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

Document:
SAP

NCT#:
NCT03461211

Document Date:
17JUN2020

Statistical Analysis Plan

[redacted]

Document Type:	Template	Document ID:	03.007A.03
Issue Date:	02 MAY 2016	Effective Date:	30 MAY 2016

Sponsor Name:	Horizon Pharma USA, Inc. 150 S. Saunders Road Lake Forest, IL 60045
Protocol Number and Title:	Multicenter, Safety and Efficacy, Open-Label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Subjects with Thyroid Eye Disease (OPTIC-X)
Protocol Version and Date:	1.0, 24OCT2017 2.0, 20APR2018 (Amendment 1) 2.1, 26JUL2018 (Amendment 1, Germany) 3.0, 31JAN2019 (Amendment 2)
Author(s):	[redacted] Senior Biostatistics
SAP Version:	2.0
SAP Version Date:	17JUN2020

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
2.0	17-Jun-2020	[redacted]	Added an appendix for impact of COVID-19 on analysis

I confirm that I have reviewed this document and agree with the content.

APPROVALS

[redacted]

[redacted]

Electronically signed by [redacted]
Reason: I am the author
Date: Jun 17, 2020 15:07 CDT

Authoring Biostatistician — Date (dd-Mmm-yyyy)

[redacted]
Senior Biostatistician

[redacted]

Electronically signed by [redacted]
Reason: I am the approver
Date: Jun 17, 2020 15:18 EDT

Senior Reviewing Biostatistician — Date (dd-Mmm-yyyy)

[redacted]
Associate Director, Biostatistics

Horizon Pharma USA, Inc.

[redacted]
Vice President, Biometrics

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 18-Jun-2020 | 12:05 CDT
93D0A2F45B9F41F19F9955813F16E479

Date (dd-Mmm-yyyy)

DocuSigned by:
[redacted]

[redacted] I have reviewed this document
Signing Time: 18-Jun-2020 | 10:38 CDT
58B5C724C9F142D9AE53592DD0CF2262

[redacted] Operations

Date (dd-Mmm-yyyy)

[redacted]
Associate Director, Biostatistics

DocuSigned by:
[redacted]
Signing Reason: I approve this document
Signing Time: 18-Jun-2020 | 10:38 CDT
849C3F094A6C47AFA4D021D75296BCEF

Date (dd-Mmm-yyyy)

[redacted]
Senior Medical Director, Clinical Development

DocuSigned by:
[redacted]
Signing Reason: I approve this document
Signing Time: 18-Jun-2020 | 10:45 CDT
0196B99A11DC424F81EC21BA5817FA21

Date (dd-Mmm-yyyy)

TABLE OF CONTENTS

Contents

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
A	Appearance
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APD	Afferent Pupillary Defect
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
CAS	Clinical Activity Score
CI	Confidence Interval
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	Europe
EUGOGO	European Group on Graves' Ophthalmopathy
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GO-QoL	Graves' Ophthalmopathy Quality of Life
HLGT	High Level Group Term
HLT	High Level Term
ICD	Intercanthal Distance
ICH	International Conference on Harmonisation
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat

Abbreviation	Description
IV	Intravenous
kg	Kilograms
lbs	Pounds
LR	Light Reflex
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mm	Millimeters
n	Number of Observations
NA	Not Applicable
NAb	Neutralizing Antibody
NaCl	Sodium Chloride
NCS	Not Clinically Significant
PK	Pharmacokinetic
PT	Preferred Term
q3W	Once Every Three Weeks
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TED	Thyroid Eye Disease
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal

Abbreviation	Description
US	United States
VF	Visual Functioning
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings. A separate vendor will be responsible for generating the pharmacokinetic (PK) analysis plan and associated analyses with the exception of listings and descriptive summaries of concentration data which will be performed by [redacted] as outlined in subsequent sections.

2.2. TIMINGS OF ANALYSES

Data Safety Monitoring Board (DSMB) Analysis: The study will be monitored by a DSMB, which will advise the Sponsor regarding the continuing safety of study subjects. The details regarding frequency of meetings, members, and the safety review criteria will be outlined in a separate DSMB Charter. As analyses are planned by treatment received in HZNP-TEP-301, an independent unmasked team from [redacted] biostatistics will perform the analyses to maintain the masking of the HZNP-TEP-301 study until HZNP-TEP-301 is unmasked.

Integrated Summary of Safety (ISS): At the time of the HZNP-TEP-301 Week 24 database lock, safety data from HZNP-TEP-302 were included in the Integrated Summary of Safety. These data included disposition, demographics, exposure, and adverse events. Further, a 120-day safety update to the ISS to examine an additional 4 months of safety data reported for HZNP-TEP-301 and HZNP-TEP-302 was prepared including disposition, demographics, exposure, adverse events, and laboratory results from HZNP-TEP-302.

Primary Study Analysis (Week 48): A Week 48 analysis of safety, efficacy, and pharmacokinetics is planned after all subjects complete the final visit (Week 24 for HZNP-TEP-301 relapse subjects and Week 48 for HZNP-TEP-301 proptosis non-responders) or terminate from the study. The analysis includes all data collected in the database through the time of the Week 48 database lock.

Follow-up Contact Analysis: A follow-up contact analysis will be conducted when all subjects complete the Follow-Up Contact Period of the study or are no longer able to be contacted. Additional data collected after the database lock from the Week 48 analysis of the study will be prepared as an addendum to the Clinical Study Report according to regulatory or scientific need.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The overall objective is to evaluate the safety and efficacy of teprotumumab in the treatment of Thyroid Eye Disease (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 met the criteria for re-treatment due to relapse during the Follow-Up Period of HZNP-TEP-301.

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 in proptosis from Study Baseline [see section 6.2.3] in the study eye without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at Week 24.

3.2. SECONDARY OBJECTIVES

Secondary objectives are:

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 Study Baseline to Week 24 in proptosis measurement in the study eye.
3. Diplopia responder rate (i.e. the percentage of subjects with Study 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 Study Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

3.3. EXPLORATORY OBJECTIVES

Exploratory objectives are:

1. The overall responder rate (percentage of subjects with >= 2 -point reduction in CAS and >=2 mm reduction in proptosis from Study 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 Study 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)
5. Mean change from Study Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Mean change from Study Baseline to Week 24 on the motility component of the Clinical Measures of Severity.
7. Evaluate PK parameters of teprotumumab to estimate exposure and understand PK-PD relationships.

3.4. BRIEF DESCRIPTION

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

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 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 to the [redacted] clinical team and study sites 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 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. The infusion rate may be reduced or the dose may be interrupted or held based on decreased tolerability. 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.

For all the assessments, if Day 1 of the extension study occurs on the same day as the final visit of HZNP-TEP-301 (Week 24 for proptosis non-responders and Week 72 [or

Premature Withdrawal (PW)] for subjects who relapse), assessments do not need to be repeated, and the final assessments from the lead-in study will serve as the Study Baseline assessments for the extension study.

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 at 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.

3.5. DETERMINATION OF SAMPLE SIZE

The sample size is not based on statistical considerations. Subjects who are proptosis non-responders at Week 24 of HZNP-TEP-301 or who are 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.

3.6. TREATMENT ASSIGNMENT & MASKING

This is an open label study. All enrolled subjects 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.

Prior to the unmasking of HZNP-TEP-301, an unmasked team from [redacted] biostatistics performed unmasked analyses as outlined in the DSMB charter. These team members otherwise had no involvement with the study.

3.7. PREPARATION AND ADMINISTRATION OF STUDY MEDICATION

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 doses 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.

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

3.8. STUDY PROCEDURES AND FLOWCHART

The Schedule of Assessments is presented in Table 1 below.

Table 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				

	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)**
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				
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.
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.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint 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.

Baseline refers to Study Baseline defined in Section 6.2.3.

4.2. SECONDARY EFFICACY ENDPOINTS

The secondary endpoints are the following:

1. Percentage of subjects with a CAS value of 0 or 1 in the study eye at Week 24.
2. Mean change from Study Baseline to Week 24 in proptosis measurement in the study eye.
3. Diplopia responder rate (percentage of subjects with Study Baseline diplopia >0 in study eye who have a reduction from Study Baseline of ≥ 1 grade with no corresponding deterioration [≥1 grade worsening] in the fellow eye) at Week 24.
4. Mean change from Study Baseline to Week 24 in the GO-QoL questionnaire overall score.

4.3. EXPLORATORY EFFICACY ENDPOINTS

Exploratory efficacy endpoints include:

1. The overall responder rate (percentage of subjects with ≥ 2-point reduction in CAS AND ≥ 2 mm reduction in proptosis from Study 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 Study 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 8.3.4 for definitions).
5. Mean change from Study Baseline to Week 24 in the GO-QoL questionnaire VF and A subscale scores.
6. Mean change from Study Baseline to Week 24 on the motility component of the Clinical Measures of Severity.

4.4. EXPLORATORY PHARMACOKINETIC ENDPOINTS

The PK endpoints covered in the scope of this SAP include:

- Descriptive summaries of serum concentrations by time point
- Listing of serum concentrations by time point

4.5. SAFETY ENDPOINTS

Safety endpoints include the following:

- Adverse events (AE), including AE of special interest (AESI)
- Concomitant medication
- Descriptive summary of immunogenicity
- Physical examination
- Ophthalmic examination
- Vital signs
- Clinical laboratory assessments (complete blood count, chemistry [including thyroid panel and HbA1C], and urinalysis)
- Pregnancy testing
- Electrocardiogram (ECG)

5. ANALYSIS POPULATIONS

5.1. INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will include all subjects who are enrolled (signed informed consent) in the study. Subjects will be analyzed according to treatment received in HZNP-TEP-301 study. The ITT Population will be used for all analyses of efficacy and safety endpoints.

