Official Title:
Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)

Document:
Protocol

NCT#:
NCT03461211

Document Date:

31 January 2019

CLINICAL STUDY PROTOCOL FOR TEPROTUMUMAB (HZN-001)

IND: 112952

Protocol Number: HZNP-TEP-302

EudraCT Number: 2017-002713-58

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

Short Title: OPTIC-X™

Treatment of Graves' Orbitopathy to Reduce Proptosis with Teprotumumab Infusions in an Open-Label Clinical Extension Study

Date: 31 January 2019

Version 3.0, incorporating Protocol Version 2.1 and Amendment 2

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

PROTOCOL

1 TITLE PAGE

Study Title:	Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)
Protocol Number:	HZNP-TEP-302
Version:	3.0, incorporating Protocol Version 2.1 and Amendment 2
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. 150 S. Saunders Road 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 electronic case report form, 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]

SPONSOR SIGNATURE PAGE

Protocol Number:	HZNP-TEP-302
Version:	3.0, incorporating Protocol Version 2.1 and Amendment 2
Protocol Title:	Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)
Version Date:	31 January 2019

Approved by:

[redacted]

06FEB2019
Date

Horizon Pharma USA, Inc.

[redacted]

2-6-19
Date

[redacted]

2.2.19
Date

[redacted]

06 FEB 2019
Date

[redacted]

Feb 6, 2019
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-TEP-302

Version: 3.0, incorporating Protocol Version 2.1 and Amendment 2

Protocol Title: Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)

Version Date: 31 January 2019

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-302
Version 3.0, incorporating Protocol Version 2.1 and Amendment 2

Version 2.0 of the protocol, which was approved 20 April 2018, has been amended to incorporate the change from Protocol Version 2.1 that was specific to Germany:

- Add the following statement in the exclusion criteria: The exclusion criteria (except those related to screening) of protocol HZNP-TEP-301 also apply to this open-label extension study.

Further revisions and clarifications to Version 2.0 of the protocol include:

- 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 evaluation of pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand the PK-PD relationships as an exploratory endpoint.
- Change the number of teprotumumab doses administered from “up to 8 infusions based on Investigator judgment” to “8 infusions”.
- Specify the End-of-Treatment (EOT) Visit as Week 24.
- Add 2 additional follow-up contacts (telephone or email) at 6 and 12 months after the last visit to assess any additional thyroid eye disease (TED) treatment received since last study contact. For subjects who were proptosis non-responders after completion of the Treatment Period in Study HZNP-TEP-301, the last clinic visit was Month 12, with the follow-up contacts at Month 18 and 24. For subjects who relapsed during the Follow-up Period of Study HZNP-TEP-301, the last clinic visit was Week 24, with the follow-up contacts at Month 12 and 18.
- 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 Baseline through 180 days after the last dose of study drug.
- 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 of HZNP-TEP-301.
- Specify the minimum duration of study drug infusions.

- Add an additional location for the clinical drug supply and distribution vendor.
- Indicate that study medication vial assignments and volume of study drug to be administered are obtained from an electronic data capture (EDC) system and not an interactive web response system (IWRS).
- 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).
- Add pharmacokinetic (PK) sampling pre- and post-infusion on Day 1, Week 3 and Week 9 of the Treatment Period, with single samples collected at Weeks 1, 4 and 24.
- Change the definition of the end of the trial to date of the last subject contact at Month 24.
- Update Sponsor Representative title.
- Correct minor typographical errors (changes are not detailed below).

The following sections of the protocol are affected: 2, 2.1, Table 6.1, 7.1.3.4.5.5.1, 7.2, 8.1, 8.2, 8.3, 9.1, Figure 9.1, 9.3.1, 9.3.2, 9.3.3, 9.3.4, 9.4.1, 9.4.6.2, 9.4.6.3.1, 9.4.6.3.2, 9.4.8, 9.5.1, 9.5.1.1, 9.5.1.2, 9.5.1.3, 9.5.2, 9.5.3, 9.5.4.1.2, 9.5.4.3, 9.5.4.4, 9.5.4.5, 9.5.4.7, 9.5.5, 9.5.6.1, 9.5.6.2, 9.5.6.3, 9.5.6.4, 9.5.6.5, 9.5.6.6, 9.5.6.7, 9.5.6.8, 9.5.6.9, 9.5.6.10, 9.5.6.11, 9.5.6.12, 9.5.6.13, 9.5.6.14.1, 9.5.6.14.2, 9.5.6.15.1, 9.5.6.15.2, 9.5.6.16, 9.6.1, 9.6.1.1, 9.6.1.2, 9.6.1.3, 9.6.3, 9.6.3.2.1, and 17.1. Additional text is marked in red, underlined, and bolded; deleted text is marked as strikethrough text.

2 SYNOPSIS

Objectives:

Primary Objective

The primary objective is to evaluate the effect of teprotumumab on the proptosis responder rate (i.e., the percentage of subjects with a ≥ 2 mm reduction from Baseline in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at **Week 24**~~the EOT Visit~~.

Secondary Objectives

Secondary objectives will evaluate the effect of teprotumumab on the following:

1. Percentage of subjects with a Clinical Activity Score (CAS) value of 0 or 1 at **Week 24**~~the EOT Visit~~ in the study eye.
2. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in proptosis measurement in the study eye.
3. **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.**
4. ~~3.~~ Mean change from Baseline to **Week 24**~~the EOT Visit~~ in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

Exploratory Objectives

Exploratory objectives will evaluate the effect of teprotumumab on the following:

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** ~~the EOT Visit~~.
2. Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at **Week 24** ~~the EOT Visit~~.
3. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the CAS.
4. Overall responder rate at **Week 24** ~~the EOT Visit~~ stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ on the motility component of the Clinical Measures of Severity.
7. **Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.**

Study Design:

All subjects who choose to participate will receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion.~~, with the number of infusions determined by the Investigator's clinical judgment (but not to exceed 8 infusions)~~ The Baseline (Day 1) Visit of this extension study will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse). During the open-label Treatment Period, study drug infusions are scheduled for Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 **(with a final visit at Week 24 of the 24-Week Treatment Period).** ~~When the Investigator considers treatment to be complete, subjects will have an End of Treatment (EOT) Visit 3 weeks after the final infusion and undergo the scheduled EOT assessments.~~

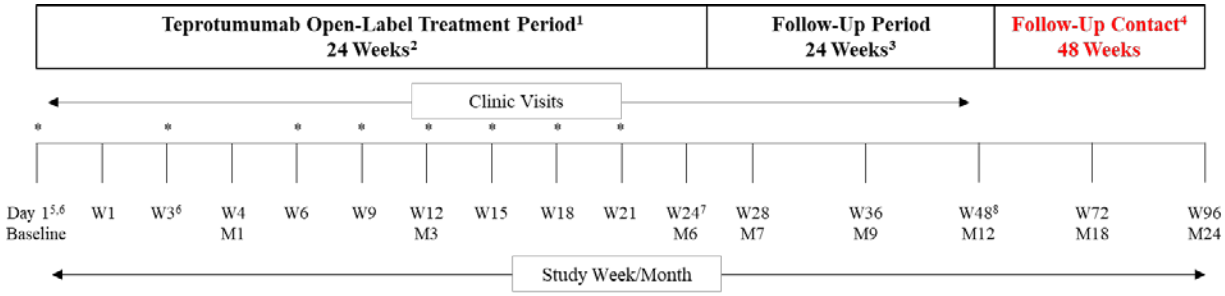
After completion of the Treatment Period, subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter a 24-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for 1, 3, and 6 months (Visits Month 7, 9 and 12) after the **Week 24** ~~EOT~~ Visit; if any of these subjects discontinue from the Follow-Up Period prior to the Month 12 Visit, they will return to the clinic and undergo the scheduled Month 12 assessments prior to study discharge. **Those who complete the Month 12 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.**

Subjects who relapse during the Follow-Up Period of HZNP-TEP-301 and choose to enter this extension study will not participate in the Follow-Up Period. **For these subjects, the last clinic visit is at Week 24. Those who complete the Week 24 Visit will be contacted 6 and**

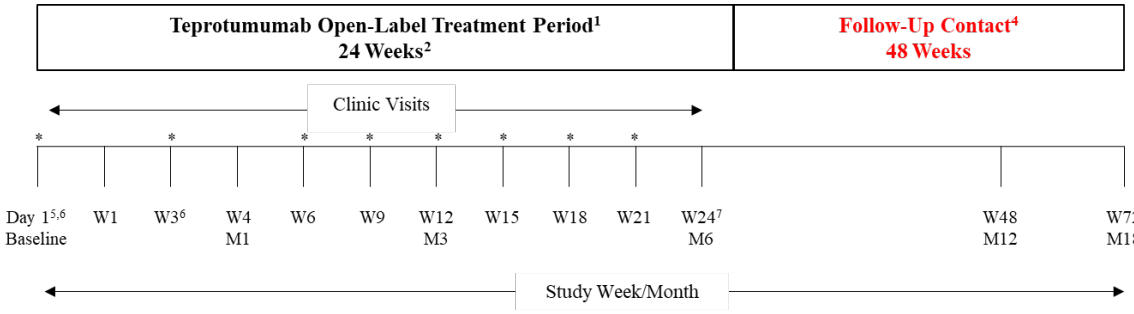
12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response. ~~and will be discharged from the study following completion of the EOT assessments 3 weeks after the last infusion~~.

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*.

Subjects who were proptosis non-responders in Study HZNP-TEP-301



Subjects who relapsed in Study HZNP-TEP-301



* Infusion of study drug. ~~EOS=End of Study; EOT=End of Treatment~~; M=Month; W=Week.

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions). ~~The number of infusions will be individualized for each subject and will be based on the Investigator's clinical judgment.~~
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** ~~EOT~~.
3. Visit windows of ± 7 days.
4. **Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 Visit.**
5. Visit must occur within 14 days after the final visit of HZNP-TEP-301.
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. ~~When the Investigator deems dosing is complete, or i~~If a subject wishes to discontinue dosing, the subject will return to the clinic and undergo the scheduled **Week 24** ~~EOT~~ assessments.
8. If a subject participates in the Follow-Up Period and prematurely discontinues prior to Month 12, he/she will return to the clinic and undergo the **Month 12**~~EOS~~ assessments prior to study discharge.

Inclusion Criteria:

8. Women of childbearing potential must have a negative urine pregnancy test at Baseline/Day 1. **Subjects who are sexually active with a non-vasectomized male partner must** ~~and~~ agree to use 2 reliable forms of contraception during the trial and continue for 180 days after the last dose of study drug. One of the 2 forms of

contraception is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be in use for at least one full cycle prior to Baseline. 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.

9. 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 Baseline through 180 days after the last dose of study drug.

Exclusion Criteria:

1. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

The exclusion criteria (except those related to screening) of protocol HZNP-TEP-301 also apply to this open-label extension study.

Dose Regimen/Route of Administration:

All study drug dosing will be performed at the clinic under the supervision of clinic staff. Subjects will receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining **7** infusions) in an open-label fashion.~~; the number of infusions will be determined by the Investigator's clinical judgment.~~

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),** ~~period~~ providing there are no significant infusion-associated events.

Duration of Treatment and Follow-up

The ~~maximum~~ duration of the Treatment Period is 24 weeks (6 months), during which ~~up to~~ 8 infusions of teprotumumab will be administered.

Subjects who complete the study (Month 12 Visit for proptosis non-responders in Study HZNP-TEP-301 and Week 24 Visit for subjects who relapsed during the Follow-up Period in Study HZNP-TEP-301) will be contacted 6 and 12 months after the last visit 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:

Study endpoints will be evaluated for all subjects from Baseline to **Week 24**~~the EOT Visit~~.

Primary Efficacy Endpoint

The primary outcome measure is the effect of teprotumumab on the proptosis responder rate at **Week 24** ~~the EOT Visit~~.

Secondary Efficacy Endpoints

Secondary efficacy endpoints include the percentage of subjects with a CAS value of 0 or 1 at **Week 24,** ~~the EOT Visit, and the~~ mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the "study eye" proptosis measurement, **diplopia responder rate at Week 24,** and **mean change from Baseline to Week 24** in ~~the~~ GO-QoL questionnaire overall score.

Exploratory Efficacy Endpoints

Week 24 ~~EOT~~ data will be summarized for the overall responder rate, the Clinical Measures of Severity individual response status frequencies, the percentage of responders for each component of the Clinical Measures of Severity, and the overall responder rate stratified by the level of response. Mean changes from Baseline to **Week 24** ~~the EOT Visit~~ will be summarized for the CAS, the GO-QoL questionnaire VF and A subscale scores, and the motility component of the Clinical Measures of Severity. **PK parameters will be summarized**.

2.1 Schedule of Assessments

	Open-Label Treatment Period [1] (≤24 Weeks) [2]											Follow-Up Period [2,3] (24 weeks)			Follow-Up Contact [3] (48 Weeks)			
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ PWEOT [4]**	**FU1**	**FU2**	**FU3/ PWEOS [5]**	**FU4**	**FU5**	**FU4**	**FU5**
Week (W)/ Month (M)	**Day 1 [6]**	**W1**	**W3**	**W4/ M1**	**W6**	**W9**	**W12/ M3**	**W15**	**W18**	**W21**	**W24/ M6**	**W28/ M7**	**W36/ M9**	**W48/ M12**	**W48/ M12**	**W72/ M18**	**W72/ M18**	**W96/ M24**
Visit Window (± days)	**(+14) [7]**	**(±1)**	**(±3)**	**(±1)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Subject response in Study HZNP-TEP-301	**Proptosis Non-responder or Relapse**											**Proptosis Non-responder Only**			**Relapse Only**		**Proptosis Non-responder Only**	
Informed Consent	X																	
Review inc/exc criteria	X																	
Weight [8]	X [9]						X				X		X	X				
Study drug infusion [10]	X		X		X	X	X	X	X	X								
Phone (email) contact for safety 24 hours postdose [11]	X		X															
Investigator assessment of active disease	X				X		X		X		X	X	X	X				
Efficacy assessments																		
CAS	X [9]				X		X		X		X	X	X	X				
Clinical Measures of Severity - includes proptosis, diplopia, and motility restriction	X [9]				X		X		X		X	X	X	X				
Safety assessments																		
Pregnancy Test [12]	X [9]		X		X	X	X	X	X	X	X	X	X	X				
Physical exam [13]	X [9,13]	X			X		X		X		X [13]			X [13]				
Ophthalmic exam [14]	X [9]	X			X		X		X		X			X				
Vital Signs [15]	X [9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
12-Lead ECG	X [9]		X		X		X				X			X				
Clinical laboratory tests [16]																		
Chemistry (excl. glucose)	X [9,17]		X		X	X	X		X		X		X	X				
Thyroid (FT3, FT4, TSH) [18]	X [9]		X		X	X	X		X		X		X	X				
Hematology	X [9]	X	X	X	X	X	X	X	X	X	X		X	X				

	Open-Label Treatment Period [1] (≤24 Weeks) [2]											Follow-Up Period [2~~3~~] (24 weeks)			Follow-Up Contact [3] (48 Weeks)			
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ PW~~EOT~~ [4]**	**FU1**	**FU2**	**FU3/ PW~~EOS~~ [5]**	**FU4**	**FU5**	**FU4**	**FU5**
Week (W)/ Month (M)	**Day 1 [6]**	**W1**	**W3**	**W4/ M1**	**W6**	**W9**	**W12/ M3**	**W15**	**W18**	**W21**	**W24/ M6**	**W28/ M7**	**W36/ M9**	**W48/ M12**	**W48/ M12**	**W72/ M18**	**W72/ M18**	**W96/ M24**
Visit Window (± days)	**(+14) [7]**	**(±1)**	**(±3)**	**(±1)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Subject response in Study HZNP-TEP-301	**Proptosis Non-responder or Relapse**											**Proptosis Non-responder Only**			**Relapse Only**		**Proptosis Non-responder Only**	
Glucose [19]	X [9]	X	X	X	X	X	X	X	X	X	X		X	X				
HbA1c	X [9]						X				X		X	X				
Urinalysis	X [9]		X		X	X	X		X		X		X	X				
ADA/NAb samples [20]	X [9]		X			X					X [21]		X	X				
AE, SAE assessment [2~~21~~]	X [9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
Concomitant medications	X [9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
GO-QoL Questionnaire	X [9]				X		X				X	X		X				
PK samples [23]	**X**	**X**	**X**	**X**		**X**					**X [21]**							
Contact (phone/email) to assess additional TED treatment [24]															**X**	**X**	**X**	**X**

ADA=anti-drug antibody; AE=adverse event; CAS=Clinical Activity Score; ECG=electrocardiogram; ~~EOT=End of Treatment; EOS=End of Study;~~ 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. Open-label Treatment Period. Subjects with TED who are proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but who meet criteria for re-treatment due to relapse during the Follow-Up Period in HZNP-TEP-301 are eligible to enroll and receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg for the first infusion titrated to 20 mg/kg for the remaining infusions) in an open-label fashion.

~~2. The number of infusions and length of participation in the open-label Treatment Period will be determined by the Investigator's clinical judgment (but not to exceed 8 infusions).~~

2~~3~~. Proptosis non-responders from Study HZNP-TEP-301 will participate in a 6-month Follow-Up Period; subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 will not participate.

3. Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 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.

4. ~~Once the Investigator deems study drug dosing to be complete, or i~~If subjects wish to discontinue study drug during the open-label Treatment Period, subjects will return for a clinic visit ~~3 weeks after the final dose~~ and undergo the **Week 24** ~~End of Treatment (EOT)~~ assessments**, except for PK and ADA evaluations.** Subjects who were proptosis non-responders at Week 24 of HZNP-TEP-301 will be encouraged to continue study participation in the Follow-Up Period.
5. If a subject wishes to prematurely discontinue from the study during the Follow-Up Period, he/she will return for a clinic visit and undergo the Month 12 ~~(End of Study [EOS])~~ assessments prior to discharge.
6. On Day 1 (Baseline), subjects will receive the first dose of study drug; however, Baseline assessments will be performed prior to dosing.
7. Day 1 will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse).
8. 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.**
9. If Day 1 of the extension study occurs on the same day as the final visit of HZNP-TEP-301 (Week 24 [or PW1] for proptosis non-responders and Week 72 [or PW2] for subjects who relapse), assessments do not need to be repeated, and the final assessments from the lead-in study will serve as the Baseline assessments for the extension study.
10. Subjects will receive teprotumumab 10 mg/kg on Day 1 followed by 20 mg/kg q3W for the **7** remaining infusions.
11. 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.
12. Perform urine pregnancy tests prior to dose (as applicable) for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Baseline of HZNP-TEP-302, non-therapy-induced amenorrhea for <12 months prior to Baseline of HZNP-TEP-302, or not surgically sterile [absence of ovaries and/or uterus]).
13. Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1 and **Week 24/PW**~~EOT~~ of the Treatment Period and **Month 12/PW**~~EOS~~ of the Follow-Up Period. If present, measurements of instep and calf will be taken.
14. 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.
15. 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 9.5.4.3 for details).
16. Non-diabetic subjects should be fasting at Weeks 1 and 4 only. Diabetic subjects should be fasting at each visit blood glucose is evaluated.
17. 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) at the most recent clinic visit to be eligible for enrollment.
18. 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 the most recent clinic visit. 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.
19. HbA1c must be < 9.0% at the most recent clinic visit. If the HbA1c is elevated and considered clinically significant at any time point after Baseline, it will be repeated approximately every 45 days until it returns to normal or the baseline value.
20. 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 48 (or PW) during the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.
21. **Not collected for subjects who prematurely discontinue from the open-label Treatment Period.**

2221. Adverse events that are ongoing at **completion of** ~~the EOS visit in~~ HZNP-TEP-301 **and/**or occur prior to dosing on Day 1 will be considered pre-dose AEs. 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.

23. **PK samples will be collected prior to, and at the end of, the infusion on Day 1 and Weeks 3 and 9 of the open-label Treatment Period; additional single samples will be collected at Weeks 1, 4, and 24.**

24. **If TED treatment has been received since last contact, the subject will be questioned regarding type of treatment and outcome/response.**

Table 6.1 Table of Non-Sponsor Study Responsibilities

Clinical drug supply and distribution	[redacted]
Immunogenicity **and PK** laboratory	[redacted]

7.1.3.4.5.5.1 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.

7.2 Rationale for this Study

Horizon is currently conducting a randomized, multicenter, double-masked, placebo-controlled study evaluating the efficacy and safety of teprotumumab in adult subjects with moderate to severe active TED (HZNP-TEP-301). This study (HZNP-TEP-302) is designed to be an open-label extension of HZNP-TEP-301, in which subjects who received 8 infusions of teprotumumab or placebo in HZNP-TEP-301 and were non-responders at the end of the Treatment Period or relapsed during the Follow-Up Period will be offered the opportunity to receive ~~up to~~ 8 infusions of teprotumumab.

8.1 Primary Objective

The primary objective is to evaluate the effect of teprotumumab on the proptosis responder rate (i.e., the percentage of subjects with a $\geq$ 2 mm reduction from Baseline in the study eye without deterioration [$\geq$ 2 mm increase] of proptosis in the fellow eye) at **Week 24** ~~the EOT Visit~~.

8.2 Secondary Objectives

Secondary objectives will evaluate the effect of teprotumumab on the following:

1. Percentage of subjects with a Clinical Activity Score (CAS) value of 0 or 1 at **Week 24** ~~the EOT Visit~~ in the study eye.
2. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in proptosis measurement in the study eye.
3. **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.**
4. ~~3.~~ Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

8.3 Exploratory Objectives

Exploratory objectives will evaluate the effect of teprotumumab on the following:

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**~~the EOT Visit~~.
2. Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at **Week 24**~~the EOT Visit~~.
3. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the CAS.
4. Overall responder rate at **Week 24** ~~the EOT Visit~~ stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Mean change from Baseline to **Week 24** ~~the EOT Visit~~ on the motility component of the Clinical Measures of Severity.
7. **Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.**

9.1 Overall Study Design and Plan

All subjects who choose to participate will receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion.~~, with the number of infusions determined by the Investigator's clinical judgment (but not to exceed 8 infusions)~~ The Baseline (Day 1) Visit of this extension study will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse). During the open-label Treatment Period, study drug infusions are scheduled for Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 **(with a final visit at Week 24 of the 24-Week Treatment Period).** ~~When the Investigator considers~~

~~treatment to be complete, subjects will have an End of Treatment (EOT) Visit 3 weeks after the final infusion and undergo the scheduled EOT assessments.~~

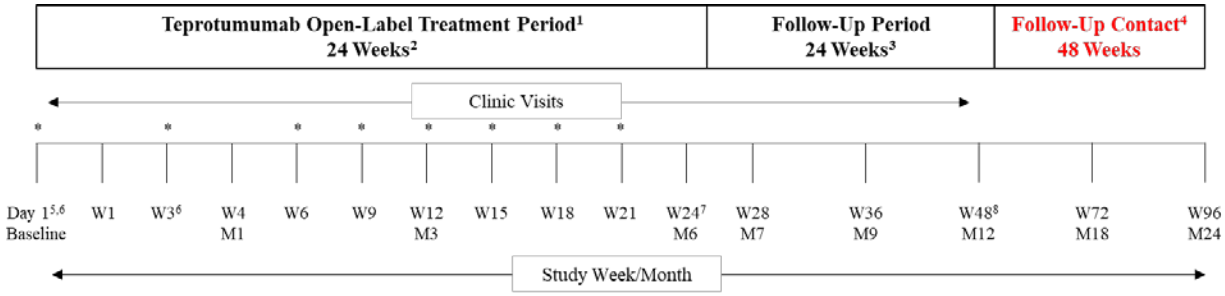
After completion of the Treatment Period, subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter a 24-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for 1, 3, and 6 months (Visits Month 7, 9 and 12) after the **Week 24** ~~EOT~~ Visit; if any of these subjects discontinue from the Follow-Up Period prior to the Month 12 Visit, they will return to the clinic and undergo the scheduled Month 12 assessments prior to study discharge. **Those who complete the Month 12 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.**

Subjects who relapse during the Follow-Up Period of HZNP-TEP-301 and choose to enter this extension study will not participate in the Follow-Up Period. **For these subjects, the last clinic visit is at Week 24. Those who complete the Week 24 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.** ~~and will be discharged from the study following completion of the EOT assessments 3 weeks after the last infusion~~.

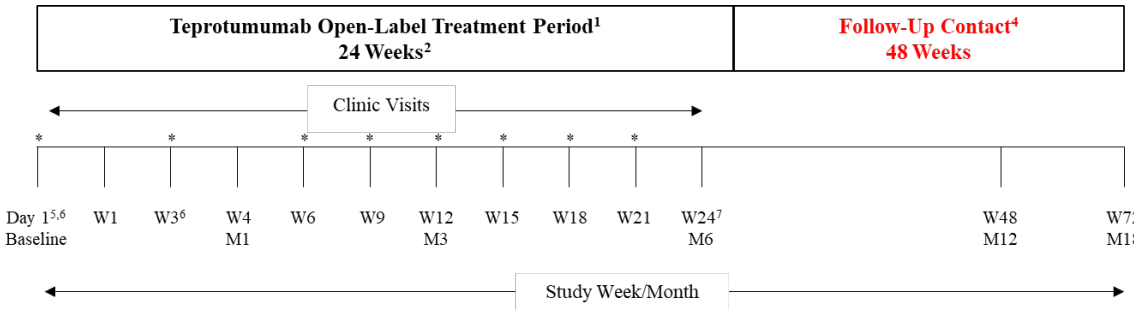
An overview of the study design is presented in the schematic below, and details of study activities are provided in Section 2.1, *Schedule of Assessments.*

Figure 9.1 Schematic of Study Design

Subjects who were proptosis non-responders in Study HZNP-TEP-301



Subjects who relapsed in Study HZNP-TEP-301



* Infusion of study drug. ~~EOS=End of Study; EOT=End of Treatment~~; M=Month; W=Week.

