CLINICAL TRIAL PROTOCOL
FOR TEPEZZA (teprotumumab-trbw)

Protocol Number: HZNP-TEP-403

A Phase 4, Randomized, Double-masked, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of TEPEZZA® in Treating Patients with Chronic (Inactive) Thyroid Eye Disease

Version 5.0, Amendment 4.0

19 May 2023

Sponsor:
Horizon Therapeutics U.S.A., Inc.
1 Horizon Way
Deerfield, IL 60015

PROTOCOL

1 TITLE PAGE

Trial Title:	A Phase 4, Randomized, Double-masked, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of TEPEZZA® in Treating Patients with Chronic (Inactive) Thyroid Eye Disease
Protocol Number:	HZNP-TEP-403
Version:	5.0, Amendment 4.0
Investigational Product:	TEPEZZA (teprotumumab-trbw; HZN-001)
Indication:	Chronic (Inactive) Thyroid Eye Disease (TED)
Sponsor:	Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015
Development Phase:	4
Sponsor's Responsible Medical Officer:	PPD Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015
Approval Date:	19 May 2023

CONTACT IN THE EVENT OF AN EMERGENCY

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

Fax: PPD
Email: clinicalsafety@horizontherapeutics.com

SPONSOR SIGNATURE PAGE

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Version Date:	19 May 2023

Approved by:

PPD

PPD
Horizon Therapeutics U.S.A., Inc.

Date

PPD

PPD
Horizon Therapeutics U.S.A., Inc.

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number:	HZNP-TEP-403
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I agree to conduct the trial according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a patient.

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

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

Signature:

_____ _____

Name
Trial Center
Address
City State Country

Date

SUMMARY OF CHANGES
Protocol HZNP-TEP-403
Version 5.0, Amendment 4.0

Key revisions and clarifications to Version 5.0, Amendment 4.0 of the protocol include:

- Per a recent Investigator's Brochure update (Ed. 14), revisions were made to safety and AESI language around hyperglycemia/diabetic complications, muscle spasms, infusion-related reactions, inflammatory bowel disease and hearing loss.
- In-text references were added to Section 7.1.1 Thyroid Eye Disease and Section 7.1.2 TEPEZZA.
- Addition of new reference (Marcovecchio, L. (2017)) to Section 16. References.

SUMMARY TABLE OF CHANGES

Text Administrative Change 1 to Version 4.0, Amendment 3.0 15 December 2022	Amended Text Version 5.0, Amendment 4.0 19 May 2023	Reason for Change
Section 7.1.1 Thyroid Eye Disease The annual incidence rate of TED in the US has been estimated to be 16 cases per 100,000 people for women and 2.9 cases per 100,000 people for men. The incidence appears to be comparable in Europe. Patients aged between 30 and 50 years are most frequently affected, with severe cases more frequent in those over 50 years. The occurrence and severity of TED are associated with smoking. A mounting body of evidence in the scientific literature indicates that the pathophysiology of active TED involves autoimmune activation and proliferation of orbital fibroblasts. The activation of fibroblasts triggers release of inflammatory cytokines, infiltration of immune cells into orbital soft tissue (muscle, interstitial and adipose), excessive synthesis of extracellular matrix and tissue expansion and fibrotic remodeling (ibid). During the inactive phase, inflammation is absent and the disease plateaus, but significant remodeling of orbital tissue remains and rarely does the patient return to Baseline. Clinical features of TED include orbital pain, swelling, dry eye, redness and discomfort of the lids and ocular surface, thickening and retraction of the eyelids and proptosis (exophthalmos) due to the expansion of tissue behind the eye. Although TED is heterogenous and variable and in presentation, proptosis is one of the most prevalent and widely known symptoms of TED. TED has high morbidity. Morbidity takes the form of orbital pain, together with a number of serious, vision or sight threatening condition, including diplopia (due to inability to correctly align the eye), corneal	Section 7.1.1 Thyroid Eye Disease The annual incidence rate of TED in the US has been estimated to be 16 cases per 100,000 people for women and 2.9 cases per 100,000 people for men [Bartley, 1994]. The incidence appears to be comparable in Europe [Abraham-Nordling et al, 2011; Mostbeck et al, 1998; Noth et al, 2001; Tanda et al, 2013]. Patients aged between 30 and 50 years are most frequently affected, with severe cases more frequent in those older than 50 years [Dickinson, 2017]. The occurrence and severity of TED are associated with smoking [Prummel et al, 1993]. A mounting body of evidence in the scientific literature indicates that the pathophysiology of active TED involves autoimmune activation and proliferation of orbital fibroblasts [Bahn, 2010; Boschi et al, 2005; Smith, 2010]. The activation of fibroblasts triggers release of inflammatory cytokines, infiltration of immune cells into orbital soft tissues (muscle, interstitial and adipose), excessive synthesis of extracellular matrix, and tissue expansion and fibrotic remodeling (ibid). During the inactive phase, inflammation is absent and the disease plateaus, but significant remodeling of orbital tissue remains and rarely does the patient return to Baseline. Clinical features of TED include orbital pain, swelling, dry eye, redness and discomfort of the lids and ocular surface, thickening and retraction of the eyelids, and proptosis (exophthalmos) due to the expansion of tissue behind the eye [Bahn, 2010; Burch et al, 1993; Dickinson, 2017; Mallika et al, 2009]. Although TED is heterogenous and variable in presentation,	Updated to include missing in-text references

ulceration (due to inability to close lids) and dysthyroid optic neuropathy (due to proptosis, tissue crowding, and stress on the optic nerve). These combine to produce marked reductions in quality of life (e.g., physical functioning, role functioning, social functioning, mental health, health perceptions and pain). TED can also produce profound psychosocial problems, in particular anxiety and depression, due to the alarming and disfiguring changes in appearance. Taken together, these data show that TED is a physically and emotionally debilitating condition (Figure 7.1).	proptosis is one of the most prevalent and widely known symptoms of TED. Thyroid eye disease has high morbidity [Bartalena et al, 2008; Bartley, 1994; Dickinson, 2017; Gerding et al, 1997]. Morbidity takes the form of orbital pain, together with a number of serious, vision- or sight-threatening conditions, including diplopia (due to inability to correctly align the eyes), corneal ulceration (due to inability to close lids) and dysthyroid optic neuropathy (due to proptosis, tissue crowding, and stress on the optic nerve). These combine to produce marked reductions in quality of life (eg, physical functioning, role functioning, social functioning, mental health, health perceptions and pain) [Gerding et al, 1997; Terwee et al, 2002]. Thyroid eye disease can also produce profound psychosocial problems, in particular anxiety and depression, due to the alarming and disfiguring changes in appearance [Bartley et al, 1996; Coulter et al, 2007; Kahaly et al, 2005]. Taken together, these data show that TED is a physically and emotionally debilitating condition (Figure 7.1).	
Section 7.1.2 TEPEZZA Previous teprotumumab clinical trials for the TED indication include 2 independent, randomized, double-masked, placebo-controlled, parallel-group, multicenter trials (Phase 2 Trial and Phase 3 Trial HZNP-TEP-301 [Douglas et al, 2020])	Section 7.1.2 TEPEZZA Previous teprotumumab clinical trials for the TED indication include 2 independent, randomized, double-masked, placebo-controlled, parallel-group, multicenter trials (Phase 2 Trial TED01RV [Smith et al, 2017] and Phase 3 Trial HZNP-TEP-301 [Douglas et al, 2020]).	Updated to include missing in-text references
Section 9.5.3.1.1.5 Adverse Events of Special Interest Based on previous clinical experience in TED, the following will be AESIs for this trial: • Infusion reactions (e.g., transient increase in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain) • Hyperglycemia • Hearing impairment	Section 9.5.3.1.1.5 Adverse Events of Special Interest Based on previous clinical experience in TED, the following will be AESIs for this trial: • Infusion reactions ~~(e.g., transient increase in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain)~~ • Hyperglycemia • Muscle spasms	Per a recent Investigator's Brochure (edition 14) update, revisions were made to the safety language and AESI sections around diabetic complications, infusion related reactions, IBD and hearing loss.

• New onset inflammatory bowel disease and exacerbation of inflammatory bowel disease Management of infusion reactions and hyperglycemia is described in Section 9.4.6.3.2. Patients experiencing hearing impairment should contact the investigational site for evaluation and assessments. Evaluation may include an audiogram.	• Hearing impairment • New onset inflammatory bowel disease and exacerbation of inflammatory bowel disease **Risk of Hypersensitivity (Infusion-related events)** Administration of mAbs may cause infusion-related symptoms, such as fever, chills, hypotension, shortness of breath, skin rash and headache. Such reactions typically occur during or shortly after the infusion of mAbs and are usually associated with the first infusion. Their incidence and severity typically decrease with subsequent infusions. Severe infusion-related reactions might be clinically indistinguishable from anaphylactic reactions Infusion-related events observed with teprotumumab to date have not been anaphylactic in nature. However, because of the protein nature of teprotumumab and the potential for infusion-related reactions and hypersensitivity reactions, teprotumumab should be administered in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to emergencies. For the first 3 infusions, patients should be monitored for any events during infusion and for 60 minutes after completion of infusion. For subsequent infusions (the fourth dose and beyond), patients who have not previously experienced an infusion reaction should be monitored during the infusion and for at least 30 minutes after the infusion. Patients who exhibit immediate hypersensitivity reactions or infusion-related reactions during an infusion of teprotumumab should have the infusion interrupted or the infusion rate slowed. Symptomatic treatment, e.g., antipyretics, antihistamines and or corticosteroids, oxygen, beta agonists and IV fluids, should be administered to the patient. Following an immediate hypersensitivity	

	reaction or infusion-associated reaction, vital signs (temperature, blood pressure, pulse and respiratory rate) will be monitored every 5 minutes until stable, and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms except in the case of patients who experience an anaphylactic reaction of life-threatening intensity; these patients should be removed from the trial. In general, the decision to keep a patient on trial treatment with teprotumumab should take into consideration potential risks and benefits to the patient. Prior to future infusions of teprotumumab, these patients may be premedicated with IV diphenhydramine 1 to 1.25 mg/kg (maximum 50 mg), IV ranitidine 50 mg, IV famotidine 0.5 mg/kg, IV dexamethasone 0.4 mg/kg (maximum 20 mg) and/or acetaminophen 500 mg. In addition, all future infusions should be administered over 90 minutes. Vital signs should be taken every 15 minutes during the infusion through 60 minutes after infusion completion. Patients who experience delayed-type hypersensitivity reactions (e.g., skin rash) may remain in the trial at the discretion of the Investigator and, prior to all future infusions of teprotumumab, may be premedicated with the above medications (diphenhydramine, ranitidine, famotidine, dexamethasone and acetaminophen). However, if a rash worsens following repeated dosing or other signs of serum sickness (e.g., delayed fever, myalgias, arthralgias) are present, trial drug dosing will be permanently discontinued **Risk of New Onset or Exacerbation of IBD** In Phase 2 TED01RV, 2 teprotumumab-treated patients with a history of IBD reported serious TEAEs (*Diarrhoea* in 1 patient and *Inflammatory bowel disease* in 1 patient) that led to discontinuation of	

	trial drug. Based on these serious events and the fact that a placebo patient with Crohn's disease did not experience these types of events, patients with a history of IBD are either excluded from current trials or must be in clinical remission. Patients who experience progressive and persistent diarrhea or other IBD symptoms, such as bloody stools or abdominal pain, should undergo prompt evaluation to exclude new onset or exacerbation of preexisting IBD or other serious conditions. If possible, medications known to cause diarrhea, such as laxatives and magnesium shall be avoided. If new onset or exacerbation of IBD is suspected, teprotumumab shall be discontinued. **Risk of Hyperglycemia** In nonclinical studies, there was no *in vitro* cross-reactivity of teprotumumab with the insulin receptor. Clinical trials in Active TED have shown a higher incidence of hyperglycemia in patients treated with teprotumumab compared to placebo. Patients with pre-existing diabetes mellitus (who were under appropriate glycemic control upon trial entry) or impaired glucose tolerance were more likely to experience an event of hyperglycemia after exposure to teprotumumab. **Management of Patients with Diabetes Mellitus** Patients with known controlled diabetes mellitus are allowed to participate in trials with teprotumumab. HbA1c levels should be monitored every 6 weeks in these patients. Investigators are strongly encouraged to adjust their patients' diabetes management to maintain HbA1c levels ≤8%. In the event a patient's HbA1c level rises to >8% while in the trial, the Investigator must assess the risk versus benefit for the patient to remain in the	

	trial, discuss with sponsor's medical monitor or designee, and document the decision. **Management of Hyperglycemia** Fasting glucose levels should be tested at Baseline. Random non-fasting glucose levels should be monitored at a minimum as per visit schedule. Patients with recurrent hyperglycemia, defined as a fasting glucose >126 mg/dL, will require evaluation for diabetes mellitus (e.g., fasting glucose, glucose tolerance and HbA1c tests) and appropriate medical management, at the discretion of the Investigator. **Management of Severe Diabetic Complications** Hyperglycemia can cause serious acute complications, presenting as endocrine emergencies, such as Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Both these conditions are caused by relative or absolute insulin deficiency associated with excessive counter-regulatory hormones (glucagon, growth hormone, cortisol, catecholamines) (**Marcovecchio 2017**). Both DKA and HHS are usually triggered by an underlying illness or event such as acute infection, infarction, non-compliance with diet and skipped insulin doses or insulin pump failure. DKA and HHS are life-threatening emergencies. Prompt clinical suspicion and confirmation of these diagnoses is very important. The goal of treatment for DKA and HHS is to correct volume deficits, hyperglycemia, and electrolyte abnormalities which will include, but is not limited to, IV fluid resuscitation, IV insulin, and IV potassium. Every effort should be made to identify the cause, so that future preventive measures can be taken. Participants experiencing DKA or HHS should be discontinued from study treatment. Management of infusion	

	reactions and hyperglycemia is also described in Section 9.4.6.3.2. **Risk of Muscle Spasms** Among teprotumumab-treated patients, *Muscle spasms* was the most commonly reported TEAE in clinical trials of Active TED (Double Masked Treatment Period: 26.2% teprotumumab compared to 7.0% placebo; Open-Label Extension Trial: 41.3%). All events were non-serious and the majority were mild in intensity. If possible, avoid medications known to cause muscle spasms or muscle toxicity, such as diuretics or statins. If muscle spasm occurs, evaluate for other causes of muscle spasm, such as electrolyte abnormalities and dehydration. **Risk of Hearing Impairment** Adverse reactions of middle- to high-range sensorineural hearing loss have been reported in both healthy volunteers and patients with malignancies who received as little as 1 dose of various IGF-1R mAbs. Eighteen events associated with hearing impairment have been observed in 14 teprotumumab treated patients in the TED trials, with no reports observed in placebo treated patients. Each of these events were nonserious, mild or moderate in intensity and none led to premature discontinuation of trial drug; these events usually improved or resolved. If possible, patients should avoid ototoxic drugs while receiving teprotumumab. A review of the post-marketing data in a larger patient population shows that while the reporting rate of hearing impairment related to AEs in a post-marketing setting and the incidence in clinical trials appears similar, there are some post-marketing cases suggestive of greater increased severity (eg, severe or, rarely, permanent hearing impairment) than what was seen	

	in clinical trials. No risk factors were identified based on current available data. In addition, patients experiencing hearing impairment should contact the investigational site for evaluation and assessments. Evaluation may include an audiogram. The audiogram report will include the following: • Pure tone The following tests may also be included: • Speech Recognition • Distortion product otoacoustic emission inner ear hair cell function test • Evaluation of Eustachian tube function Patients experiencing complete or profound hearing loss should be discontinued from study treatment.	
Section 16. References	Section 16. References Marcovecchio, L. (2017). Complications of acute and chronic hyperglycemia. US Endocrinology, 13 (1), 17-21.	Updated to include missing reference (Marcovecchio (2017), Section 9.5.3.1.1.5)

2 SYNOPSIS

Protocol Title: A Phase 4, Randomized, Double-masked, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of TEPEZZA® in Treating Patients with Chronic (Inactive) Thyroid Eye Disease	
Protocol Number: HZNP-TEP-403	**Phase**: 4
Protocol Version: 5.0, Amendment 4.0	
Test Drug: TEPEZZA (teprotumumab-trbw)	**Indication**: Chronic (Inactive) Thyroid Eye Disease (TED)
Number and Country of Sites: Approximately 10 trial centers in the United States.	