5.2. PHARMACOKINETIC POPULATION

The PK Population will include all subjects who received at least one dose of study drug and have at least one quantifiable PK serum concentration measurement. Subjects will be analyzed according to treatment received in HZNP-TEP-301 study.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

The following conventions will be utilized in the analyses:

- In general, descriptive summaries will be provided by treatment received in HZNP-TEP-301 and overall.
- The following treatment group labels will be used: "HZNP-TEP-301 Placebo" for subjects who were randomized to Placebo in HZNP-TEP-301 and "HZNP-TEP-301 HZN-001" for subjects who were randomized to HZN-001 in HZNP-TEP-301.
- Unless otherwise indicated, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- The same number of decimal places as the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- If multiple assessments occur at a given time point, the latest value will be used. If multiple assessments occur on the same day and the time is not recorded, the average of the values will be used in any descriptive summaries.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- Additional programming considerations are provided in Section 14.

6.2. KEY DEFINITIONS

6.2.1. Study Eye

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.

6.2.2. Fellow Eye

The non-study eye will be referred to as the "fellow eye".

6.2.3. Study Baseline and HZN-001 Baseline

The following two definitions of baseline will be utilized for analysis purposes:

- **Study Baseline** will be defined as the last measurement taken prior to first dose in HZNP-TEP-302 (considering unscheduled visits when available). If a Study Baseline value is not obtained in the HZNP-TEP-302 study prior to dosing, the last value measured in HZNP-TEP-301 will be used. Study Baseline comparisons will be provided for all applicable endpoints.
- **HZN-001 Baseline** will be defined as the last measurement taken prior to first dose of HZN-001 whether it occurred in HZNP-TEP-301 or HZNP-TEP-302 (considering unscheduled visits when available). HZN-001 Baseline comparisons will be provided for select assessments of safety, i.e. laboratory assessments, vital signs, ECGs, physical examinations, and ophthalmic examinations.

Change from (Study or HZN-001) Baseline will be defined as the measurement at each time point minus the relevant Baseline value.

The primary objective will be assessed using the Study Baseline.

6.2.4. Study Day and HZN-001 Study Day

The following two definitions of study day will be utilized:

- **Study Day**: For assessments on or after the date of treatment start in HZNP-TEP-302, Study Day will be calculated as assessment date - first dose date in HZNP-TEP-302 + 1. For assessments prior to dosing in HZNP-TEP-302, Study Day will be calculated as assessment date - treatment start date in HZNP-TEP-302. Further, there will be no Study Day 0. Study Day will appear in all relevant listings in which a date is provided (e.g. visit date, assessment date, and start/stop dates of events).
- **HZN-001 Study Day**: For assessments on or after the date of HZN-001 treatment start (regardless of whether HZN-001 was initiated in HZNP-TEP-301 or HZNP-TEP-302), HZN-001 Study Day will be calculated as assessment date - first dose date of HZN-001 + 1. For assessments prior to HZN-001 treatment start, HZN-001 Study Day will be calculated as assessment date - HZN-001 treatment start date. Further, there will be no HZN-001 Study Day 0. HZN-001 Study Day will appear in listings of safety data, i.e. laboratory assessments, vital signs, ECGs, physical examinations, and ophthalmic examinations.

6.3. MISSING DATA

6.3.1. Birth Dates

If the date of birth is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will not be presented in the data listings.

6.3.2. Medical History Diagnosis Dates

If the onset date of Graves' disease or TED is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will not be presented in the data listings.

6.3.3. Medication Dates

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only. Imputed dates will not be presented in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the first dose date, the day of the first dose date will be imputed. Otherwise, the first of the month will be used.
- If day and month are missing and the year matches the year of the first dose date, the month and the day of the first dose date will be imputed. Otherwise, 01 January will be used.
- If the start date is completely missing, the start date will not be imputed. If the stop date is after first dose date, the medication will be considered to be both prior and concomitant. If the stop date is prior to the first dose date, the medication will be considered to be prior only. If the stop date is after the first dose date but prior to the last dose date + 21 days, the medication will be considered prior and concomitant during the Treatment Period only. If the stop date is after the last dose date + 21 days, the medication will be considered prior and concomitant during both the Treatment Period and Follow-Up Period.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- For stop dates, if the day is missing, then the last day of the month will be used.
- If the month is missing, then December will be used.
- If the stop date is completely missing then the date of last study visit will be used.

6.3.4. Adverse Events

For adverse events with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment-emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the first dose date, the day of the first dose date will be imputed and the AE will be considered treatment-emergent. Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the dosing start date.
- If the day and month are missing, and the year matches the year of the first dose date, the month and the day of the first dose date will be imputed, and the AE will be considered treatment-emergent. Otherwise, 01 January will be used and the treatment-emergent status will be assessed relative to the dosing start date.
- If the start date is completely missing, the AE will be considered treatment-emergent unless the stop date is complete and prior to the first dose or provides enough partial information to rule out a treatment-emergent status.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date and the treatment-emergent status will be assessed relative to the dosing start date.

Any missing intensity assessments for AEs will be imputed as "severe" and any missing relationship to study drug will be considered "related" for summary purposes.

6.3.5. Efficacy Assessments

For the binary primary and secondary endpoints, subjects missing the evaluations at a given visit will be treated as failures (non-responders). No imputation of missing data will be performed for any continuous efficacy assessments.

6.4. VISIT WINDOWS

All data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). Further, premature withdrawal (PW) visits (through Week 48/Month 12) will be windowed

to the nearest scheduled visit based on the study day of occurrence relative to the target day of each scheduled visit according to Table 2 below.

Table 2: Visit Windows for Assigning PW Visits to a Scheduled Visit

Study Period	Visit	Target Day	Window for Reassignment to Scheduled Visit
Treatment Period	Day 1	1	1
	Week 1	8	2 - 15
	Week 3	22	16 - 25
	Week 4 (Month 1)	29	26 - 36
	Week 6	43	37 - 53
	Week 9	64	54 - 74
	Week 12 (Month 3)	85	75 - 95
	Week 15	106	96 - 116
	Week 18	127	117 - 137
	Week 21	148	138 - 158
	Week 24 (Month 6)	169	159 - 176
Follow-Up Period	Week 28 (Month 7)	197	177 - 225
	Week 36 (Month 9)	253	226 - 295
	Week 48 (Month 12)	337	≥ 296

In the event that a PW visit gets reassigned to a visit for which the subject has scheduled data collected, the data from the nominal scheduled visit will take precedence and the data from the PW visit will not be summarized.

6.5. POOLING OF SITES

In general, data from all sites will be summarized together for efficacy and safety analyses. Select descriptive summaries will be provided by site and region: US and EU.

6.6. SUBGROUPS

Subgroups of interest include:

- Subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period of HZNP-TEP-301)
- Tobacco use status at time of randomization in HZNP-TEP-301: Tobacco uses of "never" and "former" will be grouped as tobacco non-users, and tobacco uses of "current" will be considered tobacco users as collected on the HZNP-TEP-301 substance use eCRF (non-user, user)

- Region (US, EU)
- Site
- Age (<65 years, ≥65 years) calculated using the HZNP-TEP-302 study informed consent date.
- Gender (male, female)
- Race (white, black or African American, Asian, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

Descriptive summaries will be provided for various efficacy endpoints and TEAEs for select subgroups as specified in Section 8 and Section 10.3, respectively. If one of the subgroups has fewer than 5 subjects, no summary table will be created for that subgroup, except for site. Sites will not be pooled regardless of subject counts in the by-site subgroup analyses.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS, MEDICATION AND PROTOCOL DEVIATIONS

7.1. SUBJECT DISPOSITION AND DISCONTINUATION

A summary of subject disposition will be provided including the number of subjects screened and the number and percent of screen failures. Further, the number and percent of subjects enrolled overall and by subject enrollment type (proptosis non-responders in HZNP-TEP-301 and subjects who relapsed during the Follow-Up Period of HZNP-TEP-301) will be provided, as well as the number of subjects in each analysis population (ITT and PK Population). In addition, the number and percent of subjects in each of the following categories will be provided:

- Completed the Treatment Period
- Discontinued early from the Treatment Period
    - Proptosis non-responder in HZNP-TEP-301 and did not continue in the Follow-Up Period with reasons for discontinuations
    - Proptosis non-responder in HZNP-TEP-301 and continued in Follow-Up Period with reasons for discontinuation Subjects who relapsed in HZNP-TEP-301
- Had any data collected during the Follow-Up Period
- Completed the study
    - Completed the Treatment Period and Follow-Up Period for subjects who were proptosis non-responders in HZNP-TEP-301
    - Discontinued from the Treatment Period but completed the Follow-up Period for subjects who were proptosis non-responders in HZNP-TEP-301
    - Completed the Treatment Period for subjects who relapsed during the Follow-Up Period of HZNP-TEP-301
- Discontinued early from the study by reason for discontinuation (Did not complete the Treatment Period and did not continue in the Follow-Up Period for subjects who were proptosis non-responders in HZNP-TEP-301; did not complete the Treatment Period, continued in the Follow-Up Period, but did not complete the Follow-Up Period for subjects who were proptosis non-responders in HZNP-TEP-301; completed the Treatment Period and did not continue in the Follow-Up Period for subjects who were proptosis non-responders in HZNP-TEP-301; completed the Treatment Period, continued in the Follow-Up Period but did not complete the Follow-Up Period for subjects who were proptosis non-responders in HZNP-TEP-

301; did not complete the Treatment Period for subjects who relapsed during the Follow-Up Period of HZNP-TEP-301)

- Reasons for discontinuation

Percentages will be based on the number of subjects in the ITT Population.

Subject disposition information will be summarized by treatment received in HZNP-TEP-301 and overall.

A separate summary will be provided of the number and percentage of subjects attending each visit and participating in each Follow-Up contact. Percentages will be based on the ITT Population.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be based on information obtained on Study Baseline (Day 1 of HZNP-TEP-302, or the last measurement available in the HZNP-TEP-301 study if measurement on Day 1 of HZNP-TEP-302 is not available). Descriptive summaries of demographic and baseline characteristics will be presented overall and by treatment received in HZNP-TEP-301 study based on the ITT Population. These characteristics include study eye (right, left) as identified in HZNP-TEP-301, age, age category (<65 years, ≥65 years), gender, race, ethnicity, height, weight, body mass index, region (US, EU), tobacco use status as randomized in HZNP-TEP-301 (non-user, user), actual tobacco use status as collected on the substance use CRF in HZNP-TEP-301 (non-user, user), tobacco use history (never, current, former), alcohol use history (never, current, former), child-bearing potential (yes, no, not applicable), time since diagnosis of Graves' disease and time since diagnosis of TED. Further, baseline levels of free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH) and glycated hemoglobin A1C (HbA1C) will be summarized.

Age will be calculated as: (informed consent date of HZNP-TEP-302 - date of birth + 1) / 365.25 and truncated to complete years. Missing data imputation rules are provided in Section 6.3.1.

Weight will be converted to kilograms (kg) when reported in pounds (lbs) as follows:
Weight (in kg) = weight (in lbs) * 0.4536

Time since Graves' disease diagnosis (years) will be calculated as: (first dose date of HZNP-TEP-302 - date of diagnosis + 1) / 365.25, rounded to two decimal places. Missing data imputation rules are provided in Section 6.3.2.

Time since TED (months) will be calculated as: (first dose date of HZNP-TEP-302 - date of diagnosis + 1) / 30.4, rounded to two decimal places. Missing data imputation rules are provided in Section 6.3.2.

Separate summaries will be provided by tobacco use (non-user, user) and region (US, EU) for the ITT Population. Demographic data and baseline characteristics will be provided in subject listings.

7.3. MEDICAL HISTORY

Medical history will be based on information collected in HZNP-TEP-301 study. Medical history information will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and summarized by treatment received in HZNP-TEP-301 and overall in the ITT Population. Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT). Medical history will be provided in subject listings.

7.4. MEDICATION

Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) September 2017. Prior and concomitant medications will be summarized by presenting the counts and percentage of subjects using medications overall and by treatment received in HZNP-TEP-301 for the ITT Population. Summaries will be provided by Anatomical Therapeutic Chemical (ATC) Level 4 term and PT. Medication summaries will be sorted alphabetically by ATC Level 4 and by PT within ATC Level 4. Subjects will be counted only once for each medication class and each preferred drug name.

Prior and concomitant medications will be listed together with a designation to identify the medications as prior and/or concomitant and sorted by start date. Separate listings will be provided for thyroid eye disease medications and medications taken for other indications.

7.4.1. Prior Medication

Prior medications will be presented separately from concomitant medications in a summary table. Any medication with a start date prior to the date of first dose in study HZNP-TEP-301 will be considered a prior medication. Missing date imputation rules are provided in Section 6.3.3.

7.4.2. Concomitant Medication

Concomitant medications will be presented in two separate summary tables: concomitant medications received during the Treatment Period of HZNP-TEP-302 (up to and including 21 days after the last dose of study drug) and concomitant medications received during the Follow-Up Period HZNP-TEP-302 (the period after 21 days following the last dose of

study drug). Any medication that is ongoing or has a stop date on or after the first dose date will be considered a concomitant medication. Any concomitant medication that has a start date, stop date or is ongoing on or after the first dose but prior to 21 days following the last dose of study drug will be considered a concomitant medication during the Treatment Period. Any medication that is ongoing or has a stop date after 21 days following the last dose of study drug will be considered a concomitant medication during the Follow-Up Period. As such, the same medication may be summarized as both prior and concomitant during either or both periods. The summary tables will not be mutually exclusive.

Further, a separate summary of concomitant medications during the Follow-Up Period and Follow-Up Contact Period will be provided for TED medications. TED medications during the Follow-Up Period will be identified by a manual listing review prior to generating the primary study analyses (Week 48).

Missing date imputation rules are provided in Section 6.3.3.

7.4.3. Concomitant Procedures

A listing will be provided for subjects undergoing any concomitant procedures performed during the Treatment Period of HZNP-TEP-302 (up to and including 21 days following last dose of study drug). TED concomitant procedures during the Follow-Up Period will be identified in the listing. TED procedures during the Follow-Up Period will be identified by a manual listing review prior to generating the primary study analyses (Week 48).

7.4.4. Follow-Up Contact Thyroid Eye Disease Surgeries, Orbital Radiation, and Follow-up Treatments

A summary will be provided of the count and percent of subjects receiving no additional TED treatment (medication, procedure, surgery, and/or orbital radiation treatment), at least one additional TED treatment, at least two additional TED treatments and three or more additional TED treatments during the Follow-up Period and Follow-Up Contact Period. Separate listings will be provided for subjects undergoing any TED surgical procedures, orbital radiation, and Follow-Up treatments.

7.5. PROTOCOL DEVIATIONS

Major protocol deviations will be summarized for the ITT Population by the number and percentage of subjects overall and category of deviation during the Treatment Period and Follow-Up Period, separately; by overall and treatment received in HZNP-TEP-301 study. All protocol deviations will be listed.

8. EFFICACY

Efficacy assessments will be performed for both eyes at each assessment time point; however, only the study eye will be used to assess the primary efficacy endpoint. All summaries of efficacy endpoints will be conducted based on ITT population.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the proptosis responder rate (percentage of subjects with a ≥ 2 mm reduction from Study Baseline in proptosis in the study eye, without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at Week 24 in the ITT Population.

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.

Proptosis will be measured for each eye at Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and for HZNP-TEP-301 proptosis non-responders at Weeks 28, 36, 48 (or PW) during the Follow-Up Period. Measurements will be recorded on the Clinical Measures of Severity eCRF under exophthalmos.

Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the primary analysis. Further, subjects who prematurely discontinue study drug dosing prior to Week 21 during the Treatment Period will be analyzed as treatment failures (non-responders), unless an assessment at Week 24 (within the day range specified in Section 6.4) is available.

Descriptive summaries of responder results of study eye will be provided by treatment received in HZNP-TEP-301 and overall at Week 24.

In addition, descriptive summaries of responder results will be provided by treatment received in HZNP-TEP-301 for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period for the ITT Population, considering subjects missing the evaluations as treatment failures (non-responders). Similar summaries will also be provided separately for the fellow eye, and by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), site, age group (<65 years, ≥65 years), gender, race (white, black or African American, Asian, other), and ethnicity (Hispanic or Latino, not Hispanic or Latino). A plot of proportion of proptosis responder by visits and treatment received in HZNP-TEP-301 will also be provided.

In addition, a separate analysis will be provided for time to proptosis response. Time to proptosis response will be measured as the days from the first dose date to the earliest visit date in which the criteria are met for proptosis response (≥ 2 mm reduction from Study Baseline in proptosis in the study eye, without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) within the Treatment Period, calculated as:

first visit date in which criteria for proptosis response are met - first dose date + 1

Subjects not achieving a proptosis response within the Treatment Period will be censored at their last visit date with a proptosis assessment within the Treatment Period. Kaplan-Meier estimates will be provided by treatment received in HZNP-TEP-301 of the 25th percentile, median, and 75th percentile. 95% confidence intervals (CI) will be provided for the median. Analyses will be based on the ITT Population. Any ITT subject who is enrolled but not dosed will be censored at Day 0.

The analysis will be repeated for the fellow eye (using a definition analogous to the one used for the study eye).

Plots of the time to proptosis response will be provided by treatment received in HZNP-TEP-301 for the study eye and fellow eye.

Further, for subjects who were proptosis non-responders in HZNP-TEP-301, sustained proptosis response at a given visit in the HZNP-TEP-302 Follow-Up Period will be defined for HZNP-TEP-302 Week 24 proptosis responders as:

- ≥ 2 mm reduction from Baseline in proptosis in the study eye, without deterioration (≥ 2 mm increase) of proptosis in the fellow eye, AND
- No additional TED treatment received by the time of the visit.

Additional TED treatment will include any instances of TED medication (identified by manual listing review), TED concomitant procedures (identified by manual listing review), TED surgical procedures, and/or orbital radiation treatments.

At each assessment after Week 24, the proportion of subjects who are sustained responders will be summarized by treatment received in HZNP-TEP-301. Subjects who are missing proptosis values at a visit will be considered non-responders at that visit.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

8.2.1. CAS Categorical Response

The CAS will be completed at Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and for HZNP-TEP-301 non-responders at Weeks 28, 36, 48 (or PW) in the Follow-Up Period using the 7 item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS (Mourits et al, 1989) for each eye.

For each item present, one point is given. The sum of these points is the total score.

- Spontaneous orbital pain
- Gaze evoked orbital pain
- Eyelid swelling that is considered to be due to active (inflammatory phase) TED/GO
- Eyelid erythema
- Conjunctival redness that is considered to be due to active (inflammatory phase) TED/GO (ignore "equivocal" redness)
- Chemosis
- Inflammation of caruncle or plica

The first secondary endpoint is CAS as a categorical response variable defined as a reduction to a CAS of 0 or 1 from Study Baseline at Week 24. Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the analysis. Descriptive summaries of responder results will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population at Week 24. Only subjects with CAS > 1 at study baseline in the ITT Population will summarized.

In addition, descriptive summaries of responder results will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period, considering subjects missing the evaluations as treatment failures (non-responders). Similar summaries will also be provided separately by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), and site. The proportion of subjects with a complete CAS response (subjects who have a CAS of 0) in the study eye will be summarized for each visit in the Treatment Period and Follow-Up Period considering observed results only. Only subjects with CAS > 0 at study baseline in the ITT Population will summarized.

Summaries after Week 24 for subjects who were proptosis non-responders in HZNP-TEP-301, will also include a summary of sustained CAS response, where sustained responder

is defined for subjects who were a responder at Week 24 and remained a responder post-Week 24 (defined as having a reduction to a CAS of 0 or 1 in study eye) and did not receive any additional TED treatment by the time of the visit. Additional TED treatment will include any instances of TED medication (identified by manual listing review), TED concomitant procedure (identified by manual listing review), TED surgical procedures, and/or orbital radiation treatments. At each assessment after Week 24, the proportion of subjects who are sustained responders will be summarized by treatment received in HZNP-TEP-301. Subjects who are missing values at a visit will be considered non-responders at that visit.

A plot of proportion of CAS categorical responder by visits and treatment received in HZNP-TEP-301 will also be provided.

8.2.2. Proptosis as a Continuous Variable

The second secondary efficacy endpoint is proptosis as a continuous variable. Descriptive summaries of observed proptosis as a continuous variable, change from Study Baseline and change from HZN-001 Baseline will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population at Week 24. In addition, descriptive summaries of observed proptosis as a continuous variable will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period. Similar summaries will be provided separately by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), and site.

A plot of mean change of proptosis value from Study Baseline by visits and treatment received in HZNP-TEP-301 will also be provided.

8.2.3. Diplopia Categorical Response

Diplopia will be assessed at Day 1 and Weeks 6, 12, 18, and 24 (or PW) during the Treatment Period, and for HZNP-TEP-301 proptosis non-responders at Weeks 28, 36, 48 (or PW) in the Follow-Up Period. The subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position) is recorded for each eye. A subject will be considered to have diplopia if a score > 0 is observed in the study eye at Study Baseline

(for summaries relative to Study Baseline) or HZN-001 Baseline (for summaries relative to HZN-001 Baseline).

The third secondary endpoint is diplopia responder. Only subjects with diplopia (diplopia > 0) in the study eye at Study Baseline (for summaries relative to Study Baseline) or HZN-001 Baseline (for summaries relative to HZN-001 Baseline) will be included in this analysis. A subject will be considered a responder if the grade of diplopia (scored from 0 to 3) decreases by at least one grade in the study eye without worsening by at least one grade in the fellow eye. Subjects with diplopia at baseline who are missing the Week 24 diplopia evaluation will be considered treatment failures (non-responders). Descriptive summaries of responder results will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population at Week 24.

In addition, descriptive summaries of responder results will be provided for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period, considering subjects missing the evaluations as treatment failures (non-responders). Similar summaries will also be provided separately by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), and site. Summaries after Week 24 for subjects who were proptosis non-responders in HZNP-TEP-301, will also include the following three endpoints:

- Sustained responder: of those subjects with diplopia at Study Baseline who were a diplopia responder at Week 24, the proportion who remained a diplopia responder at each post-Week 24 assessment (defined as having a diplopia score that decreases by at least one grade in the study eye without worsening of diplopia by at least one grade in the fellow eye) and did not receive any additional TED treatment by the time of the visit.
- Sustained 0: of those subjects with diplopia at Study Baseline who had a diplopia score of 0 at Week 24, the proportion who had a diplopia score of 0 at each post-Week 24 assessment (without worsening of diplopia by at least one grade in the fellow eye) and did not receive any additional TED treatment by the time of the visit.
- No diplopia: of those subjects with diplopia at Study Baseline regardless of the value at Week 24, the number with a diplopia score of 0 at each post-Week 24 assessment (without worsening of diplopia by at least one grade in the fellow eye) and did not receive any additional TED treatment by the time of the visit.

Additional TED treatment will include any instances of TED medication (identified by manual listing review), TED concomitant procedure (identified by manual listing review), TED surgical procedures, and/or orbital radiation treatments.

For each of these assessments, subjects who are missing diplopia values at a visit will be considered non-responders at that visit.

A plot of proportion of diplopia responder by visits and treatment received in HZNP-TEP-301 will also be provided.

8.2.4. GO-QoL Questionnaire Overall Score

For the fourth efficacy endpoint analysis, the GO-QoL questionnaire (Terwee et al, 1998) will be completed at Baseline, Weeks 6, 12, 24 (or PW) during the Treatment Period, and for HZNP-TEP-301 proptosis non-responders at Weeks 28, 48 (or PW) during the Follow-Up Period. The GO-QoL is a 16-item self-administered questionnaire divided into two 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 sum of the scores from each set of eight questions will be calculated and transformed to a scale from 0 to 100 - one for visual function (VF), one for appearance (A) and one for the overall combined score. Scores will be transformed as follows:

Transformed score = [(sum of each score - number of completed items) / (2 * number of completed items)] * 100.

Descriptive summaries of the transformed scores and change from Study Baseline will be provided by treatment received in HZNP-TEP-301 group for the ITT Population at Week 24.

In addition, descriptive summaries of the transformed scores will be provided by treatment received in HZNP-TEP-301 for the ITT Population at each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period. Similar summaries will be provided separately by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), and site.

A plot of mean change of GO-QoL overall transformed score from Study Baseline by visits and treatment received in HZNP-TEP-301 will also be provided.

8.3. EXPLORATORY EFFICACY ENDPOINTS AND ANALYSIS

8.3.1. CAS and Proptosis Categorical Response

The first exploratory efficacy endpoint is the overall responder rate, measured as the percentage of subjects with ≥ 2-point reduction in CAS AND ≥ 2 mm reduction in

proptosis from Study Baseline, provided there is no corresponding deterioration (≥ 2 point/mm increase) in CAS or proptosis in the fellow eye at Week 24. Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the analysis. Only subjects with CAS > 1 and proptosis > 1 mm at Study Baseline in the ITT Population will summarized.

Descriptive summaries of responder results for both study eye and fellow eye responder definitions will be provided by treatment received in HZNP-TEP-301 for the ITT Population at Week 24.

In addition, descriptive summaries of responder results for both study eye responder definitions (study eye responder and fellow eye responder) will be provided by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period, considering subjects missing the evaluations as treatment failures (non-responders). Similar summaries will also be provided separately by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301), tobacco use status (non-user, user), region (US, EU), and site.

Summaries after Week 24 for subjects who were proptosis non-responders in HZNP-TEP-301, will also include a summary of sustained CAS and proptosis response, where sustained responder is defined for subjects who were a responder at Week 24 and remained a responder post-Week 24 (defined as having ≥ 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) and did not receive any additional TED treatment by the time of the visit. Additional TED treatment will include any instances of TED medication (identified by manual listing review), TED concomitant procedure (identified by manual listing review), TED surgical procedures, and/or orbital radiation treatments. At each assessment after Week 24, the proportion of subjects who are sustained responders will be summarized by treatment received in HZNP-TEP-301. Subjects who are missing values at a visit will be considered non-responders at that visit.

A plot of proportion of overall responder by visits and treatment received in HZNP-TEP-301 will also be provided.

8.3.2. Clinical Measures of Severity

The following items, based on the EUGOGO Consensus Statement (Bartalena et al, 2008; Wiersinga et al, 2006) will be assessed at Day 1, and Weeks 6, 12, 18, 24 (or PW) during the Treatment Period and for HZNP-TEP-301 non-responders at Weeks 28, 36, 48 (or PW) during the Follow-Up Period. Except when strictly unavoidable, the same observer should conduct each evaluation of severity measure for the full duration of the study.

8.3.2.1. Categorical Response Variables

Table 2 provides a list of each Clinical Measures of Severity item and the assessment scale for classifying overall response.

Table 2: Clinical Measures of Severity

Clinical Measures of Severity Item and Assessment Scale	Minimum change required for classifying overall response
Exophthalmos (measured in mm using the same Hertel exophthalmometer and same intercanthal distance for each individual subject)	Decrease ≥ 2 mm
Lid aperture (distance between the lid margins in mm with the subject 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, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position)	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

Clinical Measures of Severity Item and Assessment Scale	Minimum change required for classifying overall response
Optic nerve involvement (best corrected visual acuity, color vision, optic disc, relative afferent pupillary defect (absent, present), and 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

Response is assessed individually for each item.

Subjects who have a Study Baseline assessment on a particular measure for which improvement is not possible (i.e. they have the best possible assessment) will be considered to be a responder if they maintain the Study Baseline assessment. The analysis of optic nerve involvement will be generated only if at least 10% of the subjects have optic nerve decompression.

The Clinical Measures of Severity results will be summarized for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population at Week 24, with the number and percentage of subjects being classified as responders on each individual item. Subjects missing the Week 24 evaluation will be considered to be treatment failures (non-responders) for the analysis. In addition, the Clinical Measures of Severity results will be summarized for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period for the study eye and fellow eye by treatment received in HZNP-TEP-301 for the ITT Population, with the number and percentage of subjects being classified as responders on each individual item and considering subjects missing the evaluations as treatment failures (non-responders).

8.3.2.2. Motility Restriction

Motility is examiner assessed by estimating the degrees of restriction in eye movements. Monocular excursions in horizontal and vertical directions of gaze are recorded using the light reflex (LR) (Dolman et al, 2012) test.

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 four 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.

Descriptive summaries of observed results and change from Study Baseline for the study eye and fellow eye will be provided for each motility measure by treatment received in HZP-TEP-301 for the ITT Population at Week 24.

In addition, descriptive summaries for the study eye and fellow eye will be provided for each motility measure by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period.

8.3.3. CAS as a Continuous Variable

Descriptive summaries of CAS as a continuous variable and change from Study Baseline for the study eye and fellow eye will be provided by treatment received in HZNP-TEP-301 for the ITT Population at Week 24. In addition, descriptive summaries of CAS as a continuous variable for the study eye and fellow eye will be provided by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period.

8.3.4. Categorical Overall Response

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

- High responders: Subjects who had a reduction in both proptosis and CAS of 3 or more (≥ 3) from Study Baseline in the study eye, and no deterioration in the fellow eye (i.e., increase in CAS ≥ 2 points or increase in proptosis ≥ 2 mm).
- Responders: Subjects who had a reduction in both CAS and proptosis of 2 or more (but less than 3) from Study 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 Study 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

Descriptive summaries will be provided for both response definitions (study eye and fellow eye response) by treatment received in HZNP-TEP-301 for the count and percentage of subjects in each category for the ITT Population at Week 24.

8.3.5. GO-QoL Questionnaire (Visual Function and Appearance Scale Scores)

Descriptive summaries of the transformed VF scale scores and transformed A scale scores and change from Study Baseline will be provided by treatment received in HZNP-TEP-301 for the ITT Population at Week 24. In addition, descriptive summaries of transformed VF and A scale scores will be provided by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period.

8.3.6. Investigator Assessment of Active Disease

Investigator assessment of active disease (active disease, inactive disease) will be collected on Day 1, Week 6, Week 12, Week 18, and Week 24 (or PW) during the Treatment Period, and for HZNP-TEP-301 proptosis non-responders at Week 28, Week 36 and Week 48 (or PW). Descriptive summaries of the observed results will be provided by treatment received in HZNP-TEP-301 for the ITT Population at Week 24.

In addition, descriptive summaries of results will be provided by treatment received in HZNP-TEP-301 for the ITT Population for each visit in the Treatment Period and for HZNP-TEP-301 proptosis non-responders in the Follow-Up Period.

9. ANALYSIS OF PHARMACOKINETICS

PK blood samples will be collected at pre-dose (within 1 hour prior to infusion) and the end of infusion at Day 1, Weeks 3 and 9, as well as single samples at Weeks 1, 4, and 24.

Length of infusion will be approximately 90 min for infusion 1 (Day 1) and 2 (Week 3) while 60 min for remaining doses. Pre-dose PK sampling will be considered as time 0 and the end of infusion time will be recorded.

The following presentations of subject serum concentration data covered in this SAP will be provided for teprotumumab for the PK Population:

- A listing including subject, week/time point (actual, planned), treatment and serum concentrations. Actual end of infusion sampling times are expressed relative to the start time of infusion.

- A table summary of serum concentrations at each time point (n, mean, SD, coefficient of variation (CV)% calculated as $100\% \times SD/mean$, minimum, 25^{th} percentile, median, 75^{th} percentile and maximum)

Concentrations below the limit of quantification (BLQ) collected on Day 1 pre-dose will be summarized as zero. All other concentrations BLQ will be excluded from the analysis summaries.

An additional analysis of PK is described in Section 10.4.

10. SAFETY

Safety analyses will be based on the ITT Population. Safety will be assessed on the basis of AEs, concomitant medication use (refer to Section 0), immunogenicity testing, physical examinations, ophthalmic examinations, vital signs, clinical safety laboratory evaluations, pregnancy tests, and ECGs. All safety information will be provided in subject listings.

10.1. EXTENT OF EXPOSURE

Study drug exposure will be measured as the number of study drug doses administered in HZNP-TEP-302 and HZNP-TEP-301/HZNP-TEP-302 combined (including any incomplete doses), the number of days on drug in HZNP-TEP-302 and HZNP-TEP-301/HZNP-TEP-302 combined, the total duration of treatment with HZN-001, and the number of days on study in HZNP-TEP-302. The number of doses administered will be summarized by treatment received in HZNP-TEP-301 and overall as the count and percentage of subjects receiving each number of doses, as well as a continuous variable. Further, the number of days on drug and on study will be summarized descriptively by treatment received in HZNP-TEP-301 and overall and calculated as follows:

- Number of days on drug in HZNP-TEP-302 = last dose date in HZNP-TEP-302 - first dose date in HZNP-TEP-302 + 1
- Total number of days on drug in HZNP-TEP-301/HZNP-TEP-302 combined:
    - For subjects receiving Placebo in HZNP-TEP-301 = Number of days on drug in HZNP-TEP-302
    - For subjects receiving HZN-001 in HZNP-TEP-301 = Number of days on drug in HZNP-TEP-302 + (last dose date in HZNP-TEP-301 - first dose date in HZNP-TEP-301) + 1
- Total duration of treatment with HZN-001 = last dose date in HZNP-TEP-302 - first dose date of HZN-001 (whether in HZNP-TEP-301 or HZNP-TEP-302) + 1
- Number of days on study in HZNP-TEP-302 (Treatment Period):
    - For subjects who discontinue during the Treatment Period = discontinuation date in HZNP-TEP-302 - first dose date in HZNP-TEP-302 + 1
    - For subjects who complete the Treatment Period = Week 24 visit date in HZNP-TEP-302 - first dose date in HZNP-TEP-302 + 1
- Number of days on study in HZNP-TEP-302 (Follow-Up Period):

- Subjects who do not enter the Follow-Up Period in HZNP-TEP-302 (i.e., discontinue study during the Treatment Period or complete the study at the end of the Treatment Period) will not contribute to this analysis
- For subjects who participate in the Follow-Up Period = Follow-Up Period completion/discontinuation date in HZNP-TEP-302 - Week 24 (or PW) visit date in HZNP-TEP-302 + 1

- Number of days on study in HZNP-TEP-302 (overall) = study discontinuation date/completion date in HZNP-TEP-302 (study visit completion/discontinuation) - first dose date in HZNP-TEP-302 + 1

A separate summary will also be provided by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301).

10.2. TREATMENT COMPLIANCE

A descriptive summary will be provided for the count and percentages of subjects with each of the following at any infusion visit:

- Planned doses that were not administered completely
- Infusion interruptions

Summaries will be provided by treatment received in HZNP-TEP-301 and overall. A separate summary will also be provided by subject enrollment type (subjects who were proptosis non-responders in HZNP-TEP-301, subjects who relapsed during the Follow-Up Period in HZNP-TEP-301).

10.3. ADVERSE EVENTS

All adverse events will be coded using MedDRA version 20.1. The TEAE reporting period begins with administration of the first dose of study medication on HZNP-TEP-302 Day 1 and continues until 3 weeks (21 days) after the last dose of study drug. The Follow-Up AE reporting period begins 3 weeks (21 days) after the last dose of study drug through completion of the Follow-Up Period (Week 48 or PW).

Missing data conventions for AEs are described in Section 6.3.4.

An overall summary of TEAEs will be provided by treatment received in HZNP-TEP-301 and overall, including the number and percentage of subjects with each AE type as well as the number of events for each of the following:

- TEAEs

- Serious TEAEs
- Related TEAEs
- Related serious TEAEs
- TEAEs with an intensity of severe or higher
- TEAEs leading to interruption of study drug administration
- TEAEs leading to permanent withdrawal of study drug
- Related TEAEs leading to permanent withdrawal of study drug
- TEAEs leading to study discontinuation
- Related TEAEs leading to study discontinuation
- TEAEs leading to death

Additional TEAE summaries will be provided by treatment received in HZNP-TEP-301 and overall, including the number and percentage of subjects experiencing TEAEs for the following:

- TEAEs overall and by SOC and PT, including the following subgroup analyses:
    - Age (<65 years, ≥65 years)
    - Gender (male, female)
    - Race (white, black or African American, Asian, other)
    - Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Related TEAEs overall and by SOC and PT
- TEAEs by maximum intensity, overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- Related TEAEs by intensity, overall and by SOC and PT
- TEAEs leading to permanent withdrawal of study drug, overall and by SOC and PT

- TEAEs of special interest including potential infusion-related reaction, anaphylactic reaction, hearing loss, hyperglycemia, muscle spasm, and diarrhea (see Section 10.3.1), by SOC, PT and overall

- TEAEs of special interest with missing AE start times including potential infusion-related reaction of any type, infusion-related reaction excluding those of an anaphylactic nature, and anaphylactic reactions (see Section 10.3.1), by SOC, PT and overall

For summaries by SOC, PT, and maximum intensity, a subject will only be counted once for each SOC based on the maximum intensity level reported for that SOC and once for each unique PT within that SOC level at the maximum intensity level reported for that PT. For summaries by SOC and PT only, a subject will be counted at most once at the SOC level and at most once at each unique PT within the SOC level. Summaries presenting the frequency of TEAEs by SOC and PT will be ordered alphabetically by SOC and then, within a SOC, alphabetically by PT.

The aforementioned summaries will be repeated for AEs occurring during the Follow-Up Period with the exception of AEs leading to permanent withdrawal of study drug. Denominators for the Follow-Up Period AE summaries will be based on the number of subjects entering the Follow-Up Period (i.e., complete or discontinue study after Week 24/last treatment).

In addition to a listing of all AEs, separate listings will be provided for serious AEs, AEs leading to withdrawal of study drug, AEs leading to study discontinuation, AEs of special interest, and AEs leading to death. TEAEs will be identified on each listing.

10.3.1. Adverse Events of Special Interest

Adverse events of special interest will be identified as follows:

- Potential infusion-related reactions: TEAEs that occur within 2 hours after initiating infusion

- Anaphylactic reactions: TEAEs that occur within 2 hours after initiating infusion and meet any one of the 3 criteria from Section 2.6.3 of the Introductory Guide for Standardised MedDRA Queries (SMQs) (MedDRA, 2017):

    - A narrow term or a term from Category A

    - A term from Category B AND a term from Category C

    - A term from Category D AND [a term from Category B OR a term from Category C]

- Hyperglycemia: TEAEs by any PTs under the SMQ "Hyperglycaemia/new onset diabetes mellitus" (narrow).

- Muscle spasm: TEAEs by the PT "muscle spasm"

- Diarrhea: TEAEs by any PTs under the SMQ "Noninfectious diarrhea" (broad search)

- Hearing loss: TEAEs by any PTs under the SMQ "Hearing impairment" (a sub-SMQ under "Hearing and vestibular disorders") and HLT "Hearing losses"

- Potential infusion-related reactions of any type that are missing the onset time: TEAEs that are missing the AE start time, occur on the day of an infusion and meet one of the following criteria:

    - SMQ Angioedema (broad)
    - SMQ Hypersensitivity (broad)
    - SMQ Hypertension (narrow)
    - SMQ Anaphylactic reactions - meet any of the 3 criteria from Section 2.6.3 of the Introductory Guide for SMQs (MedDRA, 2017):
        - A narrow term or a term from Category A
        - A term from Category B AND a term from Category C
        - A term from Category D AND [a term from Category B OR a term from Category C]

    - HLTs: "Rashes, eruptions and exanthems NEC", "Erythemas", "Pruritus NEC"
    - PTs: Pyrexia, Flushing, Feeling hot, Chest pain, Chest discomfort, Myalgia, Myalgia intercostal, Back pain, Dizziness

- Potential infusion-related reactions excluding those of an anaphylactic nature that are missing the onset time: TEAEs that are missing the AE start time, occur on the day of an infusion and meet one of the following criteria:

    - SMQ Angioedema (broad)
    - SMQ Hypersensitivity (broad)
    - SMQ Hypertension (narrow)
    - HLTs: "Rashes, eruptions and exanthems NEC", "Erythemas", "Pruritus NEC"
    - PTs: Pyrexia, Flushing, Feeling hot, Chest pain, Chest discomfort, Myalgia, Myalgia intercostal, Back pain, Dizziness

- Anaphylactic reactions that are missing the onset time: TEAEs that are missing the AE start time, occur on the day of an infusion AND meet any one of the 3 criteria from Section 2.6.3 of the Introductory Guide for Standardised MedDRA Queries (SMQs) (MedDRA, 2017):

- A narrow term or a term from Category A
- A term from Category B AND a term from Category C
- A term from Category D AND [a term from Category B OR a term from Category C]

10.4. IMMUNOGENICITY

Serum samples will be collected prior to dose at Day 1, Weeks 3, 9, 24, 36 and 48 (or PW). If a subject tests positive for ADA after confirmatory and reactive titer testing, the sample will then be tested for neutralizing antibody (NAb). If the subject tests positive for NAb, he/she will be followed until levels either revert to Study Baseline or the subject's value decreases or remains stable.

Immunogenicity endpoints include:

- Incidence of ADA and NAb (out of positive ADA samples, if applicable) by visit and provided by treatment received in HZNP-TEP-301

The count and percent of subjects will also be provided by treatment received in HZNP-TEP-301 for the following:

- Overall positive ADA result, defined as at least one confirmed positive antibody
- Cumulative negative ADA result, defined as negative ADA results at all time points for a subject
- A negative ADA on HZNP-TEP-302 Day 1 and a positive result at any post-dose visit

Immunogenicity sampling times and results will be listed.

Further, the mean and CV% (calculated as $100\% \times SD/mean$) of pre-dose serum concentrations will be provided by visit in the subset of subjects who are confirmed ADA positive, NAb positive (if applicable) and ADA negative for each visit. This analysis will be provided for the PK Population.

10.5. PHYSICAL EXAMINATION

A physical examination will be performed at Baseline (Day 1) and thereafter at Weeks 1, 6, 12, 18, 24 or PW during the Treatment Period and at Weeks 48 (or PW) of the Follow-Up Period. The physical examination will include assessment of presence or absence of pretibial myxedema on Day 1 and Week 24 (or PW) of the Treatment Period, and Week

48 (or PW) of the Follow-Up Period. If present, measurements of instep and calf will be taken.

A shift table will be presented providing the count of subjects with a presence or absence of pretibial myxedema at Study Baseline compared to each post-baseline visit for each side by treatment received in HZNP-TEP-301 with percentages based on subjects with a non-missing value at the Study Baseline and post-baseline visit. Further, an overall shift table will be provided capturing the worst assessment between the right and left side at Study Baseline compared to each post-baseline visit.

Similar summaries will be provided comparing to the HZN-001 Baseline.

10.6. OPHTHALMIC EXAMINATION

A complete undilated ophthalmic examination will be performed as part of the physical examination. 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 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.

For each of the assessments (pupil exam, color vision assessment, intraocular pressure, and slit lamp exam), shift tables will be presented providing the count of subjects with each type of finding (normal, abnormal - not clinically significant [NCS], or abnormal - clinically significant [CS]) at Study Baseline compared to each post-baseline visit by treatment received in HZNP-TEP-301 with percentages based on subjects with a non-missing value at the Study Baseline and post-baseline visit. In addition, a summary table will be provided for loss of 2 lines or more of vision (yes or no) including the count and percent of subjects at each post-baseline visit.

Similar summaries will be provided comparing to the HZN-001 Baseline.

10.7. VITAL SIGNS

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. Assessment of vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and temperature will be performed at all clinic visits. On Day 1 and

Week 3, vital signs will be measured at pre- and post-infusion. For all other visits, vital signs will be measured prior to infusion only. 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.

Weight will be measured at baseline and Week 12 and Week 24 (or PW) during the Treatment Period and Week 36 and Week 48 (or PW) during the Follow-Up Period.

Descriptive summaries of observed, change from Study Baseline values, and change from HZN-001 Baseline values will be presented for each vital sign parameter (including weight) by visit and treatment received in HZNP-TEP-301 and overall. Vital sign measurements that are monitored as a result of an infusion-associated event as described above will not be included in the descriptive summaries but will be presented in subject listings.

The following conversion factor will be used to convert any temperatures reported in degrees Fahrenheit to Celsius:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

10.8. CLINICAL LABORATORY SAFETY EVALUATIONS

With the exception of urine pregnancy tests, a central study laboratory will be used for all protocol-specified clinical laboratory parameters. Table 3 provides the schedule of collection.

Table 3 Schedule of Clinical Laboratory Safety Tests, Including Thyroid Panel and Hyperglycemia Monitoring

Analysis Panel	Treatment Period											Follow-Up Period		
	BL[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

BL=Baseline; FT3=free triiodothyronine; FT4=free thyroxine; HbA1C=glycated hemoglobin A1C; M=Month; SCR=Screening; 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 HbA1Cis 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]).

Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings. Clinical laboratory test results (hematology, chemistry, thyroid panels, and urinalysis), their changes from Study Baseline, and their changes from HZN-001 Baseline will be summarized by visit and treatment received in HZNP-TEP-301using descriptive statistics. If a continuous laboratory value is reported as either below or above the limits of quantification, the qualifiers will be dropped and the numeric value used in the analysis (e.g., "< 3" will be summarized as "3" and "> 200" will be summarized as "200"). For hematology, chemistry and thyroid panel, results will be categorized as low, normal, or high based on their normal ranges. For urinalysis tests, results will be classified as normal or abnormal. Results out of range will be identified as such on subject listings. Shift tables for hematology and chemistry panels using categories of low, normal, and high, comparing laboratory test results from

Study Baseline and HZN-001 Baseline to each visit will be presented overall and by treatment received in HZNP-TEP-301 with percentages based on subjects with a non-missing value at Baseline and post-baseline visit. Shift tables for urinalysis results using categories of normal and abnormal, comparing laboratory test results from Study Baseline and HZN-001 Baseline to each visit will be presented overall and by treatment received in HZNP-TEP-301 with percentages based on subjects with a non-missing value at Baseline and post-baseline visit. Additionally, a shift table for glucose by Common Terminology Criteria for Adverse Events (CTCAE) grade and visit will be presented overall and by treatment received in HZNP-TEP-301. Summaries will be provided separately for hyperglycemia and hypoglycemia.

10.9. PREGNANCY TEST

Pregnancy test results will be provided in a listing only.

10.10. ECG

12-lead ECGs will be performed at Baseline and Weeks 3, 6, 12, 24 (or PW) of the Treatment Period, and Week 48 (or PW) of the Follow-Up Period. At infusion visits, ECGs 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 CS or NCS by the investigator.

Descriptive summaries of observed, change from Study Baseline, and change from HZN-001 Baseline values will be presented for each ECG parameter by visit, including RR, PR, QRS, QT, QTc, and QTcF and by treatment received in HZNP-TEP-301 and overall.

ECG shift tables will be presented providing the count of subjects with each type of finding (normal, abnormal - NCS, or abnormal - CS) at Study Baseline and HZN-001 Baseline compared to each post-baseline visit by treatment received in HZNP-TEP-301 with percentages based on subjects with a non-missing value at the Baseline and post-baseline visit.

Further, a summary will be provided of the count and percent of subjects with any post-Baseline assessment overall and by treatment received in HZN-TEP-301 in the following categories:

- QTcF >450 msec (males) or > 470 msec (females)
- QTcF >500 msec

Percentages will be based on the number of subjects with at least one post-Baseline value. Similar summaries will be provided by visit with the denominator based on the

number of subjects with data at the given visit overall and by treatment received in HZNP-TEP-301.

11. INTERIM ANALYSES

There are no planned interim analyses.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Protocol Version 3.0 (31-Jan-2019) specified that safety parameters would be summarized and presented in tables using the Safety Population. Instead, the ITT Population will be used for all summaries of efficacy and safety endpoints as it is expected that these populations will be identical. Also, PK Population was not referenced in the protocol. However, due to the addition of pharmacokinetic sampling and evaluation of pharmacokinetic parameters to the protocol, PK Population will be used for all PK analysis.

Protocol Version 3.0 (31-Jan-2019) referenced analyses relative to Study Baseline only. Analyses relative to HZN-001 Baseline will also be summarized.

Due to COVID-19 subject [redacted] delayed out of visit data will not be included in efficacy analyses. For further details refer to Appendix A.

13. REFERENCE LIST

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.

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.

MedDRA: Introductory Guide for Standardised MedDRA Queries (SMQs) Version 20.1 (Sep 2017). Available at: https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_20_1_english.pdf

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.

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.

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.

14. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in RTF format. Three PDF files will be provided for the final tables, listings, and figures separately.
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 guidance

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color)
- Specialized text styles, such as bolding, italics, borders, and shading will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., m^2, C_{trough}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
  Horizon Pharma USA, Inc.

Protocol No: HZNP-TEP-302

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Population

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and overall column (if applicable).
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be "HZNP-TEP-301 Placebo" followed by "HZNP-TEP-301 HZN-001" (teprotumumab 10 mg/kg first infusion and teprotumumab 20 mg/kg remaining 7 infusions).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;

- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least one subject represented in one or more groups should be included.
- An unknown or missing category should be added to any parameter for which information is not available for one or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to one more significant digit than the original values, and standard deviations should be printed out to two more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean (SD)	XXX.X (X.XX)
Median	XXX.X
Min, Max	XX, XX

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. The denominator for percentages will be identified in footnotes. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Missing descriptive statistics which cannot be estimated should be reported as "NE" for not estimable.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, footnotes and/or programming notes will

identify the selection criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, the subheading will be outputted followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "NA", with the footnote "NA = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as "UN" for missing days and "UNK" for missing months (e.g. UNJUL2000, UNUNK2000). Dates that are missing because they are not applicable for the subject are output as "NA", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or [1], [2], [3], etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the TLF source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted]

[redacted] and [redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. INDEX OF TABLES

Table Number	Title	Population
14.1.1.1	Subject Disposition	All Subjects
14.1.1.2	Subject Visits and Follow-Up Contact Completed	ITT
14.1.2.1	Major Protocol Deviations During Treatment Period	ITT
14.1.2.2	Major Protocol Deviations During Follow-Up Period	ITT
14.1.3.1.1	Demographic and Baseline Characteristics	ITT
14.1.3.1.2	Demographic and Baseline Characteristics by Region	ITT
14.1.3.1.3	Demographic and Baseline Characteristics by Tobacco Use Status	ITT
14.1.3.3	Medical History	ITT
14.1.4.1.1	Prior Medications	ITT
14.1.4.1.2.1	Concomitant Medications during the Treatment Period	ITT
14.1.4.1.2.2	Concomitant Medications during the Follow-Up Period	ITT
14.1.4.1.2.3	Concomitant Thyroid Eye Disease Medications during the Follow-Up and Follow-Up Contact Period	ITT
14.1.4.1.2.4	Thyroid Eye Disease Treatments in the Follow-Up Period and Follow-Up Contact Period	ITT
14.2.1.1.1	Proportion of Proptosis Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye)	ITT
14.2.1.1.2	Proportion of Proptosis Responders Relative to HZN-001 Baseline by Visit (Study Eye and Fellow Eye)	ITT
14.2.1.2	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Tobacco Use Status	ITT
14.2.1.3	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Enrollment Type	ITT
14.2.1.4	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Region	ITT
14.2.1.5	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Site	ITT
14.2.1.6	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Age Group	ITT
14.2.1.7	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Gender	ITT
14.2.1.8	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Race	ITT
14.2.1.9	Proportion of Proptosis Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Ethnicity	ITT
14.2.1.10.1	Time to Proptosis Response (Study Eye)	ITT

14.2.1.10.2	Time to Proptosis Response (Fellow Eye)	ITT
14.2.1.11	Sustained Proptosis Response in the Follow-Up Period	Week 24 Proptosis Responders
14.2.2.1.1	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye)	ITT
14.2.2.1.2	Proportion of CAS Categorical Responders Relative to HZN-001 Baseline by Visit (Study Eye and Fellow Eye)	ITT
14.2.2.2	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Tobacco Use Status	ITT
14.2.2.3	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Enrollment Type	ITT
14.2.2.4	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Region	ITT
14.2.2.5	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Site	ITT
14.2.2.6	Proportion of Complete CAS Responders by Visit (Study Eye)	ITT
14.2.2.7	Sustained CAS Categorical Response in the Follow-Up Period	Week 24 CAS Categorical Responders
14.2.3.1.1	Summary and Change from Study Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye)	ITT
14.2.3.1.2	Summary and Change from HZN-001 Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye)	ITT
14.2.3.2	Summary and Change from Study Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Tobacco Use Status	ITT
14.2.3.3	Summary and Change from Study Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Enrollment Type	ITT
14.2.3.4	Summary and Change from Study Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Region	ITT
14.2.3.5	Summary and Change from Study Baseline in Proptosis (mm) by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Site	ITT
14.2.4.1.1	Proportion of Diplopia Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye)	ITT

14.2.4.1.2	Proportion of Diplopia Responders Relative to HZN-001 Baseline by Visit (Study Eye and Fellow Eye)	ITT
14.2.4.2	Proportion of Diplopia Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Tobacco Use Status	ITT
14.2.4.3	Proportion of Diplopia Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Enrollment Type	ITT
14.2.4.4	Proportion of Diplopia Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Region	ITT
14.2.4.5	Proportion of Diplopia Responders Relative to Study Baseline by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Site	ITT
14.2.4.6.1	Proportion of Diplopia Sustained Responders by Visit (Study Eye)	ITT
14.2.4.6.2	Proportion of Diplopia Sustained 0 by Visit (Study Eye)	ITT
14.2.4.6.3	Proportion of No Diplopia by Visit (Study Eye)	ITT
14.2.5.1	Summary and Change from Study Baseline in GO-QoL Overall Transformed Score by Visit	ITT
14.2.5.2	Summary and Change from Study Baseline in GO-QoL Overall Transformed Score by Visit, Subgroup Analysis by Tobacco Use Status	ITT
14.2.5.3	Summary and Change from Study Baseline in GO-QoL Overall Transformed Score by Visit, Subgroup Analysis by Enrollment Type	ITT
14.2.5.4	Summary and Change from Study Baseline in GO-QoL Overall Transformed Score by Visit, Subgroup Analysis by Region	ITT
14.2.5.5	Summary and Change from Study Baseline in GO-QoL Overall Transformed Score by Visit, Subgroup Analysis by Site	ITT
14.2.6.1	Proportion of Overall Responders by Visit (Study Eye and Fellow Eye)	ITT
14.2.6.2	Proportion of Overall Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Tobacco Use	ITT
14.2.6.3	Proportion of Overall Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Enrollment Type	ITT
14.2.6.4	Proportion of Overall Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Region	ITT
14.2.6.5	Proportion of Overall Responders by Visit (Study Eye and Fellow Eye), Subgroup Analysis by Site	ITT

14.2.6.6	Sustained Overall Response in the Follow-Up Period	Week 24 Overall Responders
14.2.7.1	Individual Clinical Measures of Severity by Visit (Study Eye and Fellow Eye)	ITT
14.2.8.1	Summary and Change from Study Baseline in Adduction, Abduction, Supraduction, and Infraduction by Visit (Study Eye and Fellow Eye)	ITT
14.2.9.1	Summary and Change from Study Baseline in CAS by Visit (Study Eye and Fellow Eye)	ITT
14.2.10.1	Proportion of Categorical Overall Response Status at Week 24 (Study Eye and Fellow Eye)	ITT
14.2.11.1	Summary and Change from Study Baseline in Transformed GO-QoL Score by Visit - Visual Functioning and Appearance	ITT
14.2.12.1	Investigator Assessment of Active Disease by Visit	ITT
14.2.13	Summary of Serum Concentrations of HZN-001 (ng/mL)	PK
14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events During the Treatment Period	ITT
14.3.1.1.2	Overall Summary of Adverse Events During the Follow-Up Period	ITT
14.3.1.2.1.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.2.1.2	Adverse Events by System Organ Class and Preferred Term During the Follow-Up Period	ITT
14.3.1.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period, Subgroup Analysis by Age Group	ITT
14.3.1.2.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period, Subgroup Analysis by Gender	ITT
14.3.1.2.4	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period, Subgroup Analysis by Race	ITT
14.3.1.2.5	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period, Subgroup Analysis by Ethnicity	ITT
14.3.1.3.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity During the Treatment Period	ITT
14.3.1.3.2	Adverse Events by System Organ Class, Preferred Term and Maximum Intensity During the Follow-Up Period	ITT

14.3.1.4.1	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.4.2	Treatment-Related Adverse Events by System Organ Class and Preferred Term During the Follow-Up Period	ITT
14.3.1.5.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.5.2	Serious Adverse Events by System Organ Class and Preferred Term During the Follow-Up Period	ITT
14.3.1.6	Treatment-Emergent Adverse Events Leading to Permanent Withdrawal of Study Drug by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.7.1	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.7.2	Treatment-Emergent Adverse Events of Special Interest with a Missing Onset Time by System Organ Class and Preferred Term During the Treatment Period	ITT
14.3.1.7.3	Adverse Events of Special Interest by System Organ Class and Preferred Term During the Follow-Up Period	ITT
14.3.1.8.1	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity During the Treatment Period	ITT
14.3.1.8.2	Treatment-Related Adverse Events by System Organ Class, Preferred Term and Maximum Intensity During the Follow-Up Period	ITT
14.3.4.1.1.1.1	Summary and Change from Study Baseline in Hematology Laboratory Test Results	ITT
14.3.4.1.1.1.2	Summary and Change from HZN-001 Baseline in Hematology Laboratory Test Results	ITT
14.3.4.1.1.2.1	Hematology Laboratory Test Results Shift from Study Baseline	ITT
14.3.4.1.1.2.2	Hematology Laboratory Test Results Shift from HZN-001 Baseline	ITT
14.3.4.1.2.1.1	Summary and Change from Study Baseline in Chemistry Laboratory Test Results	ITT
14.3.4.1.2.1.2	Summary and Change from HZN-001 Baseline in Chemistry Laboratory Test Results	ITT
14.3.4.1.2.2.1	Chemistry Laboratory Test Results Shift from Study Baseline	ITT
14.3.4.1.2.2.2	Chemistry Laboratory Test Results Shift from HZN-001 Baseline	ITT

14.3.4.1.2.3.1	Glucose Shift from Study Baseline by CTCAE Grade	ITT
14.3.4.1.2.3.2	Glucose Shift from HZN-001 Baseline by CTCAE Grade	ITT
14.3.4.1.3.1	Summary and Change from Study Baseline in Urinalysis Continuous Laboratory Test Results	ITT
14.3.4.1.3.2	Summary and Change from HZN-001 Baseline in Urinalysis Continuous Laboratory Test Results	ITT
14.3.4.1.3.2	Categorical Urinalysis Laboratory Test Results	ITT
14.3.4.1.3.3.1	Urinalysis Test Results Shift from Study Baseline	ITT
14.3.4.1.3.3.2	Urinalysis Test Results Shift from HZN-001 Baseline	ITT
14.3.4.1.4.1.1	Summary and Change from Study Baseline in Thyroid Panel Laboratory Test Results	ITT
14.3.4.1.4.1.2	Summary and Change from HZN-001 Baseline in Thyroid Panel Laboratory Test Results	ITT
14.3.4.1.4.2.1	Thyroid Panel Laboratory Test Results Shift from Study Baseline	ITT
14.3.4.1.4.2.2	Thyroid Panel Laboratory Test Results Shift from HZN-001 Baseline	ITT
14.3.4.2.1	Summary and Change from Study Baseline in Vital Signs	ITT
14.3.4.2.2	Summary and Change from HZN-001 Baseline in Vital Signs	ITT
14.3.4.3.1.1	Summary and Change from Study Baseline in ECG Parameters	ITT
14.3.4.3.1.2	Summary and Change from HZN-001 Baseline in ECG Parameters	ITT
14.3.4.3.2.1	Overall ECG Shift from Study Baseline	ITT
14.3.4.3.2.2	Overall ECG Shift from HZN-001 Baseline	ITT
14.3.4.3.3	Categorical ECG Results	ITT
14.3.4.4.1.1	Physical Examination (Pretibial Myxedema) Shift from Study Baseline	ITT
14.3.4.4.1.2	Physical Examination (Pretibial Myxedema) Shift from HZN-001 Baseline	ITT
14.3.4.4.2.1	Ophthalmic Examination Shift from Study Baseline	ITT
14.3.4.4.2.2	Ophthalmic Examination Shift from HZN-001 Baseline	ITT
14.3.4.4.2.3	Ophthalmic Examination Loss of 2 Lines of Vision or More	ITT
14.3.4.4.3	Incidence of Anti-Drug Antibody	ITT
14.3.4.4.4	Summary of Serum Concentrations of HZN-001 (ng/mL) by Presence of Anti-Drug Antibody	PK
14.3.4.5.1.1	Extent of Exposure in HZNP-TEP-302	ITT
14.3.4.5.1.2	Extent of Exposure in HZNP-TEP-301 and HZNP-TEP-302 Combined	ITT

14.3.4.5.2.1	Extent of Exposure in HZNP-TEP-302, Subgroup Analysis by Enrollment Type	ITT
14.3.4.5.2.2	Extent of Exposure in HZNP-TEP-301 and HZNP-TEP-302 Combined, Subgroup Analysis by Enrollment Type	ITT

17. INDEX OF FIGURES

Figure Number	Title	Population
14.2.1.11.1	Proportion of Proptosis Responders Relative to Study Baseline by Visit	ITT
14.2.1.11.2	Proportion of Proptosis Responders Relative to HZN-001 Baseline by Visit	ITT
14.2.1.12.1	Time to Proptosis Response (Study Eye)	ITT
14.2.1.12.2	Time to Proptosis Response (Fellow Eye)	ITT
14.2.2.8.1	Proportion of CAS Categorical Responders Relative to Study Baseline by Visit	ITT
14.2.2.8.2	Proportion of CAS Categorical Responders Relative to HZN-001 Baseline by Visit	ITT
14.2.3.6.1	Mean Change from Study Baseline in Proptosis by Visit	ITT
14.2.3.6.2	Mean Change from HZN-001 Baseline in Proptosis by Visit	ITT
14.2.4.7.1	Proportion of Diplopia Responders Relative to Study Baseline by Visit	ITT
14.2.4.7.2	Proportion of Diplopia Responders Relative to HZN-001 Baseline by Visit	ITT
14.2.5.6	Mean Change from Study Baseline in GO-QoL Overall Transformed Score by Visit	ITT
14.2.6.7	Proportion of Overall Responders by Visit	ITT

18. INDEX OF LISTINGS

Listing Number	Title	Population
16.2.1	Subject Disposition	All Subjects
16.2.2.1	Masked Protocol Deviations	All Subjects
16.2.2.2	Unmasked Protocol Deviations	All Subjects
16.2.3.1	Inclusion/Exclusion Criteria - Description	
16.2.3.2	Inclusion/Exclusion Criteria Not Met	All Subjects
16.2.3.3	Analysis Populations	All Subjects
16.2.3.4.1	Subject Visits and Follow-Up Contact	All Subjects
16.2.3.4.2	Phone or Email Contact	All Subjects
16.2.4.1	Subject Demographics	All Subjects
16.2.4.2	Medical History	All Subjects
16.2.4.3	Substance Use	All Subjects
16.2.4.4	Prior and Concomitant Medications	All Subjects
16.2.4.5	Concomitant Procedures	All Subjects
16.2.4.6	Prior and Concomitant Thyroid Eye Disease Medications	All Subjects
16.2.4.7	Thyroid Eye Disease Surgery during Follow-Up Contact Period	All Subjects
16.2.4.8	Thyroid Eye Disease Orbital Radiation during Follow-Up Contact Period	All Subjects
16.2.4.9	Folllow-Up Contact - Thyroid Eye Disease Treatments	All Subjects
16.2.5.1	Study Drug Administration	All Subjects
16.2.5.2	Study Drug Compliance	All Subjects
16.2.5.3	Study Drug Accountability	All Subjects
16.2.6.1.1	Proptosis Responder	All Subjects
16.2.6.1.2	Time to Proptosis Response	All Subjects
16.2.6.1.3	Sustained Proptosis Response in the Follow-Up Period	Week 24 Proptosis Responders
16.2.6.2.1	CAS and Proptosis Categorical Response	All Subjects
16.2.6.2.1.1	Sustained Overall Response in the Follow-Up Period	Week 24 Overall Responders
16.2.6.2.1.2	Sustained CAS Categorical Response in the Follow-Up Period	Week 24 CAS Categorical Responders
16.2.6.2.2	Clinical Activity Score	All Subjects
16.2.6.2.3	Diplopia Response	All Subjects

16.2.6.2.4.1	Clinical Measures of Severity Scores - Exophthalmos (Proptosis), Bases, Subjective Diplopia Score and Eye Muscle Involvement	All Subjects
16.2.6.2.4.2	Clinical Measures of Severity Scores - Lid Aperture, Eyelids and Conjunctival Inflammation	All Subjects
16.2.6.2.4.3	Clinical Measures of Severity Scores - Corneal and Optic Nerve Involvement	All Subjects
16.2.6.2.5.1	Graves' Ophthalmopathy Quality of Life Scale (GO-QoL) - Visual Functioning	All Subjects
16.2.6.2.5.2	Graves' Ophthalmopathy Quality of Life Scale (GO-QoL) - Appearance	All Subjects
16.2.6.2.5.3	Graves' Ophthalmopathy Quality of Life Scale (GO-QoL) - Overall	All Subjects
16.2.6.3	Investigator Assessment of Active Disease	All Subjects
16.2.6.4	Serum Concentrations of HZN-001	All Subjects
16.2.7.1	Adverse Events	All Subjects
16.2.7.2	Serious Adverse Events	All Subjects
16.2.7.3	Adverse Events Leading to Death	All Subjects
16.2.7.4.1	Adverse Events Leading to Permanent Withdrawal of Study Drug	All Subjects
16.2.7.4.2	Adverse Events Leading to Study Discontinuation	All Subjects
16.2.7.5	Adverse Events of Special Interest	All Subjects
16.2.8.1.1	Clinical Laboratory Hematology Test Results	All Subjects
16.2.8.1.2	Clinical Laboratory Chemistry Test Results	All Subjects
16.2.8.1.3	Clinical Laboratory Urinalysis Test Results	All Subjects
16.2.8.1.4	Clinical Laboratory Thyroid Panel Results	All Subjects
16.2.8.1.5.1	Clinical Laboratory Hematology Test Results Outside of Normal Range	All Subjects
16.2.8.1.5.2	Clinical Laboratory Chemistry Test Results Outside of Normal Range	All Subjects
16.2.8.1.5.3	Clinical Laboratory Urinalysis Test Results Outside of Normal Range	All Subjects
16.2.8.1.5.4	Clinical Laboratory Thyroid Panel Test Results Outside of Normal Range	All Subjects
16.2.8.1.6	Pregnancy Test Results	Females of Childbearing Potential
16.2.8.2.1	Vital Signs	All Subjects
16.2.8.2.2	12-Lead ECG Results	All Subjects
16.2.8.2.3	Physical Examination	All Subjects
16.2.8.2.4	Ophthalmic Examination	All Subjects
16.2.8.2.5	Immunogenicity	All Subjects

19. MOCK-UPS

Table, figure and listing mock-ups are provided in a separate file.

20. APPENDIX A: COVID-19 PANDEMIC RELATED UPDATE TO THE ANALYSIS

In this study, the Week 24 assessment for subject [redacted] is the only study-related procedure impacted by the COVID-19 pandemic. The assessment could not occur during the scheduled visit window, as the site had implemented restrictions preventing the subject from returning to the site. The subject had completed treatment and all earlier assessments, with the Week 24 assessment being the only outstanding assessment. Because the Week 24 assessment did not occur within the study window (scheduled to be 3 weeks after the last infusion) due to the effects of the pandemic, the value, if obtained, may not be representative of the planned Week 24 assessment.

Under the planned analysis using the Treatment Policy Strategy estimand, if the visit did not occur, the subject would have been imputed as a non-responder for categorical endpoints of proptosis response, CAS and proptosis categorical response, CAS categorical response, diplopia response and clinical measures of severity categorical response; if the visit occurred outside of the planned window, the values obtained would have been used in the analysis. Instead, the Hypothetical Strategy estimand will be used, with the analysis ignoring outcomes that are missed or are obtained well outside of the planned window due to the effects of the pandemic. This estimand is an estimator of the outcomes that are expected in a post-pandemic world, and is appropriate if the Week 24 assessment is missing completely at random. The efficacy data that was to be obtained for this subject at Week 24 will be omitted from the analysis. The subject will not count as a responder or non-responder in this analysis. Continuous data will be analyzed without imputation or penalty for missing data.

A separate narrative regarding this subject, including any out-of-window efficacy data, will be included in the clinical study report.