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions). ~~The number of infusions will be individualized for each subject and will be based on the Investigator's clinical judgment.~~
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** ~~EOT~~.
3. Visit windows of ± 7 days.
4. **Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 Visit.**
5. Visit must occur within 14 days after the final visit of HZNP-TEP-301.
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. ~~When the Investigator deems dosing is complete, or i~~If a subject wishes to discontinue dosing, the subject will return to the clinic and undergo the scheduled **Week 24** ~~EOT~~ assessments.
8. If a subject participates in the Follow-Up Period and prematurely discontinues prior to Month 12, he/she will return to the clinic and undergo the **Month 12**~~EOS~~ assessments prior to study discharge.

9.3.1 Inclusion Criteria

8. Women of childbearing potential must have a negative urine pregnancy test at Baseline/Day 1**. Subjects who are sexually active with a non-vasectomized male partner must** ~~and~~ agree to use 2 reliable forms of contraception during the trial and continue for 180 days after the last dose of study drug. One of the 2 forms of contraception is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be in use for at least one full cycle prior to Baseline. 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.
9. 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 Baseline through 180 days after the last dose of study drug.

9.3.2 Exclusion Criteria

1. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

The exclusion criteria (except those related to screening) of protocol HZNP-TEP-301 also apply to this open-label extension study.

9.3.3 Removal of Subjects from Therapy or Assessment

When ~~the Investigator considers~~ treatment **is** ~~to be~~ complete, subjects will ~~have an EOT Visit 3 weeks after the final infusion and~~ undergo the scheduled **Week 24** ~~EOT~~ assessments. ~~Subjects who relapsed during the HZNP-TEP-301 study will be discharged after completion of the Week 24 EOT assessments.~~

~~Only s~~**S**ubjects who were proptosis non-responders in HZNP-TEP-301 will participate in the Follow-Up Period. Subjects who enter the Follow-Up Period but prematurely discontinue study participation prior to Month 12 will return for a final visit and undergo the scheduled Month 12~~/EOS~~ 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.

Subjects who relapsed during the HZNP-TEP-301 study will **not participate in the Follow-up Period.** ~~be discharged after completion of the EOT assessments.~~

Subjects who complete the study (Month 12 Visit for proptosis non-responders in Study HZNP-TEP-301 and Week 24 Visit for subjects who relapsed during the Follow-up Period in Study HZNP-TEP-301) will be contacted 6 and 12 months after the last visit via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.

9.3.4 Criteria for Responders Who Relapse

If subjects met the response criteria at Week 24 of HZNP-TEP-301 but subsequently experience a disease relapse during the 48-week Follow-Up Period of the lead-in study, they will have the option to enter this open-label extension study (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 of HZNP-TEP-301, or
- An **increase in CAS of ≥ 2 points since Week 24 with an** absolute CAS of ≥ 4 **in the study eye** following Week 24 of HZNP-TEP-301.
- 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

All study drug dosing will be performed at the clinic under the supervision of clinic staff. Subjects will receive ~~up to~~ 8 infusions of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining infusions) in an open-label fashion~~; the number of infusions will be determined by the Investigator's clinical judgment~~.

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),** ~~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 **electronic data capture (EDC)** ~~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 on Day 1 and Weeks 12 and 24 during the Treatment Period. The dose on Day 1 may be based on the weight determined at the most recent clinic visit, provided the most recent visit was within the prior 3 weeks. The doses on Week 3 through Week 9~~12~~ will be based on the weight determined on Day 1. **The weight used in the Week 12 dose calculation can be the weight determined on Day 1 or the weight obtained at Week 12. The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15 through Week 21**~~, and the doses on Weeks 18 through 21 may be adjusted based on the weight obtained 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.

9.4.8 Masking and Unmasking

In order to maintain the study mask in HZNP-TEP-301, all subjects in this open-label extension study will undergo the same dosing regimen of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining **7** infusions), regardless if they received teprotumumab or placebo in HZNP-TEP-301.

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).

9.5.1.1 Proptosis (Exophthalmos)

Proptosis will be measured for each eye on Day 1 and Weeks 6, 12, 18, and **24 (or PW)** ~~at EOT~~ during the Treatment Period, and at Months 7, 9, and 12 (or **PW**~~EOS~~) during the Follow-Up Period. Measurements will be recorded on the Clinical Measures of Severity eCRF under exophthalmos.

9.5.1.2 Clinical Activity Score (CAS)

The CAS will be completed on Day 1 and Weeks 6, 12, 18, and **24 (or PW)** ~~at EOT~~ during the Treatment Period, and at Months 7, 9, and 12 (or **PW**~~EOS~~) during the Follow-Up Period using the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS [Mourits et al, 1989] (Table 9.2).

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 on Day 1 and Weeks 6, 12, 18, and **24 (or PW)** ~~at EOT~~ during the Treatment Period, and at Months 7, 9, and 12 (or **PW**~~EOS~~) 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.

9.5.2 Quality-of-Life Assessment

The GO-QoL questionnaire [C. B. Terwee et al, 1998] will be completed on Day 1 and Weeks 6, 12, and 24 (or PW~~EOT~~) during the Treatment Period, and at Months 7 and 12 (or PW~~EOS~~) during the Follow-Up Period.

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 ≥ -70ºC at the site until shipment to the central laboratory [redacted] will store the samples at ≥ –70ºC until shipment to [redacted] 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.

9.5.4.1.2 Documentation of Adverse Events

Adverse events that are ongoing at the **completion of** ~~EOS visit in~~ HZNP-TEP-301 **and/**or occur prior to dosing on Day 1 will be considered pre-dose AEs. 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 (Month 12 or PW~~EOS~~). All pre-dose AEs, TEAEs, and AEs during the Follow-Up Period must be recorded in the source documents and in the subject's eCRF.

9.5.4.3 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 any other infusion day. 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.~~

9.5.4.4 Physical and Ophthalmic Examinations, Height, and Weight

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

Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1 and ~~EOT~~ **Week 24 (or PW)** of the Treatment Period and Month 12/**PW**~~EOS~~ of the Follow-Up Period. If present, measurements of instep and calf will be taken.

Weight will be measured at Baseline and every 12 weeks throughout the study (Weeks 12 and **24 [or PW]** ~~EOT~~ during the Treatment Period and Months 9 and 12 [or **PW**~~EOS~~] of the Follow-Up Period). The dose on Day 1 may be based on the weight determined at the most recent clinic visit, provided the most recent visit was within the prior 3 weeks. The doses on Week 3 through Week 9~~12~~ will be based on the weight determined on Day 1. **The weight used in the Week 12 dose calculation can be the weight determined on Day 1 or the weight obtained at Week 12.** ~~, and the doses on Weeks 18 through 21 may be adjusted based on the weight obtained at Week 12, as appropriate.~~ **The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15 through Week 21, as appropriate.**

9.5.4.5 ECGs

12-lead ECGs will be performed at Baseline, Weeks 3, 6, 12, and **24 (or PW)** ~~EOT~~ of the Treatment Period, and Month 12 (or **PW**~~EOS~~) 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.

9.5.4.7 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 EOT)~~ of the Treatment Period, and Months 9 and 12 (or **PW**~~EOS~~) of the Follow-Up Period. Samples will be collected, processed, and stored at ≥ -70°C at the site until shipment to the central laboratory [redacted] will store the samples at ≥ –70°C until shipment to [redacted] for immunogenicity testing. 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 Month 12 (or **PW**~~EOS~~) of the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.

9.5.5 Appropriateness of Measurements

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

9.5.6.1 Day 1/Baseline

- Collect predose blood samples for immunogenicity **and PK** testing.
- 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~~).
- ~~Contact IWRS to r~~Register enrollment **in EDC**, obtain study medication vial assignment~~,~~ and ~~to determine the~~ volume of study drug to be administered.
- **Collect blood samples for PK analyses at the end of the infusion.**

9.5.6.2 Week 1

- **Collect blood sample for PK analyses. Record date/time of sample collection.**

9.5.6.3 Week 3

- Collect predose blood samples for immunogenicity **and PK** testing.
- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.
- **Collect blood samples for PK analyses at the end of the infusion.**

9.5.6.4 Week 4

- **Collect blood sample for PK analyses. Record date/time of sample collection.**

9.5.6.5 Week 6

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).
- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.

9.5.6.6 Week 9

- Collect predose blood samples for immunogenicity **and PK** testing.
- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.
- **Collect blood samples for PK analyses at the end of the infusion.**

9.5.6.7 Week 12

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).
- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.

9.5.6.8 Week 15

- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.

9.5.6.9 Week 18

- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, **diplopia** and motility restriction).
- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.

9.5.6.10 Week 21

- ~~Contact IWRS to o~~Obtain study medication vial assignment and ~~to determine~~ volume of study drug to be administered **from EDC**.

9.5.6.11 Week 24**/Premature Withdrawal – Treatment Period** ~~**(EOT)**~~

Week 24~~EOT~~ is the final visit of the Treatment Period. ~~and will occur 3 weeks after the last infusion.~~ Study drug is not administered.

- 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 analyses (only subjects who complete the Treatment Period, not those who prematurely discontinue study drug administration).**

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

- ~~Contact IWRS to register the EOT Visit.~~

Subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter the Follow-Up Period and will be instructed to return to the clinic in one month for the first follow-up visit. Subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and chose to enter this extension study ~~will be discharged from the study following completion of the EOT assessments (they~~ will not participate in the Follow-Up Period~~). Subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter the Follow-Up Period and will be instructed to return to the clinic in one month for the first follow-up visit.~~

9.5.6.12 Month 7 – Follow-Up Period

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

9.5.6.13 Month 9 – Follow-Up Period

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

9.5.6.14 Month 12

9.5.6.14.1 Month 12/Premature Withdrawal~~EOS~~ – Follow-Up Period for Proptosis Non-responders in Study HZNP-TEP-301

- 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 Month 9 of the Follow-Up Period.

- 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.

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

9.5.6.14.2 Month 12 – Follow-Up Contact for Subjects Who Relapsed in Study HZNP-TEP-301

Subjects who complete the Week 24 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.

9.5.6.15 Month 18

9.5.6.15.1 Month 18 – Follow-Up Contact for Proptosis Non-responders in Study HZNP-TEP-301

Subjects who complete the Month 12 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.

9.5.6.15.2 Month 18 – Follow-Up Contact for Subjects Who Relapsed in Study HZNP-TEP-301

Subjects who complete the Week 24 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.

This is the final contact for subjects who relapsed in Study HZNP-TEP-301.

9.5.6.16 Month 24 – Follow-Up Contact for Proptosis Non-responders in Study HZNP-TEP-301

Subjects who complete the Month 12 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.

This is the final contact for proptosis non-responders in Study HZNP-TEP-301.

The end of the trial is defined as the date of the last subject contact at Month 24.

9.6.1 Endpoints

Study endpoints will be evaluated for all subjects from Baseline to **Week 24** ~~the EOT Visit~~.

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**~~the EOT Visit~~.

9.6.1.2 Secondary Endpoints

1. Percentage of subjects with a CAS value of 0 or 1 in the study eye at **Week 24**~~the EOT Visit.~~
2. Mean change from Baseline to **Week 24** ~~EOT~~ in proptosis measurement in the study eye.
3. **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.**
4.~~3.~~ Mean change from Baseline to **Week 24** ~~EOT~~ in the GO-QoL questionnaire overall score.

9.6.1.3 Exploratory Endpoints

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** ~~the EOT Visit~~.
2. The Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at **Week 24** ~~EOT~~.
3. The mean change from Baseline to **Week 24** ~~EOT~~ in the CAS.
4. The overall responder rate at **Week 24** ~~EOT~~ stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. The mean change from Baseline to **Week 24** ~~EOT~~ in the GO-QoL questionnaire VF and A subscale scores.
6. The mean change from Baseline to **Week 24** ~~EOT~~ on the motility component of the Clinical Measures of Severity.
7. **Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.**

9.6.3 Primary and Secondary Endpoint Analysis

Study endpoints will be evaluated for all subjects from Baseline to **Week 24** ~~the EOT Visit~~.

9.6.3.2.1 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** ~~EOT~~:

- High responders: Subjects who had a reduction in both proptosis and CAS of 3 or more ($\geq$3) from Baseline in the study eye, and no deterioration in the fellow eye (i.e., increase in CAS $\geq$ 2 points or increase in proptosis $\geq$ 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** ~~EOT~~ evaluation.

17.1 Administrative Appendix

Sponsor Representative

[redacted]
Horizon Pharma USA, Inc.
150 S. Saunders Road
Lake Forest, IL 60045
Mobile telephone number: [redacted]
Fax number: [redacted]
Email: [redacted]

2 SYNOPSIS

Protocol Title: Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)	
Protocol Number: HZNP-TEP-302	**Phase**: 3
Protocol Version: 3.0	
Test Drug: Teprotumumab (HZN-001)	**Indication**: Thyroid Eye Disease (TED)
Number and Country of Study Sites: Up to 16 study centers in the United States and Europe.	

Objectives:

The overall objective is to evaluate the safety and efficacy of teprotumumab in the treatment of TED in subjects who participated in the lead-in study (HZNP-TEP-301) and who were either proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301.

Primary Objective

The primary objective is to evaluate the effect of teprotumumab on the proptosis responder rate (i.e., the percentage of subjects with a ≥ 2 mm reduction from Baseline in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at Week 24.

Secondary Objectives

Secondary objectives will evaluate the effect of teprotumumab on the following:

1. Percentage of subjects with a Clinical Activity Score (CAS) value of 0 or 1 at Week 24 in the study eye.
2. Mean change from Baseline to Week 24 in proptosis measurement in the study eye.
3. 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.
4. Mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

Exploratory Objectives

Exploratory objectives will evaluate the effect of teprotumumab on the following:

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. Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at Week 24.
3. Mean change from Baseline to Week 24 in the CAS.
4. Overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. Mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.
7. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.

Study Design:

This is a multi-center, open-label extension study of HZNP-TEP-301 examining the safety and efficacy of teprotumumab in the treatment of TED in adult subjects. Subjects who complete the 24-week double-masked

Study Design (continued):

Treatment Period in Study HZNP-TEP-301 and are proptosis non-responders or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301 will be eligible for enrollment. The study treatment previously administered in HZNP-TEP-301 (teprotumumab or placebo) will remain masked throughout this extension study.

All subjects who choose to participate will receive 8 infusions of teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion. The Baseline (Day 1) Visit of this extension study will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse). During the open-label Treatment Period, study drug infusions are scheduled for Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 (with a final visit at Week 24 of the 24-Week Treatment Period).

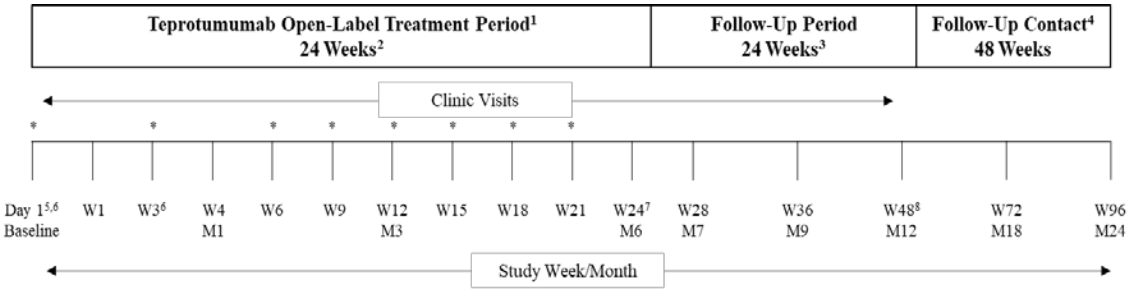
All study drug dosing will be performed at the clinic under the supervision of clinic staff, and at any scheduled infusion, the infusion rate may be reduced or the dose may be interrupted or held based on decreased tolerability (see Section 9.4.6.3.2 for details). On each dosing day, scheduled assessments (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.

After completion of the Treatment Period, subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter a 24-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for 1, 3, and 6 months (Visits Month 7, 9 and 12) after the Week 24 Visit; if any of these subjects discontinue from the Follow-Up Period prior to the Month 12 Visit, they will return to the clinic and undergo the scheduled Month 12 assessments prior to study discharge. Those who complete the Month 12 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.

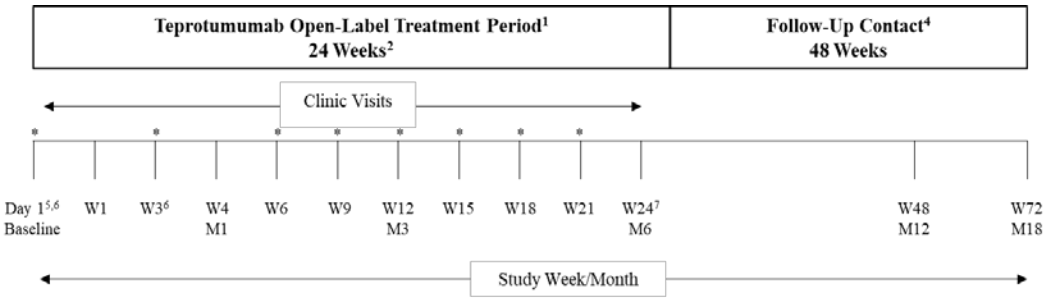
Subjects who relapse during the Follow-Up Period of HZNP-TEP-301 and choose to enter this extension study will not participate in the Follow-Up Period. For these subjects, the last clinic visit is at Week 24. Those who complete the Week 24 Visit will be contacted 6 and 12 months later via phone or email 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*.

Subjects who were proptosis non-responders in Study HZNP-TEP-301



Subjects who relapsed in Study HZNP-TEP-301



* Infusion of study drug. M=Month; W=Week.

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 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. Visit windows of ± 7 days.
4. Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 Visit.
5. Visit must occur within 14 days after the final visit of HZNP-TEP-301.
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. If a subject wishes to discontinue dosing, the subject will return to the clinic and undergo the scheduled Week 24 assessments.
8. If a subject participates in the Follow-Up Period and prematurely discontinues prior to Month 12, he/she will return to the clinic and undergo the Month 12 assessments prior to study discharge.

Subject Population:

Subjects with TED who complete the 24-week double-masked Treatment Period in HZNP-TEP-301 and are proptosis non-responders (< 2 mm reduction in proptosis in the study eye) or were proptosis responders at Week 24 in study HZNP-TEP-301 but who meet criteria for re-treatment due to relapse during the Follow-Up Period are eligible to enter this open-label extension study.

Inclusion Criteria:

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Completed the 24-week double-masked Treatment Period in Study HZNP-TEP-301.
3. Proptosis non-responder (< 2 mm reduction in proptosis in the study eye) at Week 24 of Study HZNP-TEP-301 OR proptosis responder at Week 24 who relapses (see Section 9.3.4) during the Follow-Up Period of Study HZNP-TEP-301.
4. Subject 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 the most recent clinic visit. 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.

Inclusion Criteria (continued):

5. 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 the most recent clinic visit.
6. Diabetic subjects must have well-controlled disease (defined as HbA1c < 9.0% at most recent clinic visit).
7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study.
8. Women of childbearing potential must have a negative urine pregnancy test at Baseline/Day 1. Subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial and continue for 180 days after the last dose of study drug. One of the 2 forms of contraception is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be in use for at least one full cycle prior to Baseline. 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.
9. 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 Baseline through 180 days after the last dose of study drug.
10. Subject is willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.
11. Has not received any treatment for TED since Week 24 of the HZNP-TEP-301 study.

Exclusion Criteria:

1. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

The exclusion criteria (except those related to screening) of protocol HZNP-TEP-301 also apply to this open-label extension study.

Dose Regimen/Route of Administration:

All study drug dosing will be performed at the clinic under the supervision of clinic staff. Subjects will receive 8 infusions of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) in an open-label fashion.

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.

Duration of Treatment and Follow-Up:

The duration of the Treatment Period is 24 weeks (6 months), during which 8 infusions of teprotumumab will be administered.

Subjects who were proptosis non-responders in Study HZNP-TEP-301 are scheduled to participate in a 6-month Follow-Up Period in this extension study; subjects who relapsed in Study HZNP-TEP-301 and are retreated in this extension study will not participate in the Follow-Up Period.

Subjects who complete the study (Month 12 Visit for proptosis non-responders in Study HZNP-TEP-301 and Week 24 Visit for subjects who relapsed during the Follow-up Period in Study HZNP-TEP-301) will be contacted 6 and 12 months after the last visit 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 "study eye" (i.e., most severely affected eye) will remain the same as that identified at the Baseline (Day 1) Visit of Study HZNP-TEP-301. 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.

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:

The primary analyses will be conducted on the Intent-to-Treat (ITT) population. All efficacy and safety endpoints will be summarized using descriptive statistics, and summaries will be stratified by the treatment received in HZNP-TEP-301 as well as overall.

Study endpoints will be evaluated for all subjects from Baseline to Week 24.

Primary Efficacy Endpoint

The primary outcome measure is the effect of teprotumumab on the proptosis responder rate at Week 24.

Secondary Efficacy Endpoints

Secondary efficacy endpoints include the percentage of subjects with a CAS value of 0 or 1 at Week 24, mean change from Baseline to Week 24 in the “study eye” proptosis measurement, diplopia responder rate at Week 24, and mean change from Baseline to Week 24 in GO-QoL questionnaire overall score.

Exploratory Efficacy Endpoints

Week 24 data will be summarized for the overall responder rate, the Clinical Measures of Severity individual response status frequencies, the percentage of responders for each component of the Clinical Measures of Severity, and the overall responder rate stratified by the level of response. Mean changes from Baseline to Week 24 will be summarized for the CAS, the GO-QoL questionnaire VF and A subscale scores, and the motility component of the Clinical Measures of Severity. PK parameters will be summarized.

Sample Size Estimate:

The sample size is not based on statistical considerations. Subjects who are proptosis non-responders at Week 24 of HZNP-TEP-301 or who were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse during the Follow-Up Period of HZNP-TEP-301 will be eligible for enrollment.

2.1 Schedule of Assessments

	Open-Label Treatment Period [1] (24 Weeks)											Follow-Up Period [2] (24 weeks)			Follow-Up Contact [3] (48 Weeks)			
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ PW [4]**	**FU1**	**FU2**	**FU3/ PW [5]**	**FU4**	**FU5**	**FU4**	**FU5**
Week (W)/ Month (M)	**Day 1 [6]**	**W1**	**W3**	**W4/ M1**	**W6**	**W9**	**W12/ M3**	**W15**	**W18**	**W21**	**W24/ M6**	**W28/ M7**	**W36/ M9**	**W48/ M12**	**W48/ M12**	**W72/ M18**	**W72/ M18**	**W96/ M24**
Visit Window (± days)	**(+14) [7]**	**(±1)**	**(±3)**	**(±1)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Subject response in Study HZNP-TEP-301	**Proptosis Non-responder or Relapse**											**Proptosis Non-responder Only**			**Relapse Only**		**Proptosis Non-responder Only**	
Informed Consent	X																	
Review inc/exc criteria	X																	
Weight [8]	X [9]						X				X		X	X				
Study drug infusion [10]	X		X		X	X	X	X	X	X								
Phone (email) contact for safety 24 hours postdose [11]	X		X															
Investigator assessment of active disease	X				X		X		X		X	X	X	X				
Efficacy assessments																		
CAS	X [9]				X		X		X		X	X	X	X				
Clinical Measures of Severity - includes proptosis, diplopia, and motility restriction	X [9]				X		X		X		X	X	X	X				
Safety assessments																		
Pregnancy Test [12]	X [9]		X		X	X	X	X	X	X	X	X	X	X				
Physical exam [13]	X [9,13]	X			X		X		X		X [13]			X [13]				
Ophthalmic exam [14]	X [9]	X			X		X		X		X			X				
Vital Signs [15]	X [9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
12-Lead ECG	X [9]		X		X		X				X			X				
Clinical laboratory tests [16]																		
Chemistry (excl. glucose)	X [9,17]		X		X	X	X		X		X		X	X				
Thyroid (FT3, FT4, TSH) [18]	X [9]		X		X	X	X		X		X		X	X				
Hematology	X [9]	X	X	X	X	X	X	X	X	X	X		X	X				

	Open-Label Treatment Period [1] (24 Weeks)											Follow-Up Period [2] (24 weeks)			Follow-Up Contact [3] (48 Weeks)			
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/ PW[4]**	**FU1**	**FU2**	**FU3/ PW[5]**	**FU4**	**FU5**	**FU4**	**FU5**
Week (W)/ Month (M)	**Day 1[6]**	**W1**	**W3**	**W4/ M1**	**W6**	**W9**	**W12/ M3**	**W15**	**W18**	**W21**	**W24/ M6**	**W28/ M7**	**W36/ M9**	**W48/ M12**	**W48/ M12**	**W72/ M18**	**W72/ M18**	**W96/ M24**
Visit Window (± days)	**(+14)[7]**	**(±1)**	**(±3)**	**(±1)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**	**(±14)**	**(±14)**	**(±14)**
Subject response in Study HZNP-TEP-301	**Proptosis Non-responder or Relapse**											**Proptosis Non-responder Only**			**Relapse Only**		**Proptosis Non-responder Only**	
Glucose [19]	X[9]	X	X	X	X	X	X	X	X	X	X		X	X				
HbA1c	X[9]						X				X		X	X				
Urinalysis	X[9]		X		X	X	X		X		X		X	X				
ADA/NAb samples [20]	X[9]		X			X					X[21]		X	X				
AE, SAE assessment [22]	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
Concomitant medications	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X				
GO-QoL Questionnaire	X[9]				X		X				X	X		X				
PK samples [23]	X	X	X	X		X					X[21]							
Contact (phone/email) to assess additional TED treatment [24]															X	X	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. Open-label Treatment Period. Subjects with TED who are proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but who meet criteria for re-treatment due to relapse during the Follow-Up Period in HZNP-TEP-301 are eligible to enroll and receive 8 infusions of teprotumumab (10 mg/kg for the first infusion titrated to 20 mg/kg for the remaining infusions) in an open-label fashion.
2. Proptosis non-responders from Study HZNP-TEP-301 will participate in a 6-month Follow-Up Period; subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 will not participate.
3. Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 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.
4. If subjects wish to discontinue study drug during the open-label Treatment Period, subjects will return for a clinic visit and undergo the Week 24 assessments, except for PK and ADA evaluations. Subjects who were proptosis non-responders at Week 24 of HZNP-TEP-301 will be encouraged to continue study participation in the Follow-Up Period.
5. If a subject wishes to prematurely discontinue from the study during the Follow-Up Period, he/she will return for a clinic visit and undergo the Month 12 assessments prior to discharge.
6. On Day 1 (Baseline), subjects will receive the first dose of study drug; however, Baseline assessments will be performed prior to dosing.

7. Day 1 will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse).
8. 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.
9. If Day 1 of the extension study occurs on the same day as the final visit of HZNP-TEP-301 (Week 24 [or PW1] for proptosis non-responders and Week 72 [or PW2] for subjects who relapse), assessments do not need to be repeated, and the final assessments from the lead-in study will serve as the Baseline assessments for the extension study.
10. Subjects will receive teprotumumab 10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions.
11. 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.
12. Perform urine pregnancy tests prior to dose (as applicable) for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Baseline of HZNP-TEP-302, non-therapy-induced amenorrhea for <12 months prior to Baseline of HZNP-TEP-302, or not surgically sterile [absence of ovaries and/or uterus]).
13. Physical exam will include assessment of presence or absence of pretibial myxedema on Day 1 and Week 24/PW of the Treatment Period and Month 12/PW of the Follow-Up Period. If present, measurements of instep and calf will be taken.
14. 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.
15. 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 9.5.4.3 for details).
16. Non-diabetic subjects should be fasting at Weeks 1 and 4 only. Diabetic subjects should be fasting at each visit blood glucose is evaluated.
17. 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) at the most recent clinic visit to be eligible for enrollment.
18. 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 the most recent clinic visit. 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.
19. HbA1c must be < 9.0% at the most recent clinic visit. If the HbA1c is elevated and considered clinically significant at any time point after Baseline, it will be repeated approximately every 45 days until it returns to normal or the baseline value.
20. 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 48 (or PW) during the Follow-Up Period will continue to be followed until the subject's value decreases or remains stable.
21. Not collected for subjects who prematurely discontinue from the open-label Treatment Period.
22. Adverse events that are ongoing at completion of HZNP-TEP-301 and/or occur prior to dosing on Day 1 will be considered pre-dose AEs. 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.
23. PK samples will be collected prior to, and at the end of, the infusion on Day 1 and Weeks 3 and 9 of the open-label Treatment Period; additional single samples will be collected at Weeks 1, 4, and 24.
24. If TED treatment has been received since last contact, the subject will be questioned regarding type of treatment and outcome/response.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
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
CL	Clearance
C_{max}	Maximum observed concentration
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
EDC	Electronic data capture
eCRF	Electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
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
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
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
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
PVC	Polyvinyl chloride
PW	Premature withdrawal
q3W	Once every 3 weeks
QoL	Quality of life

Abbreviation	Definition
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
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] and [redacted] (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, and statistical analysis)	[redacted]
Clinical drug supply and distribution	[redacted]
Immunogenicity and PK laboratory	[redacted]
Central safety laboratory	[redacted]
Data Safety Monitoring Board Managing Organization	[redacted]

7 INTRODUCTION

7.1 Background

7.1.1 Thyroid Eye Disease

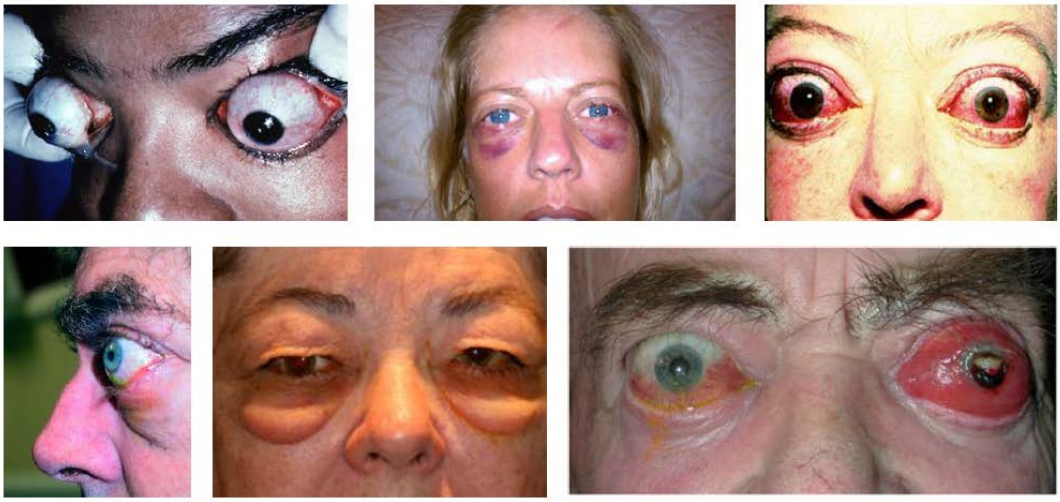
Thyroid eye disease (TED), also termed Graves' ophthalmopathy/orbitopathy (GO) and thyroid-associated ophthalmopathy (TAO), is an autoimmune condition commonly associated with Graves' hyperthyroidism/disease, but also occurs in a proportion of patients with other autoimmune thyroid diseases, including 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).

Figure 7.1 Thyroid Eye Disease Photographs



Left – upper & lower: Proptosis due to the expansion of tissue volume behind the eye, forcing the eyeball out of the orbit.
Center – upper & lower: Inflammation of orbital tissues – a hallmark symptom of active GO.
Right – upper & lower: Corneal inflammation and ulceration – a problem when patients are unable to fully close their eyelids.

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 and 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 (IgG_1) 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*, 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]

7.1.3.2 Safety Pharmacology

[redacted]

[redacted]

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

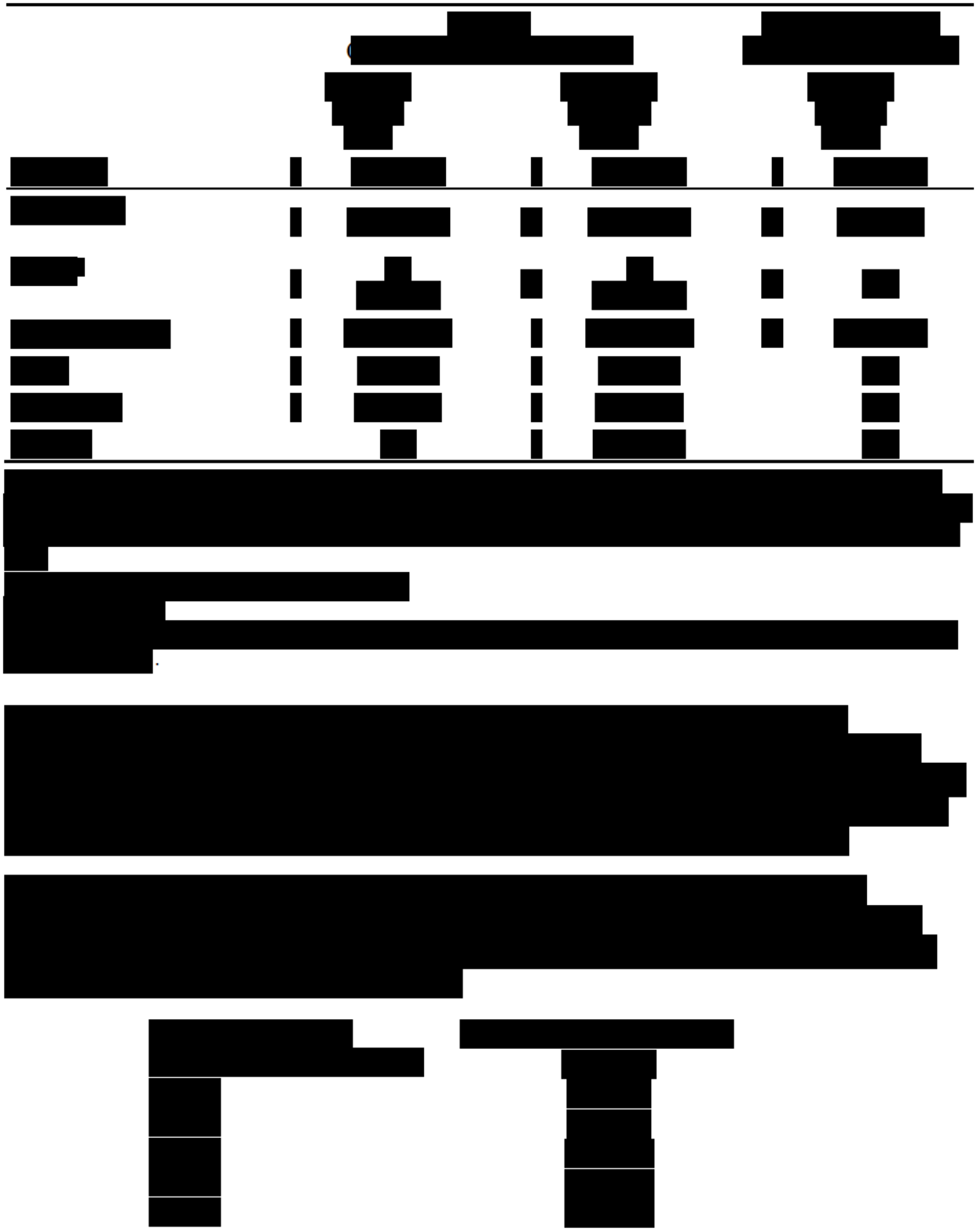
The TED01RV study demonstrated that subjects with active moderate-to-severe TED experienced statistically significant and clinically meaningful results in the proportion of responders at Week 24 in the teprotumumab group relative to placebo (69% [29/42 subjects] versus 20% [9/43 subjects], respectively; $p < 0.001$). 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

Table 7.1 Single-Dose Pharmacokinetic Parameters (CHO Material)



[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)	*E. coli* 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. 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. Safety data from the oncology studies is summarized in the IB.

7.1.3.4.5.3 Teprotumumab Material Safety Profile

[redacted]

7.1.3.4.5.4 Sarcoma Monotherapy Study with Teprotumumab CHO Material

[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 ≤ 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.

Horizon is currently conducting a randomized, multicenter, double-masked, placebo-controlled study evaluating the efficacy and safety of teprotumumab in adult subjects with moderate to severe active TED (HZNP-TEP-301). This study (HZNP-TEP-302) is designed to be an open-label extension of HZNP-TEP-301, in which subjects who received 8 infusions of teprotumumab or placebo in HZNP-TEP-301 and were non-responders at the end of the Treatment Period or relapsed during the Follow-Up Period will be offered the opportunity to receive 8 infusions of teprotumumab.

7.3 Rationale for Dose Selection

8 STUDY OBJECTIVES

The overall objective is to evaluate the safety and efficacy of teprotumumab in the treatment of TED in subjects who participated in the lead-in study (HZNP-TEP-301) and who were either proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301.

8.1 Primary Objective

The primary objective is to evaluate the effect of teprotumumab on the proptosis responder rate (i.e., the percentage of subjects with a ≥ 2 mm reduction from Baseline in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at Week 24.

8.2 Secondary Objectives

Secondary objectives will evaluate the effect of teprotumumab on the following:

1. Percentage of subjects with a Clinical Activity Score (CAS) value of 0 or 1 at Week 24 in the study eye.
2. Mean change from Baseline to Week 24 in proptosis measurement in the study eye.
3. 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.
4. Mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

8.3 Exploratory Objectives

Exploratory objectives will evaluate the effect of teprotumumab on the following:

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. Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at Week 24.
3. Mean change from Baseline to Week 24 in the CAS.
4. Overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. Mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.

7. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.

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 multi-center, open-label extension study of HZNP-TEP-301 examining the safety and efficacy of teprotumumab in the treatment of TED in adult subjects. Subjects who complete the 24-week double-masked Treatment Period in Study HZNP-TEP-301 and are proptosis non-responders or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301 will be eligible for enrollment. The study treatment previously administered in HZNP-TEP-301 (teprotumumab or placebo) will remain masked throughout this extension study.

All subjects who choose to participate will receive 8 infusions of teprotumumab (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion. The Baseline (Day 1) Visit of this extension study will occur within 14 days after the final visit of Study HZNP-TEP-301 (Week 24 for proptosis non-responders and up to Week 72 for subjects who relapse). During the open-label Treatment Period, study drug infusions are scheduled for Day 1 (Baseline), and Weeks 3, 6, 9, 12, 15, 18, and 21 (with a final visit at Week 24 of the 24-Week Treatment Period).

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.

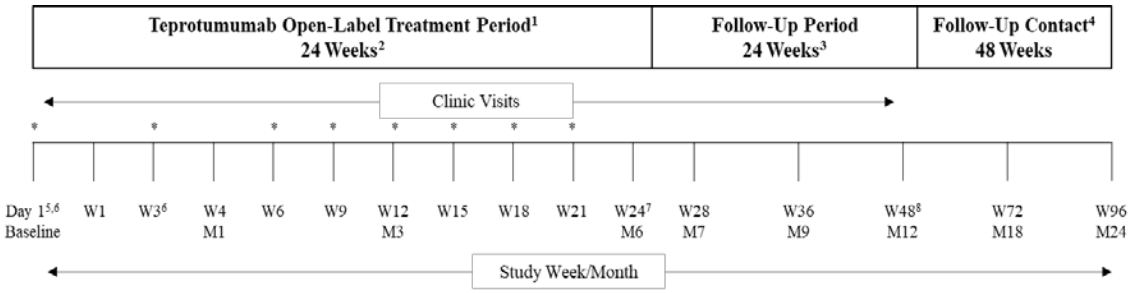
After completion of the Treatment Period, subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter a 24-week Follow-Up Period, during which study drug will not be administered and clinic visits are scheduled for 1, 3, and 6 months (visit months 7, 9, and 12) after the Week 24 Visit; if any of these subjects discontinue from the Follow-Up Period prior to the Month 12 Visit, they will return to the clinic and undergo the scheduled Month 12 assessments prior to study discharge. Those who complete the Month 12 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.

Subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and choose to enter this extension study will not participate in the Follow-Up Period. For these subjects, the last clinic visit is at Week 24. Those who complete the Week 24 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.

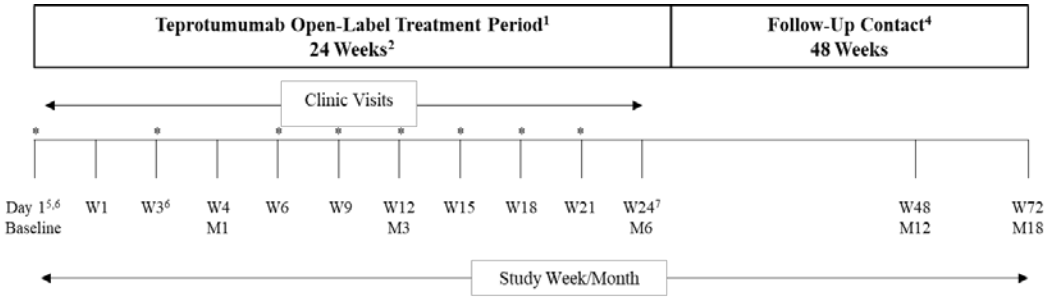
An overview of the study design is presented in Figure 9.1, and details of study activities were previously presented in Section 2.1, *Schedule of Assessments*.

Figure 9.1 Schematic of Study Design

Subjects who were proptosis non-responders in Study HZNP-TEP-301



Subjects who relapsed in Study HZNP-TEP-301



* Infusion of study drug. M=Month; W=Week.

1. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 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. Visit windows of ± 7 days.
4. Proptosis non-responders from Study HZNP-TEP-301 who complete the Month 12 Visit and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and complete the Week 24 Visit.
5. Visit must occur within 14 days after the final visit of HZNP-TEP-301.
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. If a subject wishes to discontinue dosing, the subject will return to the clinic and undergo the scheduled Week 24 assessments.
8. If a subject participates in the Follow-Up Period and prematurely discontinues prior to Month 12, he/she will return to the clinic and undergo the Month 12 assessments prior to study discharge.

9.2 Discussion of Study Design

The study population consists of subjects who participated in the lead-in study (HZNP-TEP-301) and who were either proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301. The study population enrolled in HZNP-TEP-301 was well-defined and consistent with the expected target population for whom teprotumumab will be indicated (adult subjects with active moderate-to-severe 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.

In order to maintain the study mask in HZNP-TEP-301, all subjects in this open-label extension study will undergo the same dosing regimen of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions), regardless if they received teprotumumab or placebo in HZNP-TEP-301.

Given the teratogenic effects of teprotumumab noted in a monkey embryo-fetal development toxicity study (see Section 7.1.3.2 for details) and PK 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. Completed the 24-week double-masked Treatment Period in Study HZNP-TEP-301.

3. Proptosis non-responder (< 2 mm reduction in proptosis in the study eye) at Week 24 of Study HZNP-TEP-301 OR proptosis responder at Week 24 who relapses (see Section 9.3.4) during the Follow-Up Period of Study HZNP-TEP-301.

4. Subject 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 the most recent clinic visit. 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.

5. 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 the most recent clinic visit.

6. Diabetic subjects must have well-controlled disease (defined as HbA1c < 9.0% at most recent clinic visit).

7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study.

8. Women of childbearing potential must have a negative urine pregnancy test at Baseline/Day 1. Subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial and continue for 180 days after the last dose of study drug. One of the 2 forms of contraception is

recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be in use for at least one full cycle prior to Baseline. 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.

9. 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 Baseline through 180 days after the last dose of study drug.

10. Subject is willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

11. Has not received any treatment for TED since Week 24 of the HZNP-TEP-301 study.

9.3.2 Exclusion Criteria

1. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

The exclusion criteria (except those related to screening) of protocol HZNP-TEP-301 also apply to this open-label extension study.

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.
- Voluntary Withdrawal. 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.

When treatment is complete, subjects will undergo the scheduled Week 24 assessments.

Subjects who were proptosis non-responders in HZNP-TEP-301 will participate in the Follow-Up Period. Subjects who enter the Follow-Up Period but prematurely discontinue study participation prior to Month 12 will return for a final visit and undergo the scheduled Month 12 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.

Subjects who relapsed during the HZNP-TEP-301 study will not participate in the Follow-up Period.

Subjects who complete the study (Month 12 Visit for proptosis non-responders in Study HZNP-TEP-301 and Week 24 Visit for subjects who relapsed during the Follow-up Period in Study HZNP-TEP-301) will be contacted 6 and 12 months after the last visit via phone or email by research staff to enquire if any treatment for TED has been received since last study contact.

9.3.4 Criteria for Responders Who Relapse

If subjects met the response criteria at Week 24 of HZNP-TEP-301 but subsequently experience a disease relapse during the 48-week Follow-Up Period of the lead-in study, they will have the option to enter this open-label extension study (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 of HZNP-TEP-301, or
- An increase in CAS of ≥ 2 points since Week 24 with an absolute CAS of ≥ 4 in the study eye following Week 24 of HZNP-TEP-301.
- 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:

- Poor protocol adherence.

9.4 Treatments

9.4.1 Treatments Administered

All study drug dosing will be performed at the clinic under the supervision of clinic staff. Subjects will receive 8 infusions of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining infusions) in an open-label fashion.

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.

9.4.2 Identity of Investigational Product

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).

9.4.3 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 a 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 a 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 [redacted]. The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the 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 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

[redacted] 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 electronic data capture (EDC) system 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 on Day 1 and Weeks 12 and 24 during the Treatment Period. The dose on Day 1 may be based on the weight determined at the most recent clinic visit, provided the most recent visit was within the prior 3 weeks. The doses on Week 3 through Week 9 will be based on the weight determined on Day 1. The weight used in the Week 12 dose calculation can be the weight determined on Day 1 or the weight obtained at Week 12. The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15 through Week 21, 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 policy and local regulations. 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 of preparation. 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

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

All subjects will receive teprotumumab in this open-label extension study.

9.4.8 Masking and Unmasking

This is an open-label extension study.

In order to maintain the study mask in HZNP-TEP-301, all subjects in this open-label extension study will undergo the same dosing regimen of teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions), regardless if they received teprotumumab or placebo in HZNP-TEP-301.

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 through Week 48 of Follow-Up Period.
Eye surgery for TED	Any history or planned procedure during entire study duration through Week 48 of Follow-Up Period.
Steroids for treatment of TED	Steroids (IV or oral) for treatment of TED and steroid eye drops are not allowed between Week 24 of the HZNP-TEP-301 protocol and Baseline/Day 1 of the HZNP-TEP-302 protocol through the end of study visit.
Steroids for conditions other than TED	Systemic steroid use (IV or oral) for conditions other than TED is not allowed during the study however topical steroids for dermatological conditions, inhaled steroids, and IV dexamethasone for infusion-associated AEs are allowed.
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	Selenium or biotin for TED is not allowed during the study. A multivitamin (taken maximally once daily) 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)	Use of a non-steroid immunosuppressive agent is not allowed during the study.
Investigational agent	60 days prior to study entry 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 "study eye" (i.e., most severely affected eye) will remain the same as that identified at the Baseline (Day 1) Visit of Study HZNP-TEP-301. 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)

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 on Day 1 and Weeks 6, 12, 18, and 24 (or premature withdrawal [PW]) during the Treatment Period, and at Months 7, 9, and 12 (or PW) during the Follow-Up Period. Measurements will be recorded on the Clinical Measures of Severity eCRF under exophthalmos.

9.5.1.2 Clinical Activity Score (CAS)

The CAS will be completed on Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and at Months 7, 9, and 12 (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).

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 on Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and at Months 7, 9, and 12 (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 ≥ 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 ≥ 2 mm
Swelling of the eyelids (absent, mild, moderate, severe)	Decrease ≥ One grade
Redness of the eyelids (absent, present)	Decrease ≥ One grade
Redness of the conjunctiva (absent, present)	Decrease ≥ One grade
Conjunctival edema (absent, present)	Decrease ≥ One grade
Inflammation of the caruncle or plica (absent, present)	Decrease ≥ 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 ≥ One grade
Eye muscle involvement (ductions in degrees)	Increase ≥ 8° in at least one direction of gaze
Corneal involvement (absent/punctate keratopathy/ulcer)	Decrease ≥ One grade
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.	Change of best corrected visual acuity by ≥ 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 on Day 1 and Weeks 6, 12, and 24 (or PW) during the Treatment Period, and at Months 7 and 12 (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 ≥ -70ºC at the site until shipment to the central laboratory [redacted] will store the samples at ≥ –70ºC until shipment to [redacted] 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 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.

9.5.4.1 Adverse Events

9.5.4.1.1 Definitions

9.5.4.1.1.1 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.

9.5.4.1.1.2 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.

9.5.4.1.1.3 Non-Serious Adverse Event Definition

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

9.5.4.1.1.4 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.

9.5.4.1.1.5 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

9.5.4.1.2 Documentation of Adverse Events

Adverse events that are ongoing at the completion of HZNP-TEP-301 and/or occur prior to dosing on Day 1 will be considered pre-dose AEs. 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 (Month 12 or PW). All pre-dose AEs, TEAEs, and AEs during the Follow-Up Period must be recorded in the source documents and in 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 9.5.4.1.5.

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.

9.5.4.1.3 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

9.5.4.1.4 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.

9.5.4.1.5 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 in 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.

9.5.4.1.6 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.

9.5.4.1.7 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 9.5.4.1.2 and 9.5.4.1.5, respectively.

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

9.5.4.1.8 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.

9.5.4.1.9 Reporting of IND Safety Reports

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

9.5.4.1.10 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.

9.5.4.1.11 Development Safety Update Reports

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

9.5.4.2 Pregnancy Reporting

Urine pregnancy testing will be performed for women of childbearing potential (including those with an onset of menopause <2 years prior to Screening of HZNP-TEP-301, non-therapy-induced amenorrhea for <12 months prior to Screening of HZNP-TEP-301, or not surgically sterile [absence of ovaries and/or uterus]) at all clinic visits. 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.

9.5.4.3 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 any other infusion day. 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.

9.5.4.4 Physical and Ophthalmic Examinations, Height, and Weight

A physical examination, including complete undilated ophthalmic examination, will be performed at Baseline (Day 1) and thereafter at Weeks 1, 6, 12, 18, and 24 (or PW) during the Treatment Period and Month 12 (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.

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 and Week 24 (or PW) of the Treatment Period and Month 12/PW of the Follow-Up Period. If present, measurements of instep and calf will be taken.

Weight will be measured at Baseline and every 12 weeks throughout the study (Weeks 12 and 24 [or PW] during the Treatment Period and Months 9 and 12 [or PW] of the Follow-Up Period). The dose on Day 1 may be based on the weight determined at the most recent clinic visit, provided the most recent visit was within the prior 3 weeks. The doses on Week 3 through Week 9 will be based on the weight determined on Day 1. The weight used in the Week 12 dose calculation can be the weight determined on Day 1 or the weight obtained at Week 12. The weight obtained at Week 12 can be used to adjust the dose beginning at Week 12 or Week 15 through Week 21, as appropriate.

9.5.4.5 ECGs

12-lead ECGs will be performed at Baseline, Weeks 3, 6, 12, and 24 (or PW) of the Treatment Period, and Month 12 (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.

9.5.4.6 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 9.5.4.2 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	Treatment Period											Follow-Up Period		
	Base-line [1]	W1	W3	W4 M1	W6	W9	W12 M3	W15	W18	W21	W24 M6	W28 M7	W36 M9	W48 M12
Chemistry (excl. glucose)	X [2]		X		X	X	X		X		X		X	X
Thyroid (FT3, FT4, TSH) [3]	X		X		X	X	X		X		X		X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X		X	X
Glucose [4]	X	X	X	X	X	X	X	X	X	X	X		X	X
HbA1c	X [5]						X				X		X	X
Urinalysis	X		X		X	X	X		X		X		X	X
Urine pregnancy [6]	X		X		X	X	X	X	X	X	X	X	X	X

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

1. If Day 1 (Baseline) of the extension study occurs on the same day as the final visit of HZNP-TEP-301, assessments do not need to be repeated, and the final assessments from the lead-in study will serve as the Baseline assessments for the extension study.
2. ALT/AST must be ≤ 3 x the ULN and serum creatinine must be < 1.5 x the ULN (according to age) at most recent clinic visit for enrollment.
3. 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) at the most recent clinic visit. 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.
4. 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.
5. HbA1c must be < 9.0% at most recent clinic visit for enrollment. If the HbA1c is elevated and considered clinically significant at any time point after Baseline, it will be repeated approximately every 45 days until it returns to normal or baseline value.
6. Perform for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Screening of HZNP-TEP-301, non-therapy-induced amenorrhea for <12 months prior to Screening of HZNP-TEP-301, or not surgically sterile [absence of ovaries and/or uterus]).

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

9.5.4.7 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 of the Treatment Period, and Months 9 and 12 (or PW) of the Follow-Up Period. Samples will be collected, processed, and stored at ≥ -70°C at the site until shipment to the central laboratory [redacted] will store the samples at ≥ –70°C until shipment to [redacted] for immunogenicity testing. 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 Month 12 (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.

9.5.4.8 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).

9.5.5 Appropriateness of Measurements

The study population consists of subjects with TED who participated in the lead-in study (HZNP-TEP-301) and were either proptosis non-responders at Week 24 of HZNP-TEP-301 or were proptosis responders at Week 24 but met the criteria for re-treatment due to relapse (see Section 9.3.4) during the Follow-Up Period of HZNP-TEP-301. The study population enrolled in HZNP-TEP-301 was well-defined and consistent with the expected target population for whom teprotumumab will be indicated (adult subjects with moderate-to-severe TED).

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

9.5.6 Study Procedures

Subjects who provide informed consent and who meet all the entry criteria for participation in this study will be enrolled in the open-label extension study.

9.5.6.1 Day 1/Baseline

The Baseline (Day 1) Visit must occur within 14 days of the final visit of HZNP-TEP-301. If Day 1 of the extension study occurs on the same day as the final visit of HZNP-TEP-301 and an assessment is scheduled for both visits, assessments do not need to be repeated, and the final assessments from the lead-in study will serve as the Baseline assessments for the extension study.

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, from the most recent clinic visit and will determine each candidate's suitability for the study. The Investigator must review these results before determining that a candidate is eligible for study drug treatment. The Baseline urine pregnancy test performed for all female candidates of childbearing potential must be negative in order for subjects to be eligible for treatment. The following procedures will be performed at Baseline 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.

- Determine study eligibility through review of the inclusion/exclusion criteria (see Section 9.3)

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis (see Section 9.5.4.6 for details concerning test results and study participation).

- Collect predose blood samples for immunogenicity and PK testing.

- 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.

- Enquire about prior medication use during the previous 2 weeks (see Table 9.1 for restrictions regarding medications).

- Perform predose physical and ophthalmic examinations.

- Measure weight.

- Perform predose 12-lead ECG.

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

- Administer the predose GO-QoL questionnaire.

- Register enrollment in EDC, obtain study medication vial assignment and volume of study drug to be administered.

- 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 9.5.4.3 for details).

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

- Monitor subjects regarding treatment-emergent signs and symptoms.

- Collect blood samples for PK analyses at the end of the infusion.

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.

9.5.6.2 Week 1

- Collect blood samples for hematology and glucose testing (see Section 9.5.4.6 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.

9.5.6.3 Week 3

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see Section 9.5.4.6 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 and PK testing.

- Enquire about signs and symptoms and concomitant medications throughout the visit.

- Perform predose 12-lead ECG.

- Obtain study medication vial assignment and volume of study drug to be administered from EDC.

- 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 9.5.4.3 for details).

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

- Collect blood samples for PK analyses at the end of the infusion.

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. Subjects will be instructed to return to the clinic at Week 4.

9.5.6.4 Week 4

- Collect blood samples for hematology and glucose testing (see Section 9.5.4.6 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.

9.5.6.5 Week 6

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see Section 9.5.4.6 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 9.5.4.3 for details).

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

- Administer predose GO-QoL questionnaire.
- Obtain study medication vial assignment and volume of study drug to be administered from EDC.
- 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.

9.5.6.6 Week 9

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see Section 9.5.4.6 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 and PK 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 9.5.4.3 for details).
- Obtain study medication vial assignment and volume of study drug to be administered from EDC.
- Administer study drug and record date, volume and rate of infusion, and start/stop times of dosing.
- Collect blood samples for PK analyses at the end of the infusion.

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.

9.5.6.7 Week 12

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, and HbA1c) analysis (see Section 9.5.4.6 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 9.5.4.3 for details).

- Measure weight.

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

- Administer predose GO-QoL questionnaire.

- Obtain study medication vial assignment and volume of study drug to be administered from EDC.

- 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.

9.5.6.8 Week 15

- Obtain predose blood samples for hematology and glucose analysis (see Section 9.5.4.6 for details concerning test results and study participation).

- Perform predose urine 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 9.5.4.3 for details).

- Obtain study medication vial assignment and volume of study drug to be administered from EDC.

- 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.

9.5.6.9 Week 18

- Obtain predose blood samples for hematology and chemistry (including thyroid, glucose, but not HbA1c) analysis (see Section 9.5.4.6 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 9.5.4.3 for details).
- Perform predose efficacy assessments (CAS, Clinical Measures of Severity including proptosis, diplopia and motility restriction).
- Obtain study medication vial assignment and volume of study drug to be administered from EDC.
- 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.

9.5.6.10 Week 21

- Obtain predose blood samples for hematology and glucose analysis (see Section 9.5.4.6 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 9.5.4.3 for details).
- Obtain study medication vial assignment and volume of study drug to be administered from EDC.

- 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.

9.5.6.11 Week 24/Premature Withdrawal – Treatment Period

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 9.5.4.6 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 immunogenicity testing (only subjects who complete the Treatment Period, not those who prematurely discontinue study drug administration).
- Collect blood sample for PK analyses (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.

Subjects who were proptosis non-responders in Study HZNP-TEP-301 will enter the Follow-Up Period and will be instructed to return to the clinic in one month for the first follow-up visit. Subjects who relapsed during the Follow-Up Period of HZNP-TEP-301 and chose to enter this extension study will not participate in the Follow-Up Period.

9.5.6.12 Month 7 – Follow-Up Period

- 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 for the Month 9 Follow-Up Visit.

9.5.6.13 Month 9 – Follow-Up Period

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

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 Month 12.

9.5.6.14 Month 12

9.5.6.14.1 Month 12/Premature Withdrawal – Follow-Up Period for Proptosis Non-responders in Study HZNP-TEP-301

- 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 Month 9 of the Follow-Up Period.
- 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.

9.5.6.14.2 Month 12 – Follow-Up Contact for Subjects Who Relapsed in Study HZNP-TEP-301

Subjects who complete the Week 24 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.

9.5.6.15 Month 18

9.5.6.15.1 Month 18 – Follow-Up Contact for Proptosis Non-responders in Study HZNP-TEP-301

Subjects who complete the Month 12 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.

9.5.6.15.2 Month 18 – Follow-Up Contact for Subjects Who Relapsed in Study HZNP-TEP-301

Subjects who complete the Week 24 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.

This is the final contact for subjects who relapsed in Study HZNP-TEP-301.

9.5.6.16 Month 24 – Follow-Up Contact for Proptosis Non-responders in Study HZNP-TEP-301

Subjects who complete the Month 12 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.

This is the final contact for proptosis non-responders in Study HZNP-TEP-301.

The end of the trial is defined as the date of the last subject contact at Month 24.

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.

The primary analyses will be conducted on the Intent-to-Treat (ITT) population. All efficacy and safety endpoints will be summarized using descriptive statistics and/or number and percentage of subjects, and will be stratified by the treatment received in HZNP-TEP-301 as well as overall.

9.6.1 Endpoints

Study endpoints will be evaluated for all subjects from Baseline to Week 24.

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

1. Percentage of subjects with a CAS value of 0 or 1 in the study eye at Week 24.
2. Mean change from Baseline to Week 24 in proptosis measurement in the study eye.
3. 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.
4. Mean change from Baseline to Week 24in the GO-QoL questionnaire overall score.

9.6.1.3 Exploratory Endpoints

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. The Clinical Measures of Severity individual response status frequencies and percentage of responders for each component of clinical severity at Week 24.
3. The mean change from Baseline to Week 24 in the CAS.
4. The overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 9.6.3.2.1 for definitions).
5. The mean change from Baseline to Week 24 in the GO-QoL questionnaire VF and A subscale scores.

6. The mean change from Baseline to Week 24 on the motility component of the Clinical Measures of Severity.
7. Evaluate pharmacokinetic (PK) parameters of teprotumumab to estimate exposure and understand PK-PD relationships.

9.6.2 Populations for Analysis

The following analysis populations will be defined for this study:

- Intent-to-Treat (ITT)
- Safety Population

The ITT population will include all subjects who are enrolled in the study. 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 on the ITT population. All efficacy and safety endpoints will be summarized using descriptive statistics and/or number and percentage of subjects, and will be stratified by the treatment received in HZNP-TEP-301 as well as overall.

Study endpoints will be evaluated for all subjects from Baseline to Week 24.

9.6.3.1 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.

9.6.3.1.1 Motility Component of the Clinical Measures of Severity

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

9.6.3.2 Clinical Activity Score (CAS)

CAS will be measured as a continuous variable and will be summarized at each designated visit.

9.6.3.2.1 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 ($\geq$3) from Baseline in the study eye, and no deterioration in the fellow eye (i.e., increase in CAS $\geq$ 2 points or increase in proptosis $\geq$ 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.

9.6.3.3 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. Final analysis plans will be provided in the SAP.

9.6.3.4 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.

9.6.3.5 Interim Analyses

No interim analyses are planned.

9.6.4 Sample Size and Power Considerations

The sample size is not based on statistical considerations. Subjects with TED who complete the 24-week double-masked Treatment Period in Study HZNP-TEP-301 and are proptosis non-responders or were proptosis responders at Week 24 but meet the criteria for re-treatment due to relapse during the Follow-Up Period of HZNP-TEP-301 will be eligible for enrollment.

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 premature withdrawal 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

RO 4858696/F01-01 (huMAb-IGF-1R): A 7-week intermittent intravenous toxicity, toxicokinetic and immunogenicity study with RO4858696/F01-01 (huMAb-IGF1R) in cynomolgus monkeys with an 8-week recovery period (Covance Study No. 6131-477, HLR Study No. 08954). Roche Report No. 1016123. 31 October 2005.

Method validation bioanalytical report for analysis of RO4858696 in monkey serum by ELISA (Study No. 09009). Roche Report No. 1016528. 29 June 2005.

RO4858696-000-009 (IGF-1R): Single dose pharmacokinetic study of RO4858696 following intravenous administration to monkeys (Covance Study No. 6131-471, Roche Study No. 08791). Roche Report No. 1016690. 21 April 2005.

RO4858696/F01-01 (huMAb-IGF-1R): Hemolytic potential and blood compatibility study with RO4858696/F01 01 (HuMAb IGF 1R) (Covance Study No. 6131-491, HLR Study No. 09302). Roche Report No. 1018657. 10 October 2005.

RO4858696/F01-01 (huMAb-IGF-1R): cross reactivity study of RO4858696 with normal cynomolgus monkey tissues (PAIStudy No. IM1202, HLR Study No. 09256). Roche Report No. 1019358. 03 October 2005.

Cynomolgus monkey as IGF-1R cross reactive species for RO4858696. Roche Report No. 1019598. 08 August 2005.

13-day intravenous administration toxicity study in the cynomolgus monkey (Covance Study No. 2135-005). Roche Report No. 1020097. 10 October 2005.

A 13-week toxicity and toxicokinetic study of RO4858696 administered once weekly by intravenous injection to cynomolgus monkeys, with a 12-week tecovery period (CRL Study No. AGD00022, HLR Study No. 09927). Roche Report No. 1023600. March 2008.

In vitro evaluation of the Influence of RO4858696 on human and cynomolgus monkey whole blood hemolysis and plasma flocculation (PCS MTL Study No. 600237, Roche Study No. 10218). Roche Report No. 1026030. 14 September 2007.

RO4858696-F03/F05-01: A single dose intravenous comparative pharmacokinetic and pharmacodynamic study of RO4858696 administered to male cynomolgus monkeys (Study No. 09722). Interim draft report. Roche Report No. 1026674. 2007.

A 39-week toxicity study of RO4858696 administered once weekly by intravenous injection to cynomolgus monkeys, with a 24-week recovery period. (Charles River Study No. AGD00061, Roche reference No. 10472). Roche Report No. 1030337. 22 April 2010.

Embryo-fetal Development Study of RO4858696 Administered by intravenous injection to pregnant cynomolgus monkeys (Roche Reference No. 10837). Roche Report No. 1035664. 23 December 2009.

Abraham-Nordling M, Bystrom K, Torring O, et al. Incidence of hyperthyroidism in Sweden. European journal of endocrinology. 2011; 165(6): 899-905.

Akamizu T. Antithyrotropin receptor antibody: an update. Thyroid : official journal of the American Thyroid Association. 2001; 11(12): 1123-34.

Bahn RS. Graves' ophthalmopathy. The New England journal of medicine. 2010; 362(8): 726-38.

Bahn RS. Emerging pharmacotherapy for treatment of Graves' disease. Expert review of clinical pharmacology. 2012; 5(6): 605-7.

Baldeschi L. (2010). Orbital decompression. In W. M. Wiersinga & G. J. Kahaly (Eds.), *Graves' orbitopathy: a multidisciplinary approach - questions and answers* (2nd ed.): Karger Basel.

Baril C, Pouliot D, Molgat Y. Optic neuropathy in thyroid eye disease: results of the balanced decompression technique. Canadian journal of ophthalmology Journal canadien d'ophtalmologie. 2014; 49(2): 162-6.

Bartalena L. Graves' orbitopathy: imperfect treatments for a rare disease. European thyroid journal. 2013; 2(4): 259-69.

Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. European journal of endocrinology. 2008; 158(3): 273-85.

Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. The Journal of clinical endocrinology and metabolism. 2012; 97(12): 4454-63.

Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. Endocrine reviews. 2000; 21(2): 168-99.

Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Transactions of the American Ophthalmological Society. 1994; 92: 477-588.

Bartley GB, Fatourechi V, Kadrmas EF, et al. Long-term follow-up of Graves ophthalmopathy in an incidence cohort. Ophthalmology. 1996; 103(6): 958-62.

Boschi A, Daumerie C, Spiritus M, et al. Quantification of cells expressing the thyrotropin receptor in extraocular muscles in thyroid associated orbitopathy. The British journal of ophthalmology. 2005; 89(6): 724-9.

Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. Endocrine reviews. 1993; 14(6): 747-93.

Coulter I, Frewin S, Krassas GE, et al. Psychological implications of Graves' orbitopathy. European journal of endocrinology. 2007; 157(2): 127-31.

Dickinson AJ. (2010). Clinical manifestations. In W. M. Wiersinga & G. J. Kahaly (Eds.), *Graves' orbitopathy: a multidisciplinary approach - questions and answers* (2nd ed.): Karger Basel.

Dolman PJ, Cahill K, Czyz CN, et al. Reliability of estimating ductions in thyroid eye disease: an International Thyroid Eye Disease Society multicenter study. Ophthalmology. 2012; 119(2): 382-9.

Douglas RS, Gianoukakis AG, Kamat S, et al. Aberrant expression of the insulin-like growth factor-1 receptor by T cells from patients with Graves' disease may carry functional consequences for disease pathogenesis. Journal of immunology (Baltimore, Md : 1950). 2007; 178(5): 3281-7.

Douglas RS, Naik V, Hwang CJ, et al. B cells from patients with Graves' disease aberrantly express the IGF-1 receptor: implications for disease pathogenesis. Journal of immunology (Baltimore, Md : 1950). 2008; 181(8): 5768-74.

Ezra DG, Rose GE, Bailly M. Genome Level Microarray Expression Profiling Implicates IGF-1 And Wnt Signalling Dysregulation In The Pathogenesis Of Thyroid Associated Ophthalmopathy. Investigative Ophthalmology & Visual Science. 2011; 52(14): 5100-.

Gasinska T, Borowska A, Wichary H, et al. Effect of methylprednisolone pulse therapy with and without alendronate on biochemical markers of bone turnover in patients with Graves' ophthalmopathy. Polskie Archiwum Medycyny Wewnetrznej. 2012; 122(7-8): 341-7.

Gerding MN, Terwee CB, Dekker FW, et al. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid : official journal of the American Thyroid Association. 1997; 7(6): 885-9.

Gorman CA, Garrity JA, Fatourechi V, et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. Ophthalmology. 2001; 108(9): 1523-34.

Investigator's Brochure. (2017). Investigator's brochure for teprotumumab (HZN-001), human anti-IGF-1 receptor antibody, for ophthalmic indications including thyroid eye disease; 7th edition. Horizon Pharma USA.

Kahaly GJ. (2010). Management of moderately severe Graves' orbitopathy. In W. M. Wiersinga & G. J. Kahaly (Eds.), *Graves' orbitopathy: a multidisciplinary approach - questions and answers* (2nd ed.): Karger Basel.

Kahaly GJ, Petrak F, Hardt J, et al. Psychosocial morbidity of Graves' orbitopathy. Clinical endocrinology. 2005; 63(4): 395-402.

Mallika P, Tan A, Aziz S, et al. Thyroid associated ophthalmopathy - a review. Malaysian family physician : the official journal of the Academy of Family Physicians of Malaysia. 2009; 4(1): 8-14.

Melamud B, Lurie Y, Goldin E, et al. Methylprednisolone-induced liver injury: a diagnostic challenge. The Israel Medical Association journal : IMAJ. 2014; 16(3): 180-1.

Mostbeck A, Galvan G, Bauer P, et al. The incidence of hyperthyroidism in Austria from 1987 to 1995 before and after an increase in salt iodization in 1990. European journal of nuclear medicine. 1998; 25(4): 367-74.

Mourits MP, Koornneef L, Wiersinga WM, et al. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. The British journal of ophthalmology. 1989; 73(8): 639-44.

Naik VM, Naik MN, Goldberg RA, et al. Immunopathogenesis of thyroid eye disease: emerging paradigms. Survey of ophthalmology. 2010; 55(3): 215-26.

Noth D, Gebauer M, Muller B, et al. Graves' ophthalmopathy: natural history and treatment outcomes. Swiss medical weekly. 2001; 131(41-42): 603-9.

Perez A, Jansen-Chaparro S, Saigi I, et al. Glucocorticoid-induced hyperglycemia. Journal of diabetes. 2014; 6(1): 9-20.

Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. Otolaryngologic clinics of North America. 2010; 43(4): 753-68.

Pritchard J, Han R, Horst N, et al. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. Journal of immunology (Baltimore, Md : 1950). 2003; 170(12): 6348-54.

Prummel MF, Terwee CB, Gerding MN, et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. The Journal of clinical endocrinology and metabolism. 2004; 89(1): 15-20.

Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. Jama. 1993; 269(4): 479-82.

Salvi M, Vannucchi G, Curro N, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. The Journal of clinical endocrinology and metabolism. 2015; 100(2): 422-31.

Silkiss RZ, Reier A, Coleman M, et al. Rituximab for thyroid eye disease. Ophthalmic plastic and reconstructive surgery. 2010; 26(5): 310-4.

Smith TJ. Insulin-like growth factor-I regulation of immune function: a potential therapeutic target in autoimmune diseases? Pharmacological reviews. 2010; 62(2): 199-236.

Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. The Journal of clinical endocrinology and metabolism. 2004; 89(10): 5076-80.

Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. The New England journal of medicine. 2017; 376(18): 1748-61.

Stan MN, Garrity JA, Carranza Leon BG, et al. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. The Journal of clinical endocrinology and metabolism. 2015; 100(2): 432-41.

Tanda ML, Piantanida E, Liparulo L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. The Journal of clinical endocrinology and metabolism. 2013; 98(4): 1443-9.

Terwee C, Wakelkamp I, Tan S, et al. Long-term effects of Graves' ophthalmopathy on health-related quality of life. European journal of endocrinology. 2002; 146(6): 751-7.

Terwee CB, Gerding MN, Dekker FW, et al. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. The British journal of ophthalmology. 1998; 82(7): 773-9.

Tsui S, Naik V, Hoa N, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. Journal of immunology (Baltimore, Md : 1950). 2008; 181(6): 4397-405.

Ullrich A, Gray A, Tam AW, et al. Insulin-like growth factor I receptor primary structure: comparison with insulin receptor suggests structural determinants that define functional specificity. The EMBO journal. 1986; 5(10): 2503-12.

Weightman DR, Perros P, Sherif IH, et al. Autoantibodies to IGF-1 binding sites in thyroid associated ophthalmopathy. Autoimmunity. 1993; 16(4): 251-7.

Wiersinga WM, Perros P, Kahaly GJ, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. European journal of endocrinology. 2006; 155(3): 387-9.

Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. The Journal of clinical endocrinology and metabolism. 2011; 96(2): 320-32.

17 APPENDICES

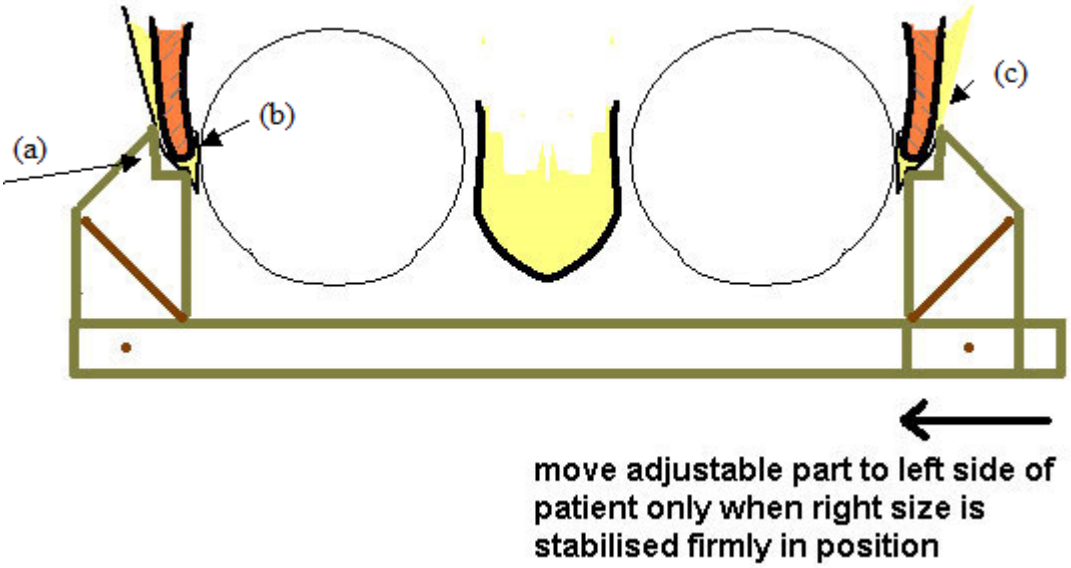
17.1 Administrative Appendix

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 Mobile telephone number: [redacted] Business telephone number: [redacted] Fax number: [redacted] Email: [redacted]
Sponsor Representative	[redacted] Horizon Pharma USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045 Mobile telephone number: [redacted] Fax number: [redacted] Email: [redacted]
Sponsor Contact for Serious Adverse Event Reporting	[redacted] Telephone number: [redacted] Fax: [redacted] [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) ☐	☐	☐	☐
2)	Driving (check here if no driver's license) ☐	☐	☐	☐
3)	Moving around the house	☐	☐	☐
4)	Walking outdoors	☐	☐	☐
5)	Reading	☐	☐	☐
6)	Watching TV	☐	☐	☐
7)	Hobby or pastime, specify: _____	☐	☐	☐
		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?	☐	☐	☐

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?	☐	☐	☐
10)	Do you feel that you are stared at in the streets because of your thyroid eye disease?	☐	☐	☐
11)	Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐
12)	Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐
13)	Do you feel socially isolated because of your thyroid eye disease?	☐	☐	☐
14)	Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐
15)	Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐
16)	Do you try to mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