Objectives:

The overall objective is to investigate the efficacy, safety and tolerability of TEPEZZA® (teprotumumab-trbw, hereafter referred to as TEPEZZA) in comparison to placebo in treating patients with chronic (inactive) TED.

Primary Objective

The primary objective is to evaluate the effect of TEPEZZA versus placebo on the change of proptosis measurements in the study eye from Baseline at Week 24 in patients with chronic (inactive) TED.

Other Objectives

1. To evaluate the effect of TEPEZZA versus placebo on the proptosis responder rate (i.e., the percentage of patients with a ≥2-mm reduction from Baseline in the study eye without deterioration [≥2-mm increase] of proptosis in the fellow eye) at Week 24.
2. To evaluate the effect of TEPEZZA versus placebo on the change from Baseline at Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire appearance and visual functioning subscales.
3. To evaluate the effect of TEPEZZA versus placebo on the CCI
4. To evaluate the effect of TEPEZZA versus placebo on the CCI CCI
5. To evaluate the effect of TEPEZZA versus placebo on the CCI CCI

Pharmacokinetic and Anti-drug Antibody Objectives

1. To evaluate the pharmacokinetics (PK) of TEPEZZA.
2. To evaluate the immunogenicity of TEPEZZA.

Safety and Tolerability Objectives

To assess safety and tolerability of TEPEZZA versus placebo based on:

1. Adverse events (AEs)
2. AEs of special interest (AESIs) (infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease and exacerbation of inflammatory bowel disease)
3. Vital signs
4. Visual acuity
5. Clinical safety laboratory evaluations (hematology, fasting chemistry, thyroid function tests and glycated hemoglobin [HbA1c])

Exploratory Objective

1. To evaluate the CCI [redacted]
2. To evaluate the CCI [redacted]
3. To evaluate the CCI [redacted]

Trial Design:

This is a randomized, double-masked, placebo-controlled, parallel-group, multicenter trial. Patients will be screened for the trial within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 57 patients who meet the trial eligibility criteria will be randomized on Day 1 in a 2:1 ratio to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo once every 3 weeks (q3W). All patients will enter a 24-week double-masked Treatment Period, during which trial drug will be infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 (with a final visit at Week 24 of the 24-week Treatment Period).

All trial drug dosing will be performed at the clinic or infusion center under adequate healthcare professional supervision. At any scheduled infusion, the infusion rate may be reduced, or the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). On each dosing day, scheduled assessments (except for AE and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to dosing. After each of the first 2 infusions, patients will be contacted by phone/email the following day for safety and tolerability assessments. An additional phone/email contact and clinic visit may be conducted for any patient experiencing an infusion-associated event.

At the end of the double-masked Treatment Period (Week 24), all patients will be assessed for treatment response: proptosis responders (study eye has ≥2-mm reduction in proptosis from Baseline without deterioration [≥2-mm increase in proptosis] in fellow eye) or proptosis non-responders (study eye has <2-mm reduction in proptosis). Proptosis non-responders who have completed the double-masked Treatment Period may choose to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion q3W at Weeks 24, 27, 30, 33, 36, 39, 42 and 45. These patients will return to the clinic at Week 48 for End-of-Treatment assessments, and patients will be contacted by phone/email 30 days after the Week 48 Visit for safety assessment. Proptosis responders, as well as non-responders who choose not to receive TEPEZZA in an open-label fashion, will enter a 30-day Follow-up Period, during which trial drug will not be administered. These patients will be contacted by phone/email 30 days after the Week 24 Visit for safety assessment.

Patients who prematurely discontinue trial drug dosing prior to Week 21 of the double-masked Treatment Period or prior to Week 45 of the open-label Treatment Period will return to the clinic, undergo the scheduled End-of-Treatment assessments (with the exception of the collection of blood samples for biomarker evaluations) and enter the Follow-up Period, provided such continued participation will not detrimentally affect the health, safety and welfare of the patient per Investigator determination. An overview of the trial design is presented in the schematic below, and details of trial activities are provided in Section 2.1, *Schedule of Assessments*.

Screen	BL	Double-masked Treatment Period TEPEZZA or Placebo × 24 Weeks								Open-label Treatment Period[1] (Proptosis Non-responders who Choose to Receive Open-label TEPEZZA)							30-day Follow-up Period[2]
	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
4 weeks predose	Day 1[3]	W3[4]	W6	W9	W12	W15	W18	W21	W24[4,5]	W27[4]	W30	W33	W36	W39	W42	W45	W48[5]
Randomization[1]	←								Trial Week								→

* Infusion of trial drug (TEPEZZA or placebo in double-masked Treatment Period and open-label TEPEZZA in open-label Treatment Period)
BL=Baseline; q3W=once every 3 weeks; W=Week.

1. Patients will be randomized in a 2:1 ratio to receive
   a. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
   b. Placebo (placebo q3W for all 8 infusions).
2. Visit windows are ±3 days for Weeks 3, 6, 9, 12, 15, 18 and 21 of double-masked Treatment Period and Weeks 27, 30, 33, 36, 39, 42 and 45 of open-label Treatment Period; and +7 days for Week 24 of double-masked Treatment Period, Week 48 of open-label Treatment Period and 30-day Follow-up Period.
3. All patients will be contacted by phone/email the day after infusion for the first and second infusions during the double-masked Treatment Period and during the open-label Treatment Period, and thereafter as deemed appropriate; additional phone/email contacts will occur the day after any clinic visit where a patient experiences an infusion-related adverse event.
4. Patients who are proptosis non-responders at Week 24 of the double-masked Treatment Period will be offered the option to receive 8 infusions of TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion.
5. All patients will be contacted via phone or email 30 days (±7 days) following the Week 24 (responders and non-responders who choose not to receive open-label TEPEZZA) or Week 48 (non-responders who receive open-label TEPEZZA) Visit.

Patient Population:

Approximately 57 male or non-pregnant female patients at least 18 years old with chronic (inactive) TED will be enrolled

Inclusion Criteria:

Eligible patients must meet provide all the following criteria:

1. Written informed consent
2. Male or female at least 18 years old at Screening
3. Initial diagnosis of TED >2 years but <10 years prior to Screening. Clinical diagnosis of stable, chronic (inactive) TED, as determined by patient medical records indicating a Clinical Activity Score (CAS) <1 in both eyes for at least 1 year prior to Screening or all of the following:
   a. no progression in proptosis for at least 1 year prior to Screening
   b. if patient has history of diplopia due to TED, no progression in diplopia for at least 1 year prior to Screening
   c. no new inflammatory TED symptoms for at least 1 year prior to Screening.
4. CAS <1 at the Screening and Baseline Visits.
5. Proptosis ≥3-mm increase from the patient's baseline (prior to diagnosis of TED), as estimated by treating physician and or proptosis >3 mm above normal for race and gender.
6. Patients must be euthyroid with the patient's baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.
7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the trial.
8. Diabetic patients must have HbA1c <8.0% at Screening.
9. Patients with a history of inflammatory bowel disease, ulcerative colitis or Crohn's disease must be in clinical remission for at least 3 months, with no history of bowel surgery within 6 months prior to screening and no planned surgery during the trial. Concomitant stable therapies for inflammatory bowel disease without modifications in the 3 months prior to Screening are allowed.

10. Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified time points (i.e., prior to each dose and throughout patient's participation); patients who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, 1 of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least 1 full cycle prior to Baseline and continue for 180 days after the last dose of trial drug. Highly effective contraceptive methods (failure rate <1% per year), when used consistently and correctly, include implants, injectables, combination oral contraceptives, some intrauterine devices, sexual abstinence and vasectomized partner.
11. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion Criteria:

Patients will be ineligible for trial participation if they meet **any** of the following criteria:

1. Decreased best-corrected visual acuity due to optic neuropathy, defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management in the study eye.
3. Decrease in proptosis of ≥2 mm in the study eye between Screening and Baseline.
4. Prior orbital irradiation or orbital decompression in the study eye.
5. Prior strabismus surgery.
6. Alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal or estimated glomerular filtration rate ≤30 mL/min/1.73 m^2 at Screening.
7. Use of any steroid (intravenous, oral, steroid eye drops) for the treatment of TED or other conditions within 3 weeks prior to Screening. Steroids cannot be initiated during the trial. Exceptions include topical and inhaled steroids and steroids used to treat infusion reactions.
8. Any treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the first infusion of trial drug or tocilizumab (Actemra® or Roactemra®) within 6 months prior to the first infusion of trial drug. Use of any other non-steroid immunosuppressive agent within 3 months prior to the first infusion of trial drug.
9. Any previous treatment with TEPEZZA, including previous enrollment in this trial or participation in a prior teprotumumab trial.
10. Treatment with any monoclonal antibody within 3 months prior to Screening.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude trial participation or complicate interpretation of trial results.
12. Use of an investigational agent for any condition within 60 days or 5 half-lives, whichever is longer, prior to Screening or anticipated use during the course of the trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
14. Pregnant or lactating women.
15. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the patient.
16. Known hypersensitivity to any of the components of TEPEZZA or prior hypersensitivity reactions to monoclonal antibodies.

17. Poorly controlled human immunodeficiency virus infection or untreated or positive viral load for hepatitis C or hepatitis B infections 18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the trial
Dose Regimen/Route of Administration: All trial drug dosing will be performed at the clinic or infusion center under adequate healthcare professional supervision. On Day 1 of the double-masked Treatment Period, patients will be randomized in a 2:1 ratio to receive IV infusions of either 1. TEPEZZA (10 mg/kg on Day 1, followed by 20 mg/kg q3W for the remaining 7 infusions), or 2. Placebo (q3W for all 8 infusions) For non-responders that receive open-label treatment following completion of the double-masked Treatment Period, all patients will receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion followed by 20 mg/kg q3W for the remaining 7 infusions) The first 2 infusions of the double-masked and open-label Treatment Periods will be administered over approximately 90 minutes (but not less than 80 minutes). All subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes). For the first 3 infusions, patients will be monitored for any AEs during the infusion and for 60 minutes after completion of the infusion. For subsequent infusions (if no previous infusion reactions), patients will be monitored during and for 30 minutes after completion of the infusion. At any scheduled infusion, the infusion rate may be reduced, or the dose interrupted or held based on tolerability (see Section 9.4.6.3.2 for details).
Dosage Form and Strength Formulation: TEPEZZA 500 mg will be provided in single-dose 20-mL glass vials as a freeze-dried powder. Each vial of TEPEZZA will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL teprotumumab antibody. Reconstituted TEPEZZA solution will be further diluted in 0.9% (w/v) sodium chloride solution prior to administration. Doses less than 1800 mg will be administered in a total infusion volume of 100 mL, and doses 1800 mg and above 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 TEPEZZA 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 TEPEZZA solution based on the patient's dose and body weight will be withdrawn from the reconstituted TEPEZZA vial(s) and transferred into an intravenous bag containing normal saline (0.9% sodium chloride) to prepare a diluted solution with total volume of 100 mL (for doses <1800 mg) or 250 mL (for doses ≥1800 mg). Placebo will consist of a normal saline (0.9% NaCl) solution and will be administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.
Duration of Treatment and Follow-up: The planned duration of the double-masked Treatment Period is 24 weeks. The planned duration of the open-label Treatment Period is 24 weeks. Patients will enter a 30-day Follow-up Period at the end of either the double-masked or open-label Treatment Period.

Criteria for Evaluation:

At the Baseline (Day 1) Visit, the "study eye" (i.e., the eye with most significant proptosis) will be identified. If both eyes are affected equally, the Investigator will choose the "study eye." Both eyes will be assessed for efficacy, but the study eye will be used to assess the primary efficacy endpoint.

Efficacy will be assessed by proptosis (measured as proptosis evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CCI [redacted] quality of life (using the GO-QoL questionnaire) and, CCI [redacted]

Safety will be assessed via AE (including AESIs) and concomitant medication use monitoring, immunogenicity testing, best-corrected visual acuity, vital signs, clinical safety laboratory evaluations (complete blood count and fasting chemistry [including thyroid panel and HbA1c]) and pregnancy testing (if applicable).

Patients experiencing hearing impairment should contact the investigational site for evaluation and assessments. Evaluation may include an audiogram.

Statistical Analyses:

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline at Week 24 in proptosis in the study eye.

Other Efficacy Endpoints

1. The proptosis responder rate (percentage of patients 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.
2. The change from Baseline at Week 24 in the GO-QoL questionnaire appearance and visual functioning subscales.
3. CCI [redacted]
4. CCI [redacted]
5. CCI [redacted]

Pharmacokinetic and Anti-drug Antibody Endpoints

1. The peak and trough concentrations of TEPEZZA.
2. The anti drug antibody (ADA) incidence and titers.

Safety and Tolerability Endpoints

1. The incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), TEAEs resulting in premature discontinuation of treatment and AESIs (infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease and exacerbation of inflammatory bowel disease).
2. The incidence of ≥Grade 3 TEAEs.
3. The change from Baseline to each scheduled visit in vital signs (blood pressure, heart rate, respiratory rate and temperature).
4. The results of best-corrected visual acuity.
5. The incidence of ≥Grade 3 fasting glucose values.
6. The change from Baseline to each scheduled visit in laboratory evaluations (hematology and fasting chemistry [including thyroid panel and HbA1c]).

Exploratory Endpoints

1. CCI
2.
3.

Statistical Analyses:

Statistical Analysis

Efficacy analyses will be performed on the intent-to-treat (ITT) set, consisting of patients who are randomized to trial drug (either TEPEZZA or placebo). Safety analyses will be performed on the safety set, consisting of patients who receive at least 1 dose of trial drug. The PK analysis set will include all patients who receive at least 1 dose of trial drug and have at least 1 post-dose PK sample.

Efficacy

Primary efficacy endpoint analysis:

The primary efficacy analysis will be conducted on the ITT set. A Mixed-Model for Repeated-Measures (MMRM) analysis of covariance model fitting to the individual change from Baseline scores for the study eye will be used for the analysis of change from Baseline in proptosis. The model includes Baseline score, treatment group, visit, visit-by-treatment and visit-by-Baseline score as covariates. The unstructured covariance will be used. The treatment difference (TEPEZZA minus placebo) based on the estimated least squares (LS) means at Week 24 will be presented with associated standard error (SE), 95% confidence interval (CI) and p-value.

The other endpoints of the proptosis responder rate, CCI CCI will assess risk difference (difference in response rates). A 95% exact CI will be provided for each risk difference observed between the treatment groups. Patients whose Week 24 evaluation is missing will be considered treatment failures (non-responders) for the responder analysis. CCI

CCI

Remaining other or exploratory endpoints analyzing change from Baseline (i.e., GQ-QoL, CCI CCI will use the same MMRM method specified for the primary efficacy endpoint.

Descriptive summaries for CCI CCI CCI

Safety and Tolerability

The number and percentage of patients experiencing at least 1 occurrence of a TEAE, SAE, TEAE resulting in premature discontinuation of treatment and AESI for each unique System Organ Class and Preferred Term will be summarized by treatment group. TEAEs and SAEs will be summarized by severity and relationship to trial drug, as assessed by the Investigator. Grade 3 and higher TEAEs, as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), will also be summarized for each unique System Organ Class and Preferred Term.

The number and percentage of patients in each treatment group using concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 term and Preferred Term.

For best-corrected visual acuity, shift tables will be presented providing the count of patients in each treatment group with each type of finding (normal, abnormal – not clinically significant, or abnormal – clinically significant) at Baseline compared to each postbaseline visit.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by treatment group and visit. A shift table for vital signs by NCI-CTCAE grade and visit will be generated by treatment group.

Safety laboratory (hematology and fasting chemistry [including thyroid panel and HbA1c]) values and change from Baseline will be summarized by visit and treatment group using descriptive statistics. The laboratory assessment will be categorized as low, normal or high based on normal ranges and graded using the NCI-CTCAE grading scale, when available. Shift tables using categories of low, normal and high from Baseline to each visit will be generated by treatment group. Additionally, a shift table for glucose by NCI-CTCAE grade and visit will be generated by treatment group. Summaries will be provided separately for hyperglycemia.

The rate and titer of positive ADA samples will be summarized by visit and treatment group using descriptive statistics. Teprotomumab peak and trough (i.e., prior to dose) concentrations will also be summarized by visit using descriptive statistics.

Sample Size Estimate:

A total of 57 patients (38 in the TEPEZZA group and 19 in the placebo group) will be enrolled in the trial to detect at least a 2-mm mean difference between the 2 treatment groups in the change from Baseline of proptosis values at Week 24 in order to have 81% power at the 2-sided 0.05 level of significance. The sample size was determined assuming that the mean difference in proptosis change between the 2 groups is at least 2.0 mm (clinically relevant) and the standard deviation of proptosis change values is 2.5 for both groups (larger than observed in Phase 2 and Phase 3 active TED trials).

2.1 Schedule of Assessments

		Double-masked Treatment Period									Open-label Treatment Period (Proptosis Non-responders who Choose to Receive Open-label TEPEZZA)								30 days[1] after W24 or W48/ EOS/ PW
Trial Visit	**Screening[2]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/EOT1/ PW1[3]**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/EOT2/ PW2[3]**	
Week (W)	**-28 days**	**Day 1/ BL**	**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W27**	**W30**	**W33**	**W36**	**W39**	**W42**	**W45**	**W48**	
Visit Window (+days)			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
Informed consent	X																		
Review inclusion/exclusion criteria	X	X																	
Demographics	X																		
Medical history and prior medications[4]	X	X																	
Weight[5]	X				X					X			X					X	
Randomization[7]		X																	
Efficacy assessments																			
Clinical Measures of Severity includes proptosis and CCI CCI	X	X[8]	X	X		X		X		X[9]	X	X		X		X		X	
CCI		X	X	X		X		X		X	X	X		X		X		X	
	X									X								X	
Clinical Activity Score[11]	X	X				X				X				X				X	
GO-QoL Questionnaire		X		X		X				X		X		X				X	
Treatment response assessment[9]										X									
Safety assessments																			
Pregnancy test[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visual acuity	X[13]	X		X		X		X		X		X		X		X		X	
Vital signs [6]	X	X [6]	X [6]	X	X	X	X	X	X	X[14]	X[14]	X	X	X	X	X	X	X	
Clinical laboratory tests																			
Fasting chemistry	X	X		X		X		X		X		X		X		X		X	
Thyroid function (FT_3, FT_4, TSH)[15]	X	X				X				X				X				X	
Hematology	X	X		X		X		X		X		X		X		X		X	

		Double-masked Treatment Period									Open-label Treatment Period (Proptosis Non-responders who Choose to Receive Open-label TEPEZZA)								30 days[1] after W24 or W48/ EOS/ PW
Trial Visit	**Screening[2]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9/EOT1/ PW1[3]**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/EOT2/ PW2[3]**	
Week (W)	**-28 days**	**Day 1/ BL**	**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W27**	**W30**	**W33**	**W36**	**W39**	**W42**	**W45**	**W48**	
Visit Window (±days)			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**
HbA1c	X[16]	X				X				X				X				X	
ADA/NAb samples[17]		X	X			X				X	X			X				X	
AE, SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic samples[18]		X	X			X				X	X			X				X	
CCI [redacted]		X	X			X				X[20]									
Photographs[21]		X								X								X	
Trial drug infusion		X	X	X	X	X	X	X	X	X[22]	X	X	X	X	X	X	X		
Contact (phone/email) for safety 24 hours post dose[23]		X[23]	X[23]							X[23]	X[23]								

ADA=anti-drug antibody; AE=adverse event; BL=Baseline; EOS=End-of-Study/Trial; EOT=End-of-Treatment; FT_3=free triiodothyronine; FT_4=free thyroxine; GO-QoL=Graves' Ophthalmopathy Quality of Life; HbA1c=glycated hemoglobin; NAb=neutralizing antibody; PW=premature withdrawal; q3W=once every 3 weeks; SAE=serious adverse event; TSH=thyroid-stimulating hormone; W=week.

Footnotes:

1. All patients will be contacted via phone or email 30 days (±7 days) following the Week 24 (responders and non-responders who choose not to receive open-label TEPEZZA) or Week 48 (non-responders who receive open-label TEPEZZA) Visit.
2. Screening procedures can occur over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window.
3. If a patient prematurely discontinues trial drug during the double-masked Treatment Period or the open-label Treatment Period, he/she will return for a clinic visit and undergo the W24/PW1 or W48/PW2 assessments, respectively, with the exception of the collection of blood samples for biomarker evaluations.
4. Medical history will include tobacco, alcohol and other substance use history and thyroid disease history and treatment.
5. Thyroid eye disease must be stable, chronic (inactive) (not progressing, non-sight-threatening but with an appreciable impact on daily life), with thyroid eye disease diagnosed ≥2 years but <10 years prior to Screening.
6. The weight obtained at Screening will be used to calculate dose for Day 1 and Weeks 3, 6 and 9. The weight obtained at Week 9 will be used in dose calculations at Weeks 12, 15, 18 and 21. The dose on Weeks 24, 27, 30 and 33 of the open-label Treatment Period will be based on the Week 24 weight; weight measured at Week 33 will be used in dose calculations at Weeks 36, 39, 42 and 45.
7. On Day 1, patients will be randomized in a 2:1 ratio to receive either: a) TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) or b) placebo (q3W for all 8 infusions); baseline assessments will be performed prior to dosing.

8. Patients who have a >2-mm decrease from Screening in proptosis in the study eye are not eligible for randomization.
9. CCI [redacted]
10. Patients at 1 clinical investigative site will undergo CCI [redacted] during Screening and at the Week 24 Visit and Week 48 Visit (proptosis non-responders who elect to receive open-label TEPEZZA). The Week 24 CCI [redacted] will not need to be performed on the same day as other Week 24 assessments as long as it is performed within the visit window and prior to the Week 24 infusion (proptosis non-responders who elect to receive open-label TEPEZZA). The Week 48 CCI [redacted] will not need to be performed on the same day as other Week 48 assessments as long as it is performed within the visit window.
11. Clinical Activity Score must be <1 in both eyes at the Screening and Baseline Visits.
12. For women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]), a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to dosing at all other visits, as applicable, and at the End-of-Treatment Visit.
13. Patients who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) are not eligible for randomization.
14. Vital signs (blood pressure, heart rate, 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 (all patients), pre- and post-infusion at Week 24 and Week 27 (proptosis non-responders who elect to receive open-label TEPEZZA) and pre-infusion on all other infusion days. Additional vital signs will be monitored if infusion-associated AEs occur (see Section 9.5.3.4 for details).
15. Patients must be euthyroid, with the Baseline disease under control or have mild hypo- or hyperthyroidism (defined as FT_4 and FT_3 levels <50% above or below the normal limits). Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.
16. HbA1c must be ≤8.0% to be eligible for the trial. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 90 days until it returns to normal or Baseline value.
17. ADA sample will be collected prior to the infusion. If the ADA test is positive after confirmatory and reactive titer testing, the sample will then be tested for NAb. If the patient tests positive for NAb, the patient may be followed until levels either return to Baseline or the patient's level decreases or remains stable. ADA samples will be collected during any visit triggered by suspected immunologically related AEs.
18. Pharmacokinetic samples will be collected prior to, and at the end of, the infusion on Day 1, Week 3 and Week 12 of the double-masked Treatment Period (all patients) and Week 24, Week 27 and Week 36 of the open-label Treatment Period (proptosis non-responders who elect to receive open-label TEPEZZA); a single sample will be collected at Week 24 (proptosis responders and proptosis non-responders who elect not to receive open-label TEPEZZA) and Week 48 (proptosis non responders who elect to receive open-label TEPEZZA).
19. CCI [redacted]
20. CCI [redacted]
21. For those patients who have consented, photographs of the patient's eyes will be taken prior to the first infusion and at Week 24 (all patients) and Week 48 (non-responders who elect to receive open-label TEPEZZA).
22. For non-responders who choose to receive open-label treatment, TEPEZZA infusion will be performed at Week 24 (first of 8 infusions). All Week 24 assessments except AE and concomitant medication monitoring, post-infusion PK sample collection and 24-hour post-dose phone/email contact must be completed prior to TEPEZZA infusion.
23. 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 during the double-masked Treatment Period and during the open-label Treatment Period, and thereafter as deemed appropriate. In addition, patients 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.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
CAS	Clinical Activity Score
CFR	Code of Federal Regulations
CI	confidence interval
CRO	Contract Research Organization
EDC	electronic data capture
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GO-QoL	Graves' Ophthalmopathy Quality of Life
HbA1c	glycated hemoglobin
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IGF	insulin-like growth factor
IGF-1R	insulin-like growth factor-1 receptor
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
mAb	monoclonal antibody
MMRM	Mixed-Model for Repeated-Measures
CCI	[redacted]
NaCl	sodium chloride
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PW	premature withdrawal
PW1	premature withdrawal during the double-masked Treatment Period
PW2	premature withdrawal during the open-label Treatment Period
q3W	once every 3 weeks
SAE	serious adverse event
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TED	thyroid eye disease
TEPEZZA	teprotumumab-trbw; HZN-001
US (or U.S.A.)	United States (United States of America)
USP	United States Pharmacopeia
CCI	

Abbreviations that appear only in figures and tables are defined with the relevant figures and tables.

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

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

5.2 Ethical Conduct of the Trial

The Investigators will ensure that this trial is conducted in a manner that fully conforms with the principles of the Declaration of Helsinki or with the laws and regulations of the United States (US), whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline or with local law if it affords greater protection to the patient. For trials conducted in the United States of America (U.S.A.) or under US Investigational New Drug program, the Investigator will additionally ensure adherence to the basic principles of GCP, as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of Sponsors and Investigators," part 50, "Protection of Human Subjects" and part 56, "Institutional Review Boards."

5.3 Patient Information and Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain a signed ICF from each patient prior to participating in this trial after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The Investigator or designee must also explain that patients are completely free to refuse to enter the trial or to withdraw from it at any time, for any reason.

Optional photographic analysis will only be performed if the patient has voluntarily signed and dated the photographic informed consent, approved by an IRB, after the nature of the photographs has been explained and the patient has had an opportunity to ask questions. The

patient must provide consent to be photographed before the procedure is performed. If the patient does not consent to being photographed, it will not impact the patient's participation in the trial.

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

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

The electronic case report forms (eCRFs) for this trial contain a section for documenting all patient informed consents, and this must be completed appropriately.

5.4 Compensation for Health Damage of Patients Insurance

The Sponsor maintains clinical trial insurance coverage for this trial in accordance with the laws and regulations of the US.

5.5 Confidentiality

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

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

If the results of the trial are published, the patient's identity will remain confidential.

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

6 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

The Sponsor of this trial is Horizon Therapeutics U.S.A., Inc. (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see Section 17.1 for details). The Sponsor will be responsible for timely reporting of serious adverse events (SAEs) to regulatory authorities as required. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators as required.

The trial will be conducted at approximately 10 sites in the US. Prior to initiation of the trial, each Investigator will provide the Sponsor or its designee a fully executed and signed Food and Drug Administration (FDA) Form 1572 (or equivalent) and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators. It is the responsibility of the Investigators or sub-investigators to advise the Sponsor of any change in the relevant financial interests that occur during the trial and the 1-year period following its completion.

Table 6.1 lists other organizations critical to the conduct of the trial:

Table 6.1 Table of Non-Sponsor Trial Responsibilities

Trial Responsibility	Organization
Contract research organization	CCI
Clinical drug supply and distribution	
Central safety laboratory	

7 INTRODUCTION

7.1 Background

7.1.1 Thyroid Eye Disease

Thyroid eye disease (TED), also termed Graves' ophthalmopathy/orbitopathy and thyroid-associated ophthalmopathy, is a serious, debilitating and painful autoimmune disease that can, in severe cases, lead to blindness. TED is commonly associated with Graves' hyperthyroidism/disease, but also occurs in a proportion of patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis. The natural history involves an "active TED," which is an autoimmune inflammatory response targeting orbital soft tissues, and "inactive TED," in which there is tissue expansion remodeling. Active TED typically lasts 1 to 3 years, and then the inflammation spontaneously subsides to leave the pathology of inactive TED [Burch et al, 1993].

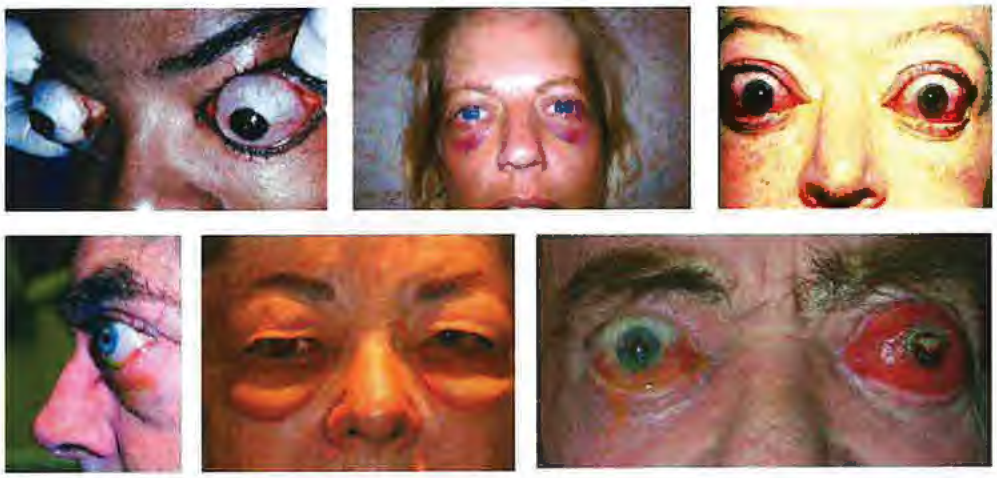
The annual incidence rate of TED in the US has been estimated to be 16 cases per 100,000 people for women and 2.9 cases per 100,000 people for men [Bartley, 1994]. The incidence appears to be comparable in Europe [Abraham-Nordling et al, 2011; Mostbeck et al, 1998; Noth et al, 2001; Tanda et al, 2013]. Patients aged between 30 and 50 years are most frequently affected, with severe cases more frequent in those older than 50 years [Dickinson, 2017]. The occurrence and severity of TED are associated with smoking [Prummel et al, 1993].

A mounting body of evidence in the scientific literature indicates that the pathophysiology of active TED involves autoimmune activation and proliferation of orbital fibroblasts [Bahn, 2010; Boschi et al, 2005; Smith, 2010]. The activation of fibroblasts triggers release of inflammatory cytokines, infiltration of immune cells into orbital soft tissues (muscle, interstitial and adipose), excessive synthesis of extracellular matrix, and tissue expansion and fibrotic remodeling (ibid). During the inactive phase, inflammation is absent and the disease plateaus, but significant remodeling of orbital tissue remains and rarely does the patient return to Baseline.

Clinical features of TED include orbital pain, swelling, dry eye, redness and discomfort of the lids and ocular surface, thickening and retraction of the eyelids, and proptosis (exophthalmos) due to the expansion of tissue behind the eye [Bahn, 2010; Burch et al, 1993; Dickinson, 2017; Mallika et al, 2009]. Although TED is heterogenous and variable in presentation, proptosis is one of the most prevalent and widely known symptoms of TED. Thyroid eye disease has high morbidity [Bartalena et al, 2008; Bartley, 1994; Dickinson, 2017; Gerding et al, 1997]. Morbidity takes the form of orbital pain, together with a number of serious, vision- or sight-threatening conditions, including diplopia (due to inability to correctly align the eyes), corneal ulceration (due to inability to close lids) and dysthyroid optic neuropathy (due to proptosis, tissue crowding, and stress on the optic nerve). These combine to produce marked reductions in quality of life (eg, physical functioning, role functioning, social functioning, mental health, health perceptions and pain) [Gerding et al, 1997; Terwee et al, 2002]. Thyroid eye disease can also produce profound psychosocial problems, in particular anxiety and depression, due to the

alarming and disfiguring changes in appearance [Bartley et al, 1996; Coulter et al, 2007; Kahaly et al, 2005]. Taken together, these data show that TED is a physically and emotionally debilitating condition (Figure 7.1).

Figure 7.1 Thyroid Eye Disease Photographs



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

7.1.2 TEPEZZA®

TEPEZZA® (teprotumumab-trbw, hereafter referred to as TEPEZZA) is a fully human immunoglobulin G1 monoclonal antibody (mAb) directed against human insulin-like growth factor (IGF)-1 receptor (IGF-1R). The IGF-1R is a tyrosine kinase cell surface receptor that shares ~50% overall homology with the insulin receptor [Ullrich et al, 1986]. TEPEZZA binds with high affinity and selectivity to the extracellular domain of IGF-1R and prevents its activation by the endogenous ligands, IGF-1 and IGF-2.

TEPEZZA has no partial agonist activity at IGF-1R, as assessed by activation of the canonical signaling pathway (phosphoinositide 3 kinase/Akt) and has no affinity for the insulin receptor. In addition, TEPEZZA causes direct inactivation of IGF-1R through antibody-induced cellular internalization and degradation. Binding of TEPEZZA has been shown to inhibit canonical signal transduction and cellular proliferation and survival functions mediated by IGF-1R in cancer cells. TEPEZZA does not induce antibody-dependent cellular cytotoxicity.

TEPEZZA® (teprotumumab-trbw) was approved by the US FDA on 21 January 2020 for the treatment of TED.

Previous teprotumumab clinical trials for the TED indication include 2 independent, randomized, double-masked, placebo-controlled, parallel-group, multicenter trials (Phase 2 Trial TED01RV

[Smith et al, 2017] and Phase 3 Trial HZNP-TEP-301 [Douglas et al, 2020]). In these 2 trials, teprotumumab resulted in statistically significant and clinically relevant improvements in measures that assessed multiple facets of TED (proptosis, inflammation as measured by Clinical Activity Score [CAS], diplopia and quality of life). In addition, the persistence of effect was demonstrated after approximately 1 year off treatment. Consistent results were shown across all efficacy endpoints and all subpopulations.

In the Phase 2 trial, the majority of reported adverse events (AEs) were mild, required no treatment and resolved while patients remained on drug. Hyperglycemia, which was monitored by assessing blood glucose and glycated hemoglobin (HbA1c), was the only mechanism-based anticipated AE clearly identified as related to trial drug.

In the Phase 3 trial, teprotumumab was well tolerated and demonstrated an acceptable safety profile, replicating the results of the Phase 2 trial.

7.2 Rationale for this Trial

IGF-1R plays a key role in TED and inhibition of this target blocks the underlying immunopathogenesis that drives the orbital inflammation, excessive synthesis of extracellular matrix and tissue proliferation that are the hallmarks of TED. *In vitro* studies demonstrating the significance of IGF-1R and pharmacologic effects of anti-IGF-1R were performed with human orbital fibroblasts obtained mainly from patients with inactive TED post-decompression surgeries. Thus, TEPEZZA may have the potential to reverse the symptomatology and pathology in patients with inactive TED.

Administering TEPEZZA for the treatment of chronic (inactive) TED may have a beneficial effect in reducing the need for corrective surgeries. Previous clinical experience indicates that, at doses that are pharmacologically relevant for blocking IGF-1R, TEPEZZA produced statistically significant and clinically relevant improvements in measures that assessed multiple facets of active TED (proptosis, inflammation as measured by CAS, diplopia and quality of life). In addition, TEPEZZA has an acceptable safety profile following intravenous (IV) infusion and is, therefore, a suitable drug candidate to be investigated in a chronic (inactive) TED patient population.

Data on natural history of proptosis change were taken from the TEPEZZA Phase 2 and Phase 3 trials. In the Phase 2 and Phase 3 trials, patients entered the trials with TED diagnosis a mean of 5 months prior to enrollment. These patients were followed for 72 weeks. In addition, the majority of the placebo patients (67.87) had a CAS score of less than or equal to 3 out of 7 (defines chronic [inactive] TED for these trials) in the fellow-eye during the treatment period. The findings with regards to proptosis in this patient population are the following: mean change from baseline in proptosis at Week 72 (n=35) for the study eye was -1.2 mm with 95% confidence interval (CI) (-1.84, -0.67), while the non-study eye change from baseline for n=35 was 0.43 with 95% CI (-1.07, 0.21). The mean change in proptosis for the inactive TED population identified above (n=31) was -0.48 with 95% CI (-1.14, 0.17). It is therefore concluded

that patients with TED, who have CAS less than or equal to 3 and were diagnosed with TED at least 2 years prior, will have a decrease from baseline in proptosis of less than 1 mm, on average, without treatment.

7.3 Rationale for Dose Selection

The US FDA-approved dosing duration for TEPEZZA is 10 mg/kg for the first dose followed by 20 mg/kg administered IV once every 3 weeks (q3W) for 7 additional infusions.

Since there is no expected difference in TEPEZZA pharmacokinetic (PK) between active and chronic (inactive) TED patients, the same dose regimen will be used in this trial.

8 TRIAL OBJECTIVES

The overall objective is to investigate the efficacy, safety and tolerability of TEPEZZA® in comparison to placebo in treating patients with chronic (inactive) TED.

8.1 Primary Objective

The primary objective is to evaluate the effect of TEPEZZA versus placebo on the change of proptosis measurements in the study eye from Baseline at Week 24 in patients with chronic (inactive) TED.

8.2 Other Objectives

1. To evaluate the effect of TEPEZZA versus placebo on the proptosis responder rate (i.e., the percentage of patients with a ≥2-mm reduction from Baseline in the study eye without deterioration [≥2-mm increase] of proptosis in the fellow eye) at Week 24.
2. To evaluate the effect of TEPEZZA versus placebo on the change from Baseline at Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire appearance and visual functioning subscales.
3. To evaluate the effect of TEPEZZA versus placebo on the CCI [redacted] CCI [redacted]
4. To evaluate the effect of TEPEZZA versus placebo on the CCI [redacted] CCI [redacted]
5. To evaluate the effect of TEPEZZA versus placebo on the CCI [redacted] CCI [redacted]

8.3 Pharmacokinetic and Anti-drug Antibody Objectives

1. To evaluate the PK of TEPEZZA.
2. To evaluate the immunogenicity of TEPEZZA.

8.4 Safety and Tolerability Objectives

To assess safety and tolerability of TEPEZZA versus placebo based on:

1. AEs
2. AEs of special interest (AESIs) (infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease and exacerbation of inflammatory bowel disease)
3. Vital signs
4. Visual acuity
5. Clinical safety laboratory evaluations (hematology, fasting chemistry, thyroid functinn tests and HbA1c)

8.5 Exploratory Objective

1. To evaluate the CCI [redacted]
2. To evaluate the CCI [redacted]
3. To evaluate the CCI [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Trial Design and Plan

This is a randomized, double-masked, placebo-controlled, parallel-group, multicenter trial. Patients will be screened for the trial within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 57 patients who meet the trial eligibility criteria will be randomized on Day 1 in a 2:1 ratio to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo q3W. All patients will enter a 24-week double-masked Treatment Period, during which trial drug will be infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 (with a final visit at Week 24 of the 24-week Treatment Period).

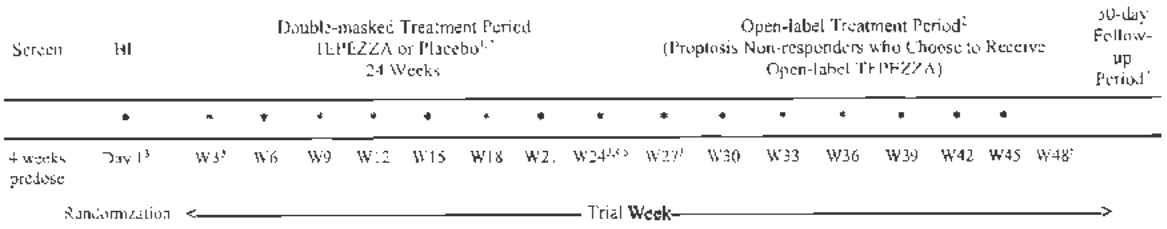
All trial drug dosing will be performed at the clinic or infusion center under adequate healthcare professional supervision. At any scheduled infusion, the infusion rate may be reduced, or the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). On each dosing day, scheduled assessments (except for AE and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to dosing. After each of the first 2 infusions, patients will be contacted by phone/email the following day for safety and tolerability assessments. An additional phone/email contact and clinic visit may be conducted for any patient experiencing an infusion-associated event.

At the end of the double-masked Treatment Period (Week 24), all patients will be assessed for treatment response: proptosis responders (study eye has ≥2-mm reduction in proptosis from Baseline without deterioration [≥2-mm increase in proptosis] in fellow eye) or proptosis non-responders (study eye has <2-mm reduction in proptosis). Proptosis non-responders who have completed the double-masked Treatment Period may choose to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) in an open-label fashion q3W at Weeks 24, 27, 30, 33, 36, 39, 42 and 45. These patients will return to the clinic at Week 48 for End-of-Treatment assessments, and patients will be contacted by phone/email 30 days after the Week 48 Visit for safety assessment. Proptosis responders, as well as non-responders who choose not to receive TEPEZZA in an open-label fashion, will enter a 30-day Follow-up Period, during which trial drug will not be administered. These patients will be contacted by phone/email 30 days after the Week 24 Visit for safety assessment.

Patients who prematurely discontinue trial drug dosing prior to Week 21 of the double-masked Treatment Period or prior to Week 45 of the open-label Treatment Period will return to the clinic, undergo the scheduled End-of-Treatment assessments (with the exception of the CCI [redacted] CCI [redacted]) and enter the Follow-up Period, provided such continued participation will not detrimentally affect the health, safety and welfare of the patient per Investigator determination.

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

Figure 9.1 Schematic of Trial Design



* Infusion of trial drug (TEPEZZA or placebo in double-masked Treatment Period and open-label TEPEZZA in open-label Treatment Period).

BL, Baseline; q3W, once every 3 weeks; W, Week

1. Patients will be randomized in a 2:1 ratio to receive:
   a. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
   b. Placebo (placebo q3W for all 8 infusions)
2. Visit windows are ±3 days for Weeks 3, 6, 9, 12, 15, 18 and 21 of double-masked Treatment Period and Weeks 27, 30, 33, 36, 39, 42 and 45 of open-label Treatment Period, and +7 days for Week 24 of double-masked Treatment Period, Week 48 of open-label Treatment Period and 30-day Follow-up Period.
3. All patients will be contacted by phone/email the day after infusion for the first and second infusions during the double-masked Treatment Period and during the open-label Treatment Period, and thereafter as deemed appropriate; additional phone/email contacts will occur the day after any clinic visit where a patient experiences an infusion related adverse event.
4. Patients who are proptosis non-responders at Week 24 of the double-masked Treatment Period will be offered the option to receive 8 infusions of TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions) in an open-label fashion.
5. All patients will be contacted via phone or email 30 days (±3 days) following the Week 24 (responders and non-responders who choose not to receive open-label TEPEZZA) or Week 48 (non-responders who receive open-label TEPEZZA) Visit.

9.2 Discussion of Trial Design

The trial population is well-defined and consistent with the US FDA-approved indication (for the treatment of TED) in the TEPEZZA prescribing information.

This trial is a randomized, double masked, placebo-controlled, parallel-group, multicenter trial designed according to standard principles for adequate and well-controlled trials. The measurements used in this trial for the efficacy endpoints (proptosis, CCI CCI and GO-QoL questionnaire) are established endpoints in TED clinical trials that have been shown to correlate significantly with TED.

The sample size for this trial was determined assuming that the mean difference in proptosis change between the 2 groups is at least 2.0 mm (clinically relevant) and the standard deviation of proptosis change values is 2.5 for both groups (larger than observed in Phase 2 and Phase 3 active TED trials). A total of 57 patients (38 in the TEPEZZA group and 19 in the placebo group) will be enrolled in the trial to detect at least a 2-mm mean difference between the 2 treatment groups in the change from Baseline of proptosis values at Week 24 in order to have 81% power at the 2-sided 0.05 level of significance.

Given the teratogenic effects of TEPEZZA noted in animal reproduction studies and its mechanism of action (see the current edition of the TEPEZZA Investigator's Brochure), women of childbearing potential who are sexually active with a non-vasectomized male partner are required to use adequate contraception and report any pregnancies for at least 6 months after the last dose of trial drug. Six months after the last dose, the estimated plasma concentration (0.2

µg mL) of teprotumumab is considered reasonably safe with a low risk of teratogenicity and is consistent with the TEPEZZA US Prescribing Information.

9.3 Selection of Trial Population

9.3.1 Inclusion Criteria

Eligible patients must meet provide **all** the following criteria:

1. Written informed consent.
2. Male or female at least 18 years old at Screening.
3. Initial diagnosis of TED ≥2 years but <10 years prior to Screening. Clinical diagnosis of stable, chronic (inactive) TED, as determined by patient medical records indicating a CAS ≤1 in both eyes for at least 1 year prior to Screening or all of the following:
   a. no progression in proptosis for at least 1 year prior to Screening
   b. if patient has history of diplopia due to TED, no progression in diplopia for at least 1 year prior to Screening
   c. no new inflammatory TED symptoms for at least 1 year prior to Screening.
4. CAS ≥1 at the Screening and Baseline Visits.
5. Proptosis >3-mm increase from the patient's baseline (prior to diagnosis of TED), as estimated by treating physician and/or proptosis >3 mm above normal for race and gender.
6. Patients must be euthyroid with the patient's baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.
7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the trial.
8. Diabetic patients must have HbA1c ≤8.0% at Screening.
9. Patients with a history of inflammatory bowel disease, ulcerative colitis or Crohn's disease must be in clinical remission for at least 3 months, with no history of bowel surgery within 6 months prior to screening and no planned surgery during the trial. Concomitant stable therapies for inflammatory bowel disease without modifications in the 3 months prior to Screening are allowed.

10. Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified time points (i.e., prior to each dose and throughout patient's participation); patients who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, 1 of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least 1 full cycle prior to Baseline and continue for 180 days after the last dose of trial drug. Highly effective contraceptive methods (failure rate <1% per year), when used consistently and correctly, include implants, injectables, combination oral contraceptives, some intrauterine devices, sexual abstinence and vasectomized partner.
11. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

9.3.2 Exclusion Criteria

Patients will be ineligible for trial participation if they meet **any** of the following criteria:

1. Decreased best-corrected visual acuity due to optic neuropathy, defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management in the study eye.
3. Decrease in proptosis of ≥2 mm in the study eye between Screening and Baseline.
4. Prior orbital irradiation or orbital decompression in the study eye.
5. Prior strabismus surgery.
6. Alanine aminotransferase or aspartate aminotransferase >3 × the upper limit of normal or estimated glomerular filtration rate ≤30 mL/min/1.73 m^2 at Screening.
7. Use of any steroid (IV, oral, steroid eye drops) for the treatment of TED or other conditions within 3 weeks prior to Screening. Steroids cannot be initiated during the trial. Exceptions include topical and inhaled steroids and steroids used to treat infusion reactions.
8. Any treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the first infusion of trial drug or tocilizumab (Actemra® or Roactemra®) within 6 months prior to the first infusion of trial drug. Use of any other non-steroid immunosuppressive agent within 3 months prior to the first infusion of trial drug.
9. Any previous treatment with TEPEZZA, including previous enrollment in this trial or participation in a prior teprotumumab trial.
10. Treatment with any mAb within 3 months prior to Screening.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude trial participation or complicate interpretation of trial results.

12. Use of an investigational agent for any condition within 60 days or 5 half-lives, whichever is longer, prior to Screening or anticipated use during the course of the trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
14. Pregnant or lactating women.
15. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the patient.
16. Known hypersensitivity to any of the components of TEPEZZA or prior hypersensitivity reactions to mAbs.
17. Poorly controlled human immunodeficiency virus infection or untreated or positive viral load for hepatitis C or hepatitis B infections.
18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the trial.

9.3.3 Removal of Patients from Treatment or the Trial

All patients are free to withdraw from trial participation at any time for any reason and without prejudice to their further medical care. In addition, the Investigator may terminate a patient from treatment or from the trial at any time, if further participation in the trial is not in the best interest of the patient.

9.3.3.1 Discontinuation of Patients from Treatment

The primary reason for discontinuation from trial drug should be recorded on the eCRF using 1 of the following categories:

- AE. The patient experiences an AE that imposes an unacceptable risk to the patient's health, or the patient is unwilling to continue because of an AE. Patients who discontinue trial drug due to an AE will remain in the trial unless they withdraw from the trial for another reason. AEs requiring permanent trial drug discontinuation per the protocol include:
    - A drug-related anaphylactic reaction as defined by Sampson criteria (see Appendix 17.3 for clinical criteria).
    - Diagnosed or suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).
- Lack of Efficacy. Discontinuation of trial drug due to lack of efficacy is at the discretion of the Investigator or patient and may occur if the Investigator determines that trial drug administration is not benefiting the patient. Patients who discontinue trial drug due to

lack of efficacy will remain in the trial unless they withdraw from the trial for another reason.

- Lost to Follow-up. The patient does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the patient.
- Withdrawal by Patient/Guardian. The patient wishes to withdraw from trial drug. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF
- Trial Terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Pregnancy.
- Death.
- Completed. The patient completed treatment.

Patients who prematurely discontinue trial drug prior to Week 21 of the double-masked Treatment Period or who enter the open-label Treatment Period and discontinue trial drug prior to Week 45 of the open-label Treatment Period will return to the clinic, undergo the scheduled End-of-Treatment assessments (with the exception of the CCI CCI and enter the Follow-up Period. Patients who discontinue due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained.

Patients who experience an infusion-associated event after any infusion will be contacted via phone/email the day after the infusion.

9.3.3.2 Removal of Patients from the Trial

The primary reason for discontinuation from the trial should be recorded on the eCRF using 1 of the following categories:

- Lost to Follow-up. The patient does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the patient.
- Withdrawal by Patient/Guardian. The patient wishes to withdraw from the trial. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF.
- Trial Terminated by Sponsor. The Sponsor, IRB or regulatory agency terminates the trial.
- Death.
- Completed. The patient completed the trial.

9.3.4 Replacement Policy

9.3.4.1 Patients

In general, patients prematurely discontinued from the trial for any reason may be replaced at the discretion of the Sponsor. Reasons for patient replacement include, but are not limited to, unevaluability due to the impact of an event, for example, a pandemic or a natural disaster, and associated restrictions on movement and work.

This may result in more patients being enrolled into the trial to allow for the planned number to be evaluable for the primary efficacy and safety analyses.

9.3.4.2 Centers

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

- Excessively slow recruitment.
- Poor protocol adherence.

9.3.4.3 Screen Failures

Patients who do not meet all the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. Screen failures may be allowed to rescreen for the trial if both the Investigator and Sponsor are in agreement regarding rescreening.

9.4 Treatments

9.4.1 Treatments Administered

The first 2 infusions of the double-masked and open-label Treatment Periods will be administered over approximately 90 minutes (but not less than 80 minutes). All subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes). For the first 3 infusions, patients will be monitored for any AEs during the infusion and for 60 minutes after completion of the infusion. For subsequent infusions (if no previous infusion reactions), patients will be monitored during and for 30 minutes after completion of the infusion. At any scheduled infusion, the infusion rate may be reduced or the dose interrupted or held based on tolerability (see Section 9.4.6.3.2 for details).

9.4.1.1 Double-masked Treatment Period

All trial drug dosing will be performed at the clinic or infusion center under adequate healthcare professional supervision. On Day 1 of the double-masked Treatment Period, patients will be randomized in a 2:1 ratio to receive infusions of either:

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

9.4.1.2 Open-label Treatment Period

At the end of the double-masked Treatment Period (Week 24), proptosis non-responders who have completed the double-masked Treatment Period may choose to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion followed by 20 mg/kg q3W for the remaining 7 infusions) in an open-label fashion.

9.4.2 Identity of Investigational Product

9.4.2.1 TEPEZZA

TEPEZZA (teprotumumab-trbw; HZN-001) is a fully human anti-IGF-1R mAb. TEPEZZA will be provided in single-dose 20-mL glass vials as a freeze-dried powder containing, in addition to the drug substance, CCI mmol/L histidine-histidine chloride, CCI mmol/L trehalose and CCI polysorbate 20 (w/v).

Prior to administration, each vial containing 500 mg TEPEZZA freeze-dried powder will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL teprotumumab antibody. Reconstituted TEPEZZA solution will be further diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration (see Section 9.4.6.3 for details).

9.4.2.2 Placebo

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

9.4.3 Labeling

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

Upon arrival of investigational products at the site, the investigational unmasked pharmacist (or designee in accordance with institutional policies and local regulations) should inspect them for damage and verify proper identity, quantity, integrity of seals and temperature conditions and report any deviations or product complaints to the unmasked monitor/Sponsor upon discovery.

9.4.4 Storage

Recommended storage conditions for the freeze-dried TEPEZZA drug product are between 2°C and 8°C (36°F to 46°F), protected from light.

The combined storage time of reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to

infusion. An Investigational Product Manual will be provided to all sites to further describe these processes in detail.

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

9.4.5 Drug Accountability

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

As permitted by site policy, all empty, partially empty and full vials of trial drug must be retained by the site under locked storage until drug accountability has been completed. Periodically throughout the trial and at the conclusion of the trial, inventory checks and accountability of trial materials will be conducted by an unmasked representative of the Sponsor. Once accountability is completed, the Sponsor's representative will either authorize onsite destruction or the return of trial drug (all used, partially used and unused vials) to PCI Clinical Services. The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the unmasked Sponsor's representative. The Investigator's copy of the Drug Accountability and Drug Return Destruction Record(s) must document accurately the return and or destruction of all trial drug and be maintained by the unmasked pharmacist or designee.

9.4.6 Trial Drug Administration and Timing of Dose for Each Patient

9.4.6.1 Description of Clinical Supplies

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

9.4.6.2 Determination of Dose Volume

The volume of trial drug to be administered will be determined by the electronic data capture (EDC) system and will be based on the patient's dose and body weight. The first dose of double-masked treatment and open-label treatment will be 10 mg/kg, and subsequent doses will be 20 mg/kg. Weight will be measured as described in Section 2.1. The dose on Day 1 and Weeks 3, 6 and 9 of the double-masked Treatment Period will be based on the Screening weight; weight measured at Week 9 will be used in dose calculations at Weeks 12, 15, 18 and 21. The dose on Weeks 24, 27, 30 and 33 of the open-label Treatment Period will be based on the

Week 24 weight; weight measured at Week 33 will be used in dose calculations at Weeks 36, 39, 42 and 45.

9.4.6.3 Details Concerning Timing and Dose Administration

9.4.6.3.1 Preparation and Administration of TEPEZZA

TEPEZZA will be prepared by the site pharmacist (or designee in accordance with institutional policy and local regulations) who is not masked to the identity of the trial drug. Each vial of TEPEZZA will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL teprotumumab antibody. Prior to administration, the reconstituted TEPEZZA solution must be further diluted in 0.9% (w/v) NaCl solution by the site pharmacist or designee.

Doses less than 1800 mg will be administered in a total infusion volume of 100 mL, and doses 1800 mg and above 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 TEPEZZA 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 TEPEZZA solution based on the patient's dose and body weight will be withdrawn from the reconstituted TEPEZZA vial(s) and transferred into an IV bag containing normal saline (0.9% NaCl).

The infusion is to be administered at room temperature (20°C to 25°C [68°F to 77°F]).

The combined storage time of reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, USP is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

No incompatibilities between TEPEZZA and polyethylene, polyvinyl chloride, polyurethane or polyolefin bags and IV administration sets have been observed. Exposure of the solution to direct sunlight should be avoided.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Upon reconstitution, TEPEZZA is a colorless or slightly brown, clear to opalescent solution that is free of foreign particulate matter. Discard the solution if any particulate matter or discoloration is observed.

Do not freeze the reconstituted or diluted solution.

Partially used vials should not be re-used.

The first 2 infusions of the double-masked and open-label Treatment Periods will be administered over approximately 90 minutes (but not less than 80 minutes). All subsequent

infusions will be administered over approximately 60 minutes (but not less than 50 minutes) in the absence of any infusion-associated events. For the first 3 infusions, patients will be monitored for any AEs during the infusion and for 60 minutes after completion of the infusion. For subsequent infusions (if no previous infusion reactions), patients will be monitored during and for 30 minutes after completion of the infusion.

9.4.6.3.2 Dose Modifications, Interruptions and Delays

All dosing instructions are applicable for TEPEZZA and placebo administration.

Patients will be evaluated for safety throughout the trial. For the first 3 infusions, patients will be monitored for any AEs during the infusion and for 60 minutes after completion of the infusion for immediate infusion-associated events (e.g., transient increase in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain) and delayed infusion-associated events (e.g., rash). For subsequent infusions (if no previous infusion reactions), patients will be monitored during and for at least 30 minutes after completion of the infusion.

If immediate infusion-associated events are noted, the infusion rate may be slowed or interrupted and symptomatic treatment (e.g., antipyretics, antihistamines, beta-agonists, glucocorticoids, oxygen, IV fluid) may be administered, as necessary. Vital signs (temperature, blood pressure, pulse and respiratory rate) will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms; however, TEPEZZA dosing will be permanently discontinued if the event is an anaphylactic reaction.

If delayed infusion-associated events are noted, patients may continue dosing at the Investigator's discretion; however, if a rash worsens following repeated dosing or other signs of serum sickness (e.g., delayed fever, myalgias, arthralgias) are present, TEPEZZA dosing will be permanently discontinued. If an infusion-associated event is experienced after patients are discharged from the site, the Investigator is to be contacted as soon as possible.

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

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

Increase in blood glucose is a known AE observed in previous clinical trials with TEPEZZA and other IGF-1R antagonists and is known to respond to treatment. Since a referral for treatment of hyperglycemia may take some time, if the Investigator considers it appropriate to continue the

patient in the trial, the next scheduled infusion visit may be skipped to allow modified anti-diabetic treatment to take effect and hyperglycemia to return to mild/moderate level before dosing. The patient would then be dosed at the next scheduled visit (i.e., 6 weeks after the previous infusion). Fasting blood glucose levels must return to mild/moderate severity before the next scheduled infusion. The above process of withholding a scheduled infusion is recommended to occur at most twice during the trial for a single patient, after which dosing should continue only if the benefit of receiving continued treatment clearly outweighs the risk.

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

9.4.7 Method of Assigning Patients to Treatment Groups

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

9.4.8 Masking

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

The trial mask should be broken only if the safety of a patient is at risk and the treatment plan depends on which trial drug he or she received. Unless the patient is at immediate risk, the Investigatnr must make diligent attempts to contact the Sponsor or Sponsor's designee before unmasking the patient's data. The Investigator must use the Randomization and Trial Supply Management (RTSM) application to unmask the patient's data. If a patient's data are unmasked without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented.

The Sponsor or designee will unmask the identity of the trial drug for an unexpected, drug -related SAE for submission to health authorities and IRB/Independent Ethics Committee according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at investigative sites. Details of patients who are unmasked during the trial will be included in the clinical study report.

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

All investigative site staff directly involved in this trial, except for unmasked pharmacy personnel, will remain masked from Screening through analysis of the open-label treatment data and all site close-out visits. The Sponsor and its designees may be unmasked after the double-masked Treatment Period database lock.

9.4.9 Concomitant Therapy and Restricted Medications

Local supportive measures for TED, simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies) and medications/supplements for conditions other than TED are permitted during the trial.

9.4.9.1 Concomitant Therapy

Topical and inhaled corticosteroids for conditions other than TED are allowed; however, oral corticosteroid use during the trial is restricted to patients who experience infusion-associated AEs.

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

9.4.9.2 Restrieted Therapy and Medications

Patients with a previous orbital irradiation, orbital decompression or strabismus surgery or who have a planned orbital irradiation or surgery for TED during this trial are not eligible for the trial. In addition, oral corticosteroids, immunosuppressive agents, investigational agents and illicit drug/alcohol use are restricted, as shown in Table 9.1.

Table 9.1 Restricted Medications and Therapies

Medication/Therapy	Restricted Dose or Time Period
Orbital irradiation, orbital decompression or strabismus surgery	Any history or planned irradiation or surgery during the trial.
Steroids	Steroids (intravenous or oral) and steroid eye drops within 3 weeks prior to Screening. Systemic steroid use (intravenous or oral) and steroid eye drops are not to be initiated during the trial; however, topical and inhaled steroids are allowed. Steroids for the treatment of infusion reaction are allowed.
Non-steroid eye drops	Non-steroid drops, such as saline or methylcellulose, antihistamines and vasoconstrictors are allowed but must not be used on the day of a clinic visit.
Rituximab (Rituxan® or MabThera®)	Within 12 months prior to the first infusion of trial drug and during the trial.
Tocilizumab (Actemra® or Roactemra®)	Within 6 months prior to the first infusion of trial drug and during the trial.
TEPEZZA	Any previous treatment with TEPEZZA or teprotumumab, including, but not limited to enrollment in this trial or participation in a prior TEPEZZA trial or program.
Monoclonal antibody	Within 3 months prior to Screening.
Non-steroid immunosuppressive agent (other than rituximab or tocilizumab)	Within 3 months prior to the first infusion of trial drug and during the trial.
Investigational agent	Within 60 days or 5 half-lives, whichever is longer prior to Screening or anticipated use during the trial.
Neonatal Fc receptor (FcRn) agents	During the trial.
Illicit drug/alcohol use	History of abuse within the past 2 years or abuse during the trial.

It is recommended to avoid ototoxic medications and medications that may cause muscle spasm/cramps during the trial.

All concomitant treatment (for TED and other conditions) must be documented in the eCRF.

9.4.10 Treatment Compliance

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

All infusions of trial drug will be administered at the clinic or infusion center under adequate healthcare professional supervision. Calculated trial drug dose and start and stop times of the infusions will be recorded in the eCRF.

An inventory of the trial drug supplies will be performed by the authorized site designee and recorded onto the Drug Accountability Log in the patient's source document records or equivalent

9.5 Efficacy, Pharmacokinetic, Safety and CCI Variables

The Schedule of Assessments is provided in Section 2.1.

9.5.1 Efficacy Variables

At the Baseline (Day 1) Visit, the "study eye" (i.e., the eye with most significant proptosis) will be identified. If both eyes are affected equally, the Investigator will choose the "study eye." Both eyes will be assessed for efficacy, but the study eye will be used to assess the primary efficacy endpoint.

Efficacy will be assessed by proptosis (measured as proptosis evaluation of the Clinical Measures of Severity using a Hertel instrument provided by the Sponsor for consistency in measurement), CCI [redacted], quality of life (using the GO-QoL questionnaire) and, CCI [redacted]

9.5.1.1 Proptosis

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 duration of the trial. Additionally, the same intercanthal distance must be used on each occasion. Instructions for the measurement of proptosis are included in Appendix 17.4.

Proptosis will be measured for each eye at Screening, Day 1 and Weeks 3, 6, 12, 18 and 24 (or premature withdrawal 1 [PW1]) (all patients) and Weeks 27, 30, 36, 42 and 48 (or premature withdrawal 2 [PW2]) (proptosis non-responders who elect to receive open-label TEPEZZA) (see Section 2.1). Patients who have a >2-mm decrease in proptosis from Screening to Baseline in the study eye are not eligible for randomization. Measurements will be recorded on the Clinical Measures of Severity eCRF under exophthalmos.

9.5.1.2 CCI [redacted]

Based on the European Group on Graves' Ophthalmopathy Consensus Statement, CCI [redacted]

CCI [redacted]

CCI

Table 9.2 Clinical Measures of Severity

CCI

9.5.1.3 CCI

CCI on Day 1 and Weeks 3, 6, 12, 18 and 24 (or PW1) (all patients) and at Weeks 27, 30, 36, 42 and 48 (or PW2) (proptosis non-responders who elect to receive open-label TEPEZZA) (see Section 2.1). Patients will be asked to CCI CCI CCI is included in Appendix 17.2.

CCI

CCI

Section 2.1 CCI CCI

9.5.1.5 Clinical Activity Score

The CAS assessment (Table 9.3) will be completed at Screening, Day 1 and Weeks 12 and 24 (or PW1) (all patients) and Weeks 36 and 48 (or PW2) (proptosis non-responders who elect to receive open-label TEPEZZA) using the 7-item European Group on Graves' Ophthalmopathy amended CAS (see Section 2.1).

Table 9.3 CCI

Item[1]	Description
CCI	

Each item is scored (CCI and scores for each item are summed for total score.

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

9.5.1.6 CCI

CCI

The CCI
CCI The English version of the questionnaire is included in Appendix 17.5.

9.5.2 Pharmacokinetic Measurements

Blood samples will be collected in 5-mL serum separator collection tubes to evaluate PK at the following visits: pre- and post-infusion on Day 1, Weeks 3 and 12 of the double-masked Treatment Period (all patients) and at Weeks 24, 27 and 36 (non-responders who elect to receive open-label TEPEZZA); a single sample will also be collected at Week 24 (or PW1) of the double-masked Treatment Period (proptosis responders and proptosis non-responders who elect not to receive open-label TEPEZZA) and Week 48 (or PW2) of the open-label Treatment Period (non-responders who elect to receive open-label TEPEZZA) (see Section 2.1).

PK samples will be collected, processed and stored at ≥-70°C at the site until shipment to the central laboratory (CCI). The central laboratory will store the samples at ≥-70°C until shipment to the appropriate laboratory for testing.

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

9.5.3 Safety Variables

Safety will be assessed via AE (including AESIs) and concomitant medication use monitoring, immunogenicity testing, best-corrected visual acuity, vital signs, clinical safety laboratory evaluations (complete blood count and fasting chemistry [including thyroid panel and HbA1c]) and pregnancy testing (if applicable).

9.5.3.1 Adverse Events

9.5.3.1.1 Definitions

9.5.3.1.1.1 Adverse Event Definition

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

Pre-existing conditions that worsen during the trial are to be reported as AEs. New findings reported from the on-trial visual acuity assessments will not be reported as AEs if, according to the Investigator, the abnormalities are related to TED and not considered related to the trial drug.

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

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

9.5.3.1.1.2 Serious Adverse Event Definition

A treatment-emergent adverse event (TEAE), Baseline event, or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death. This includes any death that occurs during the conduct of a clinical trial, including deaths that appear to be completely unrelated to the trial drug (e.g., due to car accident).
- Life-threatening adverse experience. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Persistent or significant disability or incapacity.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- Congenital anomaly or birth defect.
- Another medically important event that, according to appropriate medical judgment, may require medical or surgical intervention to prevent 1 of the outcomes listed above.

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

Elective surgeries that require hospitalization and treatment received at an emergency room or similar facility will not be considered as SAEs unless 1 of the definitions of an SAE listed above is met.

In addition, a hospitalization for planned procedures is not considered an AE unless the hospitalization becomes prolonged. An emergency room visit less than 24 hours in duration is not considered a hospitalization.

9.5.3.1.1.3 Non-Serious Adverse Event Definition

A non-serious AE includes any AE that is not included in the SAE definition.

9.5.3.1.1.4 Unexpected Adverse Event Definition

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

9.5.3.1.1.5 Adverse Events of Special Interest

Based on previous clinical experience in TFD, the following will be AESIs for this trial:

- Infusion reactions
- Hyperglycemia
- Muscle spasms
- Hearing impairment
- New onset inflammatory bowel disease and exacerbation of inflammatory bowel disease

Risk of Hypersensitivity (Infusion-related events)

- Administration of mAbs may cause infusion-related symptoms, such as fever, chills, hypotension, shortness of breath, skin rash and headache. Such reactions typically occur

during or shortly after the infusion of mAbs and are usually associated with the first infusion. Their incidence and severity typically decrease with subsequent infusions. Severe infusion-related reactions might be clinically indistinguishable from anaphylactic reactions.

- Infusion-related events observed with teprotumumab to date have not been anaphylactic in nature. However, because of the protein nature of teprotumumab and the potential for infusion-related reactions and hypersensitivity reactions, teprotumumab should be administered in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to emergencies. For the first 3 infusions, patients should be monitored for any events during infusion and for 60 minutes after completion of infusion. For subsequent infusions (the fourth dose and beyond), patients who have not previously experienced an infusion reaction should be monitored during the infusion and for at least 30 minutes after the infusion.
- Patients who exhibit immediate hypersensitivity reactions or infusion-related reactions during an infusion of teprotumumab should have the infusion interrupted or the infusion rate slowed. Symptomatic treatment, e.g., antipyretics, antihistamines and/or corticosteroids, oxygen, beta agonists and IV fluids, should be administered to the patient. Following an immediate hypersensitivity reaction or infusion-associated reaction, vital signs (temperature, blood pressure, pulse and respiratory rate) will be monitored every 5 minutes until stable, and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms except in the case of patients who experience an anaphylactic reaction of life-threatening intensity; these patients should be removed from the trial.
- In general, the decision to keep a patient on trial treatment with teprotumumab should take into consideration potential risks and benefits to the patient. Prior to future infusions of teprotumumab, these patients may be premedicated with IV diphenhydramine 1 to 1.25 mg/kg (maximum 50 mg), IV ranitidine 50 mg, IV famotidine 0.5 mg/kg, IV dexamethasone 0.4 mg/kg (maximum 20 mg) and/or acetaminophen 500 mg. In addition, all future infusions should be administered over 90 minutes. Vital signs should be taken every 15 minutes during the infusion through 60 minutes after infusion completion.
- Patients who experience delayed-type hypersensitivity reactions (e.g., skin rash) may remain in the trial at the discretion of the Investigator and, prior to all future infusions of teprotumumab, may be premedicated with the above medications (diphenhydramine, ranitidine, famotidine, dexamethasone and acetaminophen). However, if a rash worsens

following repeated dosing or other signs of serum sickness (e.g., delayed fever, myalgias, arthralgias) are present, trial drug dosing will be permanently discontinued.

Risk of New Onset or Exacerbation of IBD

- In Phase 2 TED01RV, 2 teprotumumab-treated patients with a history of IBD reported serious TEAEs (*Diarrhoea* in 1 patient and *Inflammatory bowel disease* in 1 patient) that led to discontinuation of trial drug. Based on these serious events and the fact that a placebo patient with Crohn's disease did not experience these types of events, patients with a history of IBD are either excluded from current trials or must be in clinical remission.
- Patients who experience progressive and persistent diarrhea or other IBD symptoms, such as bloody stools or abdominal pain, should undergo prompt evaluation to exclude new onset or exacerbation of preexisting IBD or other serious conditions. If possible, medications known to cause diarrhea, such as laxatives and magnesium shall be avoided. If new onset or exacerbation of IBD is suspected, teprotumumab shall be discontinued.

Risk of Hyperglycemia

- In nonclinical studies, there was no *in vitro* cross-reactivity of teprotumumab with the insulin receptor. Clinical trials in Active TED have shown a higher incidence of hyperglycemia in patients treated with teprotumumab compared to placebo. Patients with pre-existing diabetes mellitus (who were under appropriate glycemic control upon trial entry) or impaired glucose tolerance were more likely to experience an event of hyperglycemia after exposure to teprotumumab.

Management of Patients with Diabetes Mellitus

- Patients with known controlled diabetes mellitus are allowed to participate in trials with teprotumumab. HbA1c levels should be monitored every 6 weeks in these patients.
- Investigators are strongly encouraged to adjust their patients' diabetes management to maintain HbA1c levels ~8%. In the event a patient's HbA1c level rises to >8% while in the trial, the Investigator must assess the risk versus benefit for the patient to remain in the trial, discuss with sponsor's medical monitor or designee, and document the decision.

Management of Hyperglycemia

- Fasting glucose levels should be tested at Baseline. Random non-fasting glucose levels should be monitored at a minimum as per visit schedule.

- Patients with recurrent hyperglycemia, defined as a fasting glucose >126 mg/dL, will require evaluation for diabetes mellitus (e.g., fasting glucose, glucose tolerance and HbA1c tests) and appropriate medical management, at the discretion of the Investigator.

Management of Severe Diabetic Complications

Hyperglycemia can cause serious acute complications, presenting as endocrine emergencies, such as Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Both of these conditions are caused by relative or absolute insulin deficiency associated with excessive counter-regulatory hormones (glucagon, growth hormone, cortisol, catecholamines) (Marcovecchio 2017). Both DKA and HHS are usually triggered by an underlying illness or event such as acute infection, infarction, non-compliance with diet and skipped insulin doses or insulin pump failure. DKA and HHS are life-threatening emergencies. Prompt clinical suspicion and confirmation of these diagnoses is very important. The goal of treatment for DKA and HHS is to correct volume deficits, hyperglycemia, and electrolyte abnormalities which will include, but is not limited to, IV fluid resuscitation, IV insulin, and IV potassium. Every effort should be made to identify the cause, so that future preventive measures can be taken. Participants experiencing DKA or HHS should be discontinued from study treatment. Management of infusion reactions and hyperglycemia is also described in Section 9.4.6.3.2.

Risk of Muscle Spasms

Among teprotumumab-treated patients, *Muscle spasms* was the most commonly reported TEAE in clinical trials of Active TED (Double-Masked Treatment Period: 26.2% teprotumumab compared to 7.0% placebo; Open-Label Extension Trial: 41.3%). All events were non-serious and the majority were mild in intensity.

If possible, avoid medications known to cause muscle spasms or muscle toxicity, such as diuretics or statins. If muscle spasm occurs, evaluate for other causes of muscle spasm, such as electrolyte abnormalities and dehydration.

Risk of Hearing Impairment

Adverse reactions of middle- to high-range sensorineural hearing loss have been reported in both healthy volunteers and patients with malignancies who received as little as 1 dose of various IGF-1R mAbs.

Eighteen events associated with hearing impairment have been observed in 14 teprotumumab treated patients in the TED trials, with no reports observed in placebo treated patients. Each of these events were nonserious, mild or moderate in intensity and none led to premature discontinuation of trial drug; these events usually improved or resolved. If possible, patients should avoid ototoxic drugs while receiving teprotumumab.

A review of the post-marketing data in a larger patient population shows that while the reporting rate of hearing impairment related to AEs in a post-marketing setting and the incidence in clinical trials appears similar, there are some post-marketing cases suggestive of greater increased severity (eg, severe or, rarely, permanent hearing impairment) than what was seen in clinical trials. No risk factors were identified based on current available data.

In addition, patients experiencing hearing impairment should contact the investigational site for evaluation and assessments. Evaluation may include an audiogram. The audiogram report will include the following:

- Pure tone

The following tests may also be included:

- Speech Recognition
- Distortion product otoacoustic emission inner ear hair cell function test
- Evaluation of Eustachian tube function

Patients experiencing complete or profound hearing loss should be discontinued from study treatment.

9.5.3.1.2 Documentation of Adverse Events

AEs that occur during Screening and prior to dosing on Day 1 will be considered pre-treatment AEs. The TEAE reporting period begins with administration of the first dose of trial drug on Day 1 and continues until 3 weeks after the last dose of trial drug. The Follow-up AE reporting period begins 3 weeks after the last dose of trial drug through completion of the Follow-up Period. All pre-treatment AEs, TEAEs and AEs during the Follow-up Period must be recorded in the source documents and on the patient's eCRF.

If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described in Section 9.5.3.1.5.

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

9.5.3.1.3 Intensity of Adverse Events

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

Intensity	Definition	Corresponding National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade
Mild	discomfort noticed but no disruption of normal daily activity	1
Moderate	discomfort sufficient to reduce or affect daily activity	2
Severe	inability to work or perform normal daily activity	3
Life-Threatening	represents an immediate threat to life	4
Fatal	results in death	5

9.5.3.1.4 Relationship to Trial Drug

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

- No reasonable causal relationship (not related): There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.
- Reasonable causal relationship (related): There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least 1 of the following criteria apply:
    - There is a reasonable pharmacological relationship (or known class effect).
    - There is no other more plausible explanation.
    - There is a positive de-challenge (without active treatment of the event).
    - There is a positive re-challenge.
    - There is a distinguishable dose effect.

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

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the trial population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.5.3.1.5 Reporting and Documenting Serious Adverse Events

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

1. Report the SAE to the Sponsor **by entering the information in the eCRF within 24 hours** after becoming aware that a patient has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to clinicalsafety@horizontherapeutics.com, or via fax **within 24 hours** after becoming aware that a patient has experienced an SAE (see Appendix 17.1 for contact information).

2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative.

3. Respond in a timely manner to any queries from Sponsor regarding the SAE.

4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator.

5. Review each SAE report and evaluate the relationship of the SAE to trial treatment. The Sponsor will determine whether the SAE is unexpected in nature.

6. The Investigator must report to the IRB all AEs or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others.

9.5.3.1.6 Follow-up of Adverse Events

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

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

9.5.3.1.7 Medication Error and Overdose

An overdose is defined as a deliberate or accidental administration of investigational drug to or by a trial patient, at a dose equivalent to 27 mg/kg q3W or greater.

A medication error is defined as any unintended failure in the drug treatment process, such as mistakes in the prescribing, dispensing, storing, preparing or administering of a medicine that leads to, or has the potential to lead to, harm to the patient.

All cases of medication errors and overdose (with or without associated AEs) will be documented on the eCRF in order to capture this important safety information consistently in the database. AEs associated with an overdose and SAEs of overdose are to be reported according to the procedures outlined in Sections 9.5.3.1.2 and 9.5.3.1.5, respectively.

There is no antidote for TEPEZZA; therefore, in the event of drug overdose, the patient is to be treated with symptomatic and supportive care as required.

9.5.3.1.8 Review of Adverse Events and Emerging New Safety Information

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

9.5.3.1.9 Reporting of Investigational New Drug Safety Reports

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

9.5.3.1.10 Development Safety Update Reports

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

9.5.3.2 Pregnancy Reporting

Serum pregnancy testing will be performed for women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) at Screening; urine pregnancy testing will be performed prior to dosing at all subsequent clinic visits, as applicable, and at the End-of-Treatment Visit.

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

If a female patient becomes pregnant during treatment, she should immediately notify the Investigator, and trial drug dosing should be permanently discontinued. Pregnancies occurring up to 180 days after the last dose must be reported to the Investigator.

The Investigator should report pregnancies to the Sponsor by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com or via fax within 24 hours after becoming aware that the patient/patient's female partner has become pregnant (see Appendix 17.1 for contact information). The Investigator should counsel the patient and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the patient signs the pregnancy consent form, monitoring should continue to the conclusion of the pregnancy.

9.5.3.3 Medical History

Medical history, including tobacco, alcohol and other substance use history and thyroid disease history and treatment, will be captured at Screening. The initial diagnosis of TED must be ≥2 years but <10 years prior to Screening for trial enrollment. Stable, chronic (inactive) TED must be determined by medical records indicating a CAS ≤1 in both eyes for at least 1 year prior to Screening or no progression in proptosis, no progression of diplopia (in those with a history of diplopia due to TED) and no new TED symptoms for at least 1 year prior to Screening.

9.5.3.4 Vital Signs and Weight

Detailed timing of vital sign and weight measurements is described in Section 2.1.

Vital signs (blood pressure, heart rate, 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 (all patients), pre- and post-infusion at Week 24 and Week 27 (proptosis non-responders who elect to receive open-label TEPEZZA) and pre-infusion on all other infusion days. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. Also, vital signs will be monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion for any subsequent infusions after the previous occurrence of immediate or delayed infusion-associated events.

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

Weight will be measured at Screening and Weeks 9 and 24 (or PW1) (all patients) and Weeks 33 and 48 (or PW2) (proptosis non responders who elect to receive open-label TEPEZZA). The dose on Day 1 and Weeks 3, 6 and 9 of the double-masked Treatment Period will be based on the Screening weight; weight measured at Week 9 will be used in dose calculations at Weeks 12, 15, 18 and 21. The dose on Weeks 24, 27, 30 and 33 of the open-label Treatment Period will be

based on the Week 24 weight; weight measured at Week 33 will be used in dose calculations at Weeks 36, 39, 42 and 45.

9.5.3.5 Photographs

For patients who provide written consent and taking photographs is part of site routine or standard of care, photographs of patient's eyes will be taken prior to the first infusion and at Week 24 (or PW1) (all patients) and at Week 48 (or PW2) (non-responders who elect to receive open-label TEPEZZA).

9.5.3.6 Visual Acuity

Best-corrected visual acuity will be assessed at Screening, Day 1 and Weeks 6, 12, 18, and 24 (or PW1) and at Weeks 30, 36, 42 and 48 (or PW2) (non-responders who elect to receive open-label TEPEZZA) (see Section 2.1).

If significant abnormalities are noted compared with previous visits, including a loss of 2 lines or more of vision or other abnormalities not otherwise specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist's decision.

New findings reported from on-trial visual acuity assessments will not be reported as AEs if, according to the Investigator, the abnormalities are unequivocally due to disease progression and should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of trial drug.

9.5.3.7 Clinical Laboratory Safety Tests

With the exception of urine pregnancy tests, a central laboratory will be used for all protocol-specified clinical laboratory parameters. Details of timing concerning the collection of these samples are presented in Section 2.1.

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

9.5.3.8 Immunogenicity Testing

Blood samples will be collected in a 5-mL serum separator collection tube for immunogenicity testing (anti-drug antibody [ADA] and possibly neutralizing antibodies) from all patients prior to dosing on Day 1, and Weeks 3, 12 and 24 (or PW1) (all patients) and Weeks 27, 36 and 48 (or PW2) (non-responders who elect to receive open-label TEPEZZA).

Detailed timing of sample collection for immunogenicity evaluations is described in Section 2.1.

Samples will be collected, processed and stored at ≥-70°C at the site until shipment to the central laboratory (CCI [redacted]). The central laboratory will store the samples at ≥-70°C until shipment to the appropriate laboratory for testing. If a patient tests positive for ADA after

confirmatory and reactive titer testing, the sample will be tested for neutralizing antibodies. If the patient tests positive for neutralizing antibodies, the patient may be followed until levels either return to Baseline or the patient's level decreases or remains stable. ADA samples will be collected during any visit triggered by suspected immunologically related AEs.

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

9.5.4 CCI

CCI

CCI

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

9.5.5 Appropriateness of Measurements

This trial, which is a randomized, double-masked, placebo-controlled, multicenter trial, is designed according to standard principles for adequate and well-controlled trials.

The measurements used in this trial for the efficacy endpoints (proptosis, CCI and GO-QoL questionnaire) are established and have been shown to correlate significantly with TED.

9.5.6 Trial Procedures

9.5.6.1 Screening

Due to the number of screening assessments, the Screening Visit may be completed in more than 1 day clinic visit provided consent is obtained first and all assessments are completed within the designated window. During the Screening Visit, potential trial patients will be informed fully regarding the nature of the trial and possible AEs and will receive a copy of the ICF for review. Potential trial patients must read the ICF and sign the document after the Investigator or designee has answered all questions to the trial candidate's satisfaction. Further procedures can begin only after the ICF has been signed. The original signed ICF will be retained by the Investigator and a copy will be given to the patient.

Trial candidates will be evaluated for trial entry according to the stated inclusion and exclusion criteria (Section 9.3). The Investigator will evaluate the results of all examinations, including clinical laboratory tests, and will determine each candidate's suitability for the trial. The Investigator must review the results of all screening tests before determining that a candidate is eligible for trial drug treatment. The serum pregnancy test performed at Screening on all female candidates of childbearing potential must be negative for those patients to be eligible for initiation of treatment. All screening procedures must be completed within 28 days prior to Day 1 (i.e., the first day of administration of trial drug). The following procedures will be performed during Screening to establish each candidate's general health and eligibility for enrollment into the trial:

- Obtain signed, written informed consent, including permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act), with an optional consent to being photographed. Refusal to provide permission for photographing does not exclude an individual from eligibility for trial participation Record date and time informed consent was given and who conducted the process.
- Collect medical history, including tobacco, alcohol and other substance use history and thyroid disease history and treatment. Ensure TED is stable, chronic (inactive) (not progressing, non-sight-threatening but with an appreciable impact on daily life) and diagnosed ≥2 years but <10 years prior to Screening.
- Determine trial eligibility through review of the inclusion exclusion criteria (see Section 9.3).
- Obtain demographics.
- Inquire about prior medications (see Table 9.1 for restrictions regarding medications).
- Perform visual acuity assessment. Patients who have decreased best-corrected visual acuity due to optic neuropathy (defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months) are not eligible for randomization.
- Record vital signs (blood pressure, heart rate, respiratory rate and temperature) and weight. These measurements will be performed according to standardized instructions.
- Complete the following efficacy assessments: proptosis, CCI [redacted] CCI [redacted]
- Complete CAS.
- Query patients regarding signs and symptoms.

- Obtain blood samples for hematology and fasting chemistry (including thyroid and HbA1c) analysis for all patients (see Section 9.3 for details concerning test results and trial participation) and pregnancy testing for females of childbearing potential.
- Enter Screening Visit data in the EDC system.

9.5.6.2 Double-masked Treatment Period

9.5.6.2.1 Day 1

On Day 1, patients will return to the clinic for Baseline assessments and the first dose of trial drug.

- Determine trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Review medical history.
- Obtain signed, written informed consent for optional photographic analysis if not obtained at Screening; the consent must be obtained prior to photographs being obtained.
- Obtain predose blood samples for hematology and fasting chemistry (including thyroid and HbA1c) analysis.
- Collect predose blood samples for PK analysis, immunogenicity and CCI testing.
- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive trial drug.
- Inquire about AEs and prior medication use (see Table 9.1 for restrictions regarding medications).
- Perform predose visual acuity assessment.
- Perform predose Baseline efficacy assessments (proptosis, CCI CCI and GO-QoL questionnaire).
- Perform predose Baseline CAS.
- Take predose photograph of the patient's eyes for those patients who have consented.
- Record vital signs prior to and at the end of the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).

- Register enrollment in EDC in order for the unmasked site personnel to obtain randomization assignment, calculated trial drug dose, vial assignment (if applicable) and volume of trial drug to be administered.

- Administer trial drug and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 60 minutes after the completion of the infusion.

- Collect post-dose blood samples for PK analyses following the end of the infusion.

- Enter visit data in the EDC system.

Patients will be discharged from the site after all Day 1 procedures have been completed, instructed to return for a clinic visit in 3 weeks and contacted the following day to perform a safety check following the first infusion.

9.5.6.2.2 Week 3

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive trial drug

- Inquire about AEs and concomitant medication use.

- Collect predose blood samples for PK analysis, immunogenicity and CCI [redacted].

- Perform efficacy assessments (proptosis, CCI [redacted]).

- Record vital signs prior to and at the end of the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).

- Obtain calculated trial drug dose, vial assignment (if applicable) and volume of trial drug to be administered from the EDC system.

- Administer trial drug and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 60 minutes after the completion of the infusion.

- Collect post-dose blood samples for PK analyses following the end of the infusion.

- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed, instructed to return for a clinic visit in 3 weeks and contacted the following day to perform a safety check following the second infusion.

9.5.6.2.3 Weeks 6, 12 and 18

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive trial drug.
- Obtain predose blood samples for hematology and fasting chemistry (including thyroid and HbA1c at Week 12 only).
- Inquire about AEs and concomitant medication use.
- Perform predose visual acuity assessment.
- Perform predose efficacy assessments (proptosis, CCI and GO-QoL questionnaire [Weeks 6 and 12 only]).
- Perform predose CAS at Week 12 only.
- Record vital signs prior to the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Collect predose blood samples for PK analysis, immunogenicity and CCI at Week 12 only.
- Obtain calculated trial drug dose, vial assignment (if applicable) and volume of trial drug to be administered from the EDC system.
- Administer trial drug and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 60 minutes (Week 6) or 30 minutes (Week 12 and Week 18) after the completion of the infusion.
- Collect post-dose blood samples for PK analyses following the end of the infusion at Week 12 only.
- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed and instructed to return for a clinic visit in 3 weeks.

9.5.6.2.4 Weeks 9, 15 and 21

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive trial drug.
- Inquire about AEs and concomitant medication use.
- Measure predose weight (Week 9 only).
- Record vital signs prior to the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Obtain calculated trial drug dose, vial assignment (if applicable) and volume of trial drug to be administered from the EDC system.
- Administer trial drug and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 30 minutes after the completion of the infusion.
- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed and instructed to return for a clinic visit in 3 weeks.

9.5.6.2.5 Week 24/End-of-Treatment 1/First Infusion of Open-label Treatment Period

Week 24 is the final visit of the double-masked Treatment Period. Trial drug is not administered for responders and non-responders who elect not to receive open-label TEPEZZA. For proptosis non-responders who elect to receive open-label TEPEZZA, the infusion will be performed at Week 24 (first of 8 infusions); all Week 24 procedures except AE and concomitant medication monitoring, post-infusion PK sample collection and 24-hour post-dose phone/email contact must be completed prior to TEPEZZA infusion.

- Perform efficacy assessments (proptosis, CCI [redacted] CCI [redacted] and GO-QoL questionnaire). The CCI [redacted] will not need to be performed on the same day as other Week 24 assessments as long as it is performed within the visit window and prior to the first open-label infusion (proptosis non-responders who elect to receive open-label TEPEZZA).
- Perform CAS.
- Perform treatment response assessment, including whether the patient is a proptosis responder or non-responder, and enter data in EDC.

- Obtain blood samples for hematology and fasting chemistry (including thyroid and HbA1c) analysis.
- Collect urine sample for a pregnancy test for females of childbearing potential.
- Perform visual acuity assessment.
- Measure weight.
- Record vital signs (prior to and at the end of the infusion for non-responders who elect to receive open-label TEPEZZA). Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Collect blood samples for immunogenicity and CCI (NOTE: Collection should be prior to dose for non-responders who elect to receive open-label TEPEZZA.) Collect a single blood sample for PK analyses (proptosis responders and proptosis non-responders who elect not to receive open-label TEPEZZA). NOTE: CCI CCI
- Inquire about AEs and concomitant medication use.
- Take photograph of the patient's eyes for those patients who have consented.
- Obtain calculated dose, vial assignment and volume of TEPEZZA to be administered from the EDC system for non-responders who elect to receive open-label TEPEZZA only.
- Collect blood samples for PK analyses prior to and at the end of the infusion (non-responders who elect to receive open-label TEPEZZA only).
- Administer TEPEZZA and record date, volume and start/stop times of the infusion (non-responders who elect to receive open-label TEPEZZA only).
- Enter remaining visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed. Patients who are proptosis responders, as well as non-responders who elect not to receive open-label TEPEZZA, will enter the Follow-up Period and will be contacted via phone or email in 30 days. Patients in the open-label Treatment Period will be instructed to return for a clinic visit in 3 weeks and will be contacted the following day to perform a safety check following the first open-label infusion.

9.5.6.3 Open-label Treatment Period Visits After Week 24 – Proptosis Non-responders Who Choose to Receive Open-label TEPEZZA

Proptosis non-responders who elect to receive open-label TEPEZZA during the open-label Treatment Period will receive additional infusions at Weeks 27, 30, 33, 36, 39, 42 and 45.

9.5.6.3.1 Week 27

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive TEPEZZA.
- Perform efficacy assessments (proptosis, CCI [redacted]).
- Inquire about AEs and concomitant medication use.
- Collect blood samples for PK analyses prior to and at the end of the infusion.
- Collect predose blood sample for immunogenicity testing.
- Record vital signs prior to and at the end of the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Obtain calculated dose, vial assignment and volume of TEPEZZA to be administered from the EDC system.
- Administer TEPEZZA and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 60 minutes after the completion of the infusion.
- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed, instructed to return for a clinic visit in 3 weeks and contacted the following day to perform a safety check following the second open-label infusion.

9.5.6.3.2 Weeks 30, 36 and 42

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive TEPEZZA.
- Obtain predose blood samples for hematology and fasting chemistry (including thyroid and HbA1c at Week 36 only).
- Inquire about AEs and concomitant medication use.

- Perform predose visual acuity assessment.
- Perform predose efficacy assessments (proptosis, CCI [redacted] CCI as well as GO-QoL questionnaire [Weeks 30 and 36 only]).
- Perform predose CAS at Week 36 only.
- Collect predose blood samples for PK analysis and immunogenicity testing at Week 36 only.
- Record vital signs prior to the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Obtain calculated dose, vial assignment and volume of TEPEZZA to be administered from the EDC system.
- Administer TEPEZZA and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 60 minutes (Week 30) or 30 minutes (Week 36 and Week 42) after the completion of the infusion.
- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed and instructed to return for a clinic visit in 3 weeks.

9.5.6.3.3 Weeks 33, 39 and 45

- Collect predose urine sample for a pregnancy test for females of childbearing potential; the pregnancy test must be negative for the patient to receive TEPEZZA.
- Inquire about AEs and concomitant medication use.
- Measure predose weight (Week 33 only).
- Record vital signs prior to the infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.3.4 for details).
- Obtain calculated dose, vial assignment and volume of TEPEZZA to be administered from the EDC system.
- Administer TEPEZZA and record date, volume and start/stop times of the infusion. Monitor the patient for any AEs during the infusion and for 30 minutes after the completion of the infusion.

- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed and instructed to return for a clinic visit in 3 weeks.

9.5.6.3.4 Week 48/End-of-Treatment 2

Week 48 is the final visit of the open-label Treatment Period. Trial drug is not administered.

- Obtain blood samples for hematology and fasting chemistry (including thyroid and HbA1c) analysis.
- Collect urine sample for a pregnancy test for females of childbearing potential.
- Perform visual acuity assessment.
- Measure weight.
- Perform efficacy assessments (proptosis, CCI [redacted] CCI [redacted] and GO-QoL questionnaire). The CCI will not need to be performed on the same day as other Week 48 assessments as long as it is performed within the visit window.
- Perform CAS.
- Record vital signs.
- Collect blood samples for immunogenicity testing. Collect a single blood sample for PK analyses.
- Inquire about AEs and concomitant medication use.
- Take photograph of the patient's eyes for those patients who have consented.
- Enter visit data in the EDC system.

Patients will be discharged from the site after all procedures have been completed and enter the Follow-up Period.

9.5.6.4 Follow-up Period (End-of-Study/Trial)

All patients will be contacted via phone or email 30 days after the Week 24 (responders and non-responders who choose not to receive open-label TEPEZZA) or Week 48 (non-responders who receive open-label TEPEZZA) Visit. Inquire about AEs and concomitant medication use.

The end of the trial is defined as the date of the last patient contact at the end of the Follow-up Period.

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Endpoints

9.6.1.1 Primary Endpoint

The primary efficacy endpoint is the change from Baseline at Week 24 in proptosis in the study eye.

9.6.1.2 Other Efficacy Endpoints

1. The proptosis responder rate (percentage of patients 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.
2. The change from Baseline at Week 24 in the GO-QoL questionnaire appearance and visual functioning subscales.
3. CCI
4. CCI
5. CCI

9.6.1.3 Pharmacokinetic and Anti-drug Antibody Endpoints

1. The peak and trough concentrations of TEPEZZA.
2. The ADA incidence and titers.

9.6.1.4 Safety and Tolerability Endpoints

1. The incidence of TEAEs, SAEs, TEAEs resulting in premature discontinuation of treatment and AESIs (infusion reactions, hyperglycemia, hearing impairment, new onset inflammatory bowel disease and exacerbation of inflammatory bowel disease).
2. The incidence of ≥Grade 3 TEAEs.
3. The change from Baseline to each scheduled visit in vital signs (blood pressure, heart rate, respiratory rate and temperature).
4. The results of best-corrected visual acuity.
5. The incidence of ≥Grade 3 fasting glucose values.
6. The change from Baseline to each scheduled visit in laboratory evaluations (hematology and fasting chemistry [including thyroid panel and HbA1c]).

9.6.1.5 Exploratory Endpoint

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9.6.2 Analysis Sets

Efficacy analyses will be performed on the intent-to-treat (ITT) analysis set, consisting of patients who are randomized to trial drug (either TEPEZZA or placebo). Safety analyses will be performed on the safety set, consisting of patients who receive at least 1 dose of trial drug. The PK analysis set will include all patients who receive at least 1 dose of trial drug and have at least 1 post-dose PK sample.

9.6.3 Primary Efficacy Endpoint Analysis

The primary efficacy analysis will be conducted on the ITT analysis set. A Mixed-Model for Repeated-Measures (MMRM) analysis of covariance model fitting to the individual change from Baseline scores for the study eye will be used for the analysis of change from Baseline in proptosis. The model includes Baseline score, treatment group, visit, visit-by-treatment and visit-by-Baseline score as covariates. The unstructured covariance will be used. The treatment difference (TEPEZZA minus placebo) based on the estimated least squares (LS) means at Week 24 will be presented with associated standard error (SE), 95% confidence interval (CI) and p-value.

9.6.4 Other Efficacy Endpoints Analyses

The other endpoints of the proptosis responder rate, CCI CCI CCI. A 95% exact CI will be provided for each risk difference observed between the treatment groups. Patients whose Week 24 evaluation is missing will be considered treatment failures (non-responders) for the responder analysis.

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Remaining other or exploratory endpoints analyzing change from Baseline (such as in GO-QoL, CCI will use the same MMRM method specified for the primary efficacy endpoint.

Descriptive summaries for observed and change from Baseline values in CCI

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9.6.5 Safety and Tolerability Analyses

The number and percentage of patients experiencing at least 1 occurrence of a TEAE, SAE, TEAE resulting in premature discontinuation of treatment and AESI for each unique System Organ Class and Preferred Term will be summarized by treatment group. TEAEs and SAEs will also be summarized by severity and relationship to trial drug, as assessed by the Investigator. Grade 3 and higher TEAEs, as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), will also be summarized for each unique System Organ Class and Preferred Term.

The number and percentage of patients in each treatment group using concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 term and Preferred Term.

For best-corrected visual acuity, shift tables will be presented providing the count of patients in each treatment group with each type of finding (normal, abnormal – not clinically significant, or abnormal – clinically significant) at Baseