moderate to severe in intensity (non-sight threatening but appreciable impact on daily life) with an onset of ophthalmic symptoms (as determined by subject records) within 9 months prior to the projected Baseline Visit.
- Determine study eligibility through review of the inclusion/exclusion criteria (see [Section 9.3](#))
- Obtain demographics.
- Enquire about prior medications (see [Table 9.1](#) for restrictions regarding medications).
- Obtain a serum sample from all females of childbearing potential for performance of a pregnancy test.
- Perform a physical examination, including measurements of height and weight.
- Perform ophthalmic examination. Subjects who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) are not eligible for enrollment.
- Perform 12-lead ECG.
- Record vital signs (blood pressure, pulse, respiration rate, and temperature). These measurements will be performed according to standardized instructions. Record on the appropriate source documentation.
- Obtain blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Obtain a urine sample for urinalysis.
- Complete the efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Query subjects regarding signs and symptoms.
- Contact IWRS to register the Screening Visit.

For all subjects enrolled in the study, the source documentation record will be transcribed onto the eCRF.

9.5.7.2 Day 1/Baseline

On Day 1, subjects will return to the clinic for Baseline assessments, randomization, and the first dose of study drug.

- Perform review of inclusion/exclusion criteria.
- Review medical history.
- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose blood samples for immunogenicity testing.
- Collect predose blood samples for biomarker analyses.
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Enquire about signs and symptoms within previous 2 weeks and concomitant medications.
- Perform predose physical and ophthalmic examinations.
- Perform predose 12-lead ECG.
- Perform predose Baseline efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction). Proptosis and CAS may not decrease ≥ 2 mm/points in the study eye from Screening to be eligible for enrollment.
- Administer the predose GO-QoL questionnaire.
- Contact IWRS to obtain randomization number in order for the unmasked pharmacy to receive study drug dosing information.
- Monitor vital signs prior to and at the end of the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Collect blood samples for PK analyses prior to and at the end of the infusion.

- Administer the first dose of study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the Study Day 1 procedures have been completed and will be contacted the following day to enquire about AEs and concomitant medication use.

9.5.7.3 Week 1

- Collect blood samples for hematology and glucose testing (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect blood sample for PK analyses. Record date/time of sample collection.
- Perform physical and ophthalmic examinations, including vital signs.
- Enquire about AEs and concomitant medication use.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return to the clinic at Week 3.

9.5.7.4 Week 3

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Collect predose blood sample for immunogenicity testing.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform predose 12-lead ECG.
- Monitor vital signs prior to and at the end of the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Collect blood samples for PK analyses prior to and at the end of the infusion.
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.

- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and will be contacted the following day to enquire about AEs and concomitant medication use.

9.5.7.5 Week 4

- Collect blood samples for hematology and glucose testing (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect blood sample for PK analyses. Record date/time of sample collection.
- Collect vital signs.
- Enquire about AEs and concomitant medication use.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return to the clinic at Week 6.

9.5.7.6 Week 6

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform predose 12-lead ECG.
- Perform predose physical and ophthalmic examinations, including vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Administer predose GO-QoL questionnaire.
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.

- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and instructed to return for a clinic visit at Week 9.

9.5.7.7 Week 9

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Collect predose blood samples for immunogenicity testing.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect predose vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Collect blood samples for PK analyses prior to and at the end of the infusion.
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and instructed to return for a clinic visit at Week 12.

9.5.7.8 Week 12

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Collect predose blood samples for biomarker analyses.
- Enquire about signs and symptoms and concomitant medications throughout the visit.

- Perform predose 12-lead ECG.
- Perform predose physical and ophthalmic examinations, including vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Measure weight.
- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Administer predose GO-QoL questionnaire.
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 15.

9.5.7.9 Week 15

- Obtain predose blood samples for hematology and glucose analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect predose vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 18.

9.5.7.10 Week 18

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for urinalysis and also for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform predose physical and ophthalmic examinations, including vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 21.

9.5.7.11 Week 21

- Obtain predose blood samples for hematology and glucose analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect predose urine sample for a pregnancy test for females of childbearing potential. The pregnancy test must be negative for those subjects to receive study drug.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect predose vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see [Section 9.5.5.4](#) for details).
- Contact IWRS to obtain study medication vial assignment and to determine the volume of study drug to be administered.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 24.

9.5.7.12 Week 24

Week 24 is the final visit of the Treatment Period. Study drug is not administered.

- Obtain blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis (see [Section 9.5.5.7](#) for details concerning test results and study participation).
- Collect urine sample for urinalysis and also for a pregnancy test for females of childbearing potential.
- Collect blood sample for biomarker analyses.
- Collect blood sample for immunogenicity testing (only subjects who complete the Treatment Period, not those who prematurely discontinue study drug administration).
- Collect blood sample for PK analysis (only subjects who complete the Treatment Period, not those who prematurely discontinue study drug administration).
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform 12-lead ECG.
- Perform physical and ophthalmic examinations, including vital signs.
- Measure weight.
- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Administer GO-QoL questionnaire.
- Contact IWRS to register the End-of-Treatment Visit.

Subjects will be discharged from the study center after all of the procedures have been completed.

Subjects who are proptosis non-responders will be offered the opportunity to receive 8 infusions of teprotumumab in an open-label extension study, HZNP-TEP-302.

Subjects who are proptosis responders and those who are non-responders and do not elect to participate in the open-label extension study will enter the Follow-Up Period and will be instructed to return to the clinic in 4 weeks for the first follow-up visit.

9.5.7.13 Week 28

- Collect urine sample for a pregnancy test for females of childbearing potential.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect vital signs.
- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Administer GO-QoL questionnaire.

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 36.

9.5.7.14 Week 36

- Obtain blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis.
- Collect urine sample for urinalysis and also for a pregnancy test for females of childbearing potential.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect blood sample for immunogenicity testing.
- Collect vital signs.
- Measure weight.
- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 48.

9.5.7.15 Week 48

- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform physical and ophthalmic examinations, including vital signs.
- Measure weight.
- Administer GO-QoL questionnaire.

- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 60.

9.5.7.16 Week 60

- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Collect vital signs.
- Measure weight.
- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).

Subjects will be discharged from the study center after all of the procedures have been completed and will be instructed to return to the clinic at Week 72.

9.5.7.17 Week 72 (Termination Visit or Premature Withdrawal Visit)

- Obtain blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis.
- Collect urine sample for urinalysis.
- Collect urine sample for a pregnancy test for females of childbearing potential if the subject discontinued from the study prior to Week 36.
- Collect blood sample for immunogenicity testing.
- Enquire about signs and symptoms and concomitant medications throughout the visit.
- Perform 12-lead ECG.
- Perform physical and ophthalmic examinations, including vital signs.
- Measure weight.
- Perform efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia, and motility restriction).
- Administer GO-QoL questionnaire.

Subjects will be discharged from the study center after all of the procedures have been completed.

9.5.7.18 Week 96 – Follow-Up Contact

Subjects who complete the Week 72 Visit will be contacted 6 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

9.5.7.19 Week 120 – Follow-Up Contact

Subjects who complete the Week 72 Visit will be contacted 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

The end of the trial is defined as the date of the last subject contact at Week 120.

9.6 Statistical Methods and Determination of Sample Size

Detailed statistical analyses will be presented in a separate statistical analysis plan (SAP), and analyses presented in the SAP will supersede those presented in the protocol. Some key points identified for statistical analyses are outlined below.

9.6.1 Endpoints

9.6.1.1 Primary Endpoint

The primary outcome measure is the proptosis responder rate (percentage of subjects 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.

9.6.1.2 Secondary Endpoints (analyzed hierarchically)

1. The overall responder rate (percentage of subjects with ≥ 2 -point reduction in CAS AND ≥ 2 mm reduction in proptosis from Baseline, provided there is no corresponding deterioration [≥ 2 point/mm increase] in CAS or proptosis in the fellow eye) at Week 24.
2. Percentage of subjects with a CAS value of 0 or 1 in the study eye at Week 24.
3. Mean change from Baseline to Week 24 in proptosis measurement in the study eye.
4. Diplopia responder rate (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.
5. Mean change from Baseline to Week 24 in the GO-QoL questionnaire overall score.

9.6.1.3 Exploratory Endpoints

1. Evaluate the effect of teprotumumab versus placebo on the Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to Week 24.
2. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 in the CAS.

3. Evaluate the effect of teprotumumab versus placebo on the overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see [Section 9.6.4.3.1](#) for definitions).
4. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.
5. Mean change from Baseline to Week 24 in the GO-QoL questionnaire VF and A subscale scores.
6. Evaluate the effect of teprotumumab on the mean change from Baseline to Week 24 in blood and serum biomarkers.
7. Evaluate the effect of teprotumumab versus placebo on the mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.

9.6.2 Populations for Analysis

The following analysis populations will be defined for this study:

- Intent-to-Treat (ITT)
- Modified Intent-to-Treat (MITT) population
- Per Protocol (PP) population
- Safety Population

The ITT population will include all subjects who are randomized to treatment. Full details of the analysis populations will be described in the SAP.

9.6.3 Primary and Secondary Endpoint Analysis

The primary analyses will be conducted in the ITT population. The analysis of the primary proptosis responder endpoint will assess risk difference (difference in response rates) in a stratified analysis. The analysis will use Cochran-Mantel-Haenszel (CMH) weighting to estimate the common risk difference within strata and to estimate the standard error of the common risk difference. Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the primary analysis. Further, subjects who prematurely discontinue study drug dosing prior to Week 21 during the double-masked Treatment Period will be considered to be treatment failures (non-responders), unless an assessment at Week 24 is available. Stratification for the analysis will use the same factor as was used to stratify randomization, tobacco use (non-user, user). The difference in response rates, comparing teprotumumab to placebo, will be estimated along with the corresponding 95% confidence interval (CI) and p-value.

An analysis of risk difference with stratification by tobacco use (non-user vs. user) will also be used to analyze the 3 secondary categorical endpoints. For the analysis of proptosis and GO-QoL (see [Section 9.6.4.4](#) for details) as continuous secondary endpoints, a Mixed-Model Repeated-Measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the individual change from baseline scores for the study eye, with terms in the model being the baseline score,

tobacco use status, treatment group, visit, and the visit-by-treatment and visit-by-baseline-score interactions. The main focus of the analysis will be to test the treatment differences at Week 24, with the main results consisting of the Week 24 estimated Least Square (LS) means and their differences with 95% CIs and p-values.

To control the overall Type 1 error rate of the study, taking into consideration the one primary and 5 secondary outcome measures, the outcome measures will be tested in a hierarchical stepwise fashion. For each outcome measure, teprotumumab will be tested against placebo at the 0.05 level only if teprotumumab was statistically significant for the outcome measure preceding it in the hierarchical order.

9.6.4 Exploratory Analyses

9.6.4.1 Pharmacokinetics/Pharmacodynamics

All PK data and parameters will be presented descriptively, including arithmetic means, standard deviations, geometric means, CVs, medians, and ranges. The key data are C_{trough} plasma levels at Week 9 prior to infusion and at Week 24, important to confirm that plasma concentrations were maintained above the 20 µg/ml level through the course of the dosing period.

The relationship between clinical endpoints and the plasma concentrations of teprotumumab will be explored in a descriptive manner.

9.6.4.2 Clinical Measures of Severity

The Clinical Measures of Severity results (see [Table 9.3](#)) for each item will be summarized at each designated visit for each eye with the number and percentage of subjects being classified as responders on each individual criterion. The proportions of responders will be analyzed using the same risk difference method described for the primary endpoint in [Section 9.6.3](#).

9.6.4.2.1 Motility Component of the Clinical Measures of Severity

The monocular ductions of the study eye (degrees) will be compared between the 2 treatment groups at each evaluation period for adduction, abduction, supraduction and infraduction.

For each motility measure, the analysis of the changes from baseline in the target eye will be conducted using the same MMRM ANCOVA analysis as the continuous secondary endpoint analysis in [Section 9.6.3](#), substituting the appropriate baseline assessments.

9.6.4.3 Clinical Activity Score (CAS)

CAS will be measured as a continuous variable using the MMRM ANCOVA model described above to compare the treatment groups.

9.6.4.3.1 Stratification of Proptosis and CAS Response into Four Responses Categories

To further explore the response based on both proptosis and CAS reduction, each subject will be classified into one of 4 response categories at Week 24:

- High responders: Subjects who had a reduction in both proptosis and CAS of 3 or more (≥ 3) from Baseline in the study eye, and no deterioration in the fellow eye (i.e., increase in CAS ≥ 2 points or increase in proptosis ≥ 2 mm).
- Responders: Subjects who had a reduction in both CAS and proptosis of 2 or more (but less than 3) from Baseline in the study eye, and no deterioration in the fellow eye.
- Low Responders: Subjects who had a reduction in both CAS and proptosis of 1 or more (but less than 2) from Baseline in the study eye, and no deterioration in the fellow eye.
- Non-Responders: Subjects who did not fit into any of the above categories, or were not present for the Week 24 evaluation.

A logistic regression analysis will be used to compare the treatment groups on the basis of this ordered 4-category classification.

9.6.4.4 Quality of Life Analysis

QoL assessments will be used to derive pre-specified QoL scores according to the directions for the GO-QoL scale. These scores will be summarized by descriptive summary tables at Baseline and over time. The overall score, and the VF and A subscale scores, will be evaluated at Week 24 using the MMRM model described above. Final analysis plans will be provided in the SAP.

9.6.4.5 Blood and Serum Biomarkers

Biomarker data will be summarized using descriptive statistics.

9.6.4.6 Safety Analyses

The safety analysis population will include all subjects who receive at least one dose and had at least one post-dose safety assessment. All safety parameters will be summarized and presented in tables based on this safety population. Details of the safety data analysis will be presented in the SAP.

9.6.4.7 Interim Analyses

No interim analyses are planned.

9.6.5 Sample Size and Power Considerations

In the prior study, TED01RV, a 51% difference (71% vs 20%) between teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) and placebo was observed at Week 24 in favor of teprotumumab in proptosis reduction of 2 mm or more. A sample size of 38 subjects per group provides 90% power at the 2-sided alpha 0.05 level to detect a difference of 39% between teprotumumab and placebo; the sample size has been adjusted to allow for a 16% discontinuation rate.

9.7 Changes in the Conduct of the Study

If any modifications in the experimental design, dosages, parameters, subject selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before any such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approved from the appropriate IRB/IEC.

The Sponsor's Medical Monitor will consider any requests for exceptions to protocol entry criteria on a case-by-case basis. The Investigator or other health professional in attendance must contact the Sponsor as soon as possible. All protocol deviations and the reasons for such deviations **must** be documented in [REDACTED]. In the event of a protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB/IEC and Sponsor.

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The Investigator must maintain adequate and accurate records to document fully the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified in 2 separate categories: (1) Investigator study file and (2) subject clinical source documents that corroborate data collected in the eCRFs. Subject clinical source documents would include, as applicable, original hospital/clinic subject records; physicians' and nurses' notes; appointment book; original laboratory, ECG, electroencephalogram, radiology, pathology, and special assessment reports; dispensing records; signed ICFs; consultant letters; and subject screening and enrollment logs.

In order to comply with regulatory requirements, it is the policy of the Sponsor that, at a minimum, the following be documented in source documents at the study center:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify that the subject meets protocol entry criteria.
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each study visit including each study assessment and the identity of the staff member performing the assessment.
- Study drug dispensing and return.

- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- Adverse events (start and stop date, description, action taken, and resolution).
- Investigator or sub-investigator's signed assessment of each AE.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or PW from, the study.

11 CASE REPORT FORMS

An eCRF is required for every subject who signs the ICF. Required data must be entered on the eCRF within the required time period, which will be outlined within each site agreement, after data collection or the availability of test results. Separate source records are required to support all eCRF entries. Data captured on the eCRF, and requested anonymized copies of supporting documents, will be transferred to the Sponsor at study completion.

The Investigator will ensure that the eCRFs are accurate, complete, legible, and timely, and will review and provide an electronic signature for the eCRF according to the standard operating procedure of the CRO Data Management System. Final eCRFs will be provided to the Investigator and Sponsor by CRO Data Management.

12 STUDY MONITORING

The Investigator will ensure that the study is conducted in accordance with all regulations governing the protection of human subjects. The Investigator will adhere to the basic principles of GCP as outlined in Title 21 of the CFR, Part 312, Subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators"; and the ICH guideline entitled "Good Clinical Practice: Consolidated Guidance". Additionally, this study will be conducted in compliance with the Declaration of Helsinki and with all local laws and regulations.

The Investigator will ensure that all work and services described in, or associated with, this protocol are conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice. The Investigator will provide copies of the study protocol and IB to all Sub-Investigators, pharmacists, and other staff responsible for study conduct.

All aspects of the study will be monitored by qualified individuals designated by the Sponsor. The Sponsor will ensure that the study is monitored adequately in accordance with GCP guidelines.

Prior to initiation of the study, the Sponsor's representatives will review with study center personnel information regarding the investigational drug, protocol requirements, monitoring requirements, and reporting of SAEs.

At intervals during the study, as well as after the completion of subject enrollment, the study center will be monitored by the Sponsor or designee for compliance. During these visits, the masked monitor will discuss study progress, verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies, and check on various aspects of study conduct (e.g., drug accountability, sample storage). The Investigator agrees to allow unmasked monitors access to the clinical supplies, dispensing and storage areas, and clinical records of the study subjects, and, if requested, agrees to assist the monitors. The Investigator must cooperate with the monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

A secondary audit may be conducted by Quality Assurance designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the US FDA and/or representatives of other regulatory authorities may also conduct an inspection of the study at the investigative site. If informed of such an inspection, the Investigator should notify the Sponsor immediately.

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical study. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this study. A statement to this effect should be included in the ICF.

13 DATA MANAGEMENT

Data will be entered into a clinical database as specified in the CRO's Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

The coding of an AE, medical history and concomitant medication terms will be performed by the CRO vendor and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) and AE/medical history/surgery/non-drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

14 RETENTION OF RECORDS

No study documents at the study site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, IRB/IEC correspondence, and correspondence with the Sponsor must be kept by the Investigator for at least 2 years and or as required by the local law following the date of the last approval of a marketing application in an ICH region (including the US) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all study-related files must be retained for at least 2 years following the date of discontinuation of the clinical development program for teprotumumab and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any study-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the study was conducted.

15 PUBLICATION

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications) as detailed in the Clinical Trial Agreement.

16 REFERENCES

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17 APPENDICES

17.1 Administrative Appendix

This appendix provides names and contact information for the study administrative structure. The IRB/IEC must be notified of changes that are made to this section, but IRB/IEC review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment number.

Medical Monitor
Senior Medical Director

[REDACTED]
Horizon Pharma USA, Inc.
150 S. Saunders Road
Lake Forest, IL 60045
[REDACTED]
[REDACTED]

Sponsor
Representative

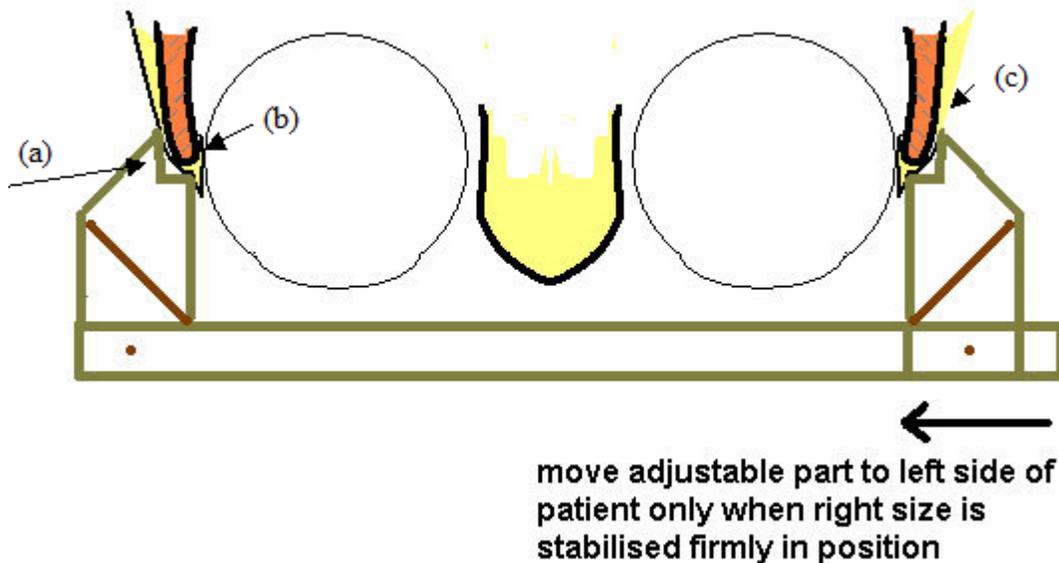
[REDACTED]
Horizon Pharma USA, Inc.
150 S. Saunders Road
Lake Forest, IL 60045
[REDACTED]
[REDACTED]

Sponsor Contact for
Serious Adverse Event Reporting

[REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

17.2 Proptosis (Exophthalmometry) Method

1. Choose a Hertel exophthalmometer provided by the Study Sponsor for consistency in measurement with a snug mechanism and preferably a square angle where it sits against the orbital rim (a).
2. Open it wider than required.
3. Sit opposite the patient and at the same level.
4. Keep the patient relaxed, avoiding breath holding and excessive eyelid retraction.



5. Position left foot of Hertel against the patient's right lateral orbital rim, at level of lateral canthus (b).
It should sit firmly as medially as possible, but outside lateral canthus and without distorting position of globe.
6. Slide right foot medially into identical position on left orbital rim (c). *This will feel tight and slightly uncomfortable, but minimizes potential side slippage of Hertel.*
7. Ask patient to fix their right eye on your left eye while you occlude the patient's left visual axis with your right thumb. In this position, align the instrument such that the vertical mark (or cone) is aligned with the manufacturer's pre-marked position on the ruler. Once aligned, rotate the instrument *slightly* around the horizontal plane such as to view the apex of the cornea in the mirror. Record the position of the corneal apex on the ruler. This is Hertel value.
8. To record the left eye, hold the instrument stationary and move your head. Then use your right eye to record the patients left eye. Again, the opposite visual axis is occluded by your left thumb, while the patient is asked to fix on your right eye. Ensure that the corneal apex is measured by rotating the instrument slightly around the horizontal plane if required.

17.3 Graves' Ophthalmopathy Quality of Life Questionnaire

Directions:

- The following questions deal specifically with your thyroid eye disease. **Please focus on the past week while answering these questions.**
- Please tick only one box that matches your answer. The boxes correspond with the answers above them.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

	Yes – seriously limited	Yes – a little limited	No – not at all limited
1) Bicycling (check here if never learned to ride a bike) <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2) Driving (check here if no driver's license) <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3) Moving around the house	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4) Walking outdoors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5) Reading	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6) Watching TV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7) Hobby or pastime, specify: _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes – severely hindered	Yes – a little hindered	No – not at all hindered
8) During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following questions deal with your thyroid eye disease in general.

	Yes – very much so	Yes – a little	No – not at all
9) Do you feel that your appearance has changed because of your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10) Do you feel that you are stared at in the streets because of your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11) Do you feel that people react unpleasantly because of your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12) Do you feel that your thyroid eye disease has an influence on your self-confidence?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13) Do you feel socially isolated because of your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14) Do you feel that your thyroid eye disease has an influence on making friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15) Do you feel that you appear less often on photos than before you had thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16) Do you try to mask changes in appearance caused by your thyroid eye disease?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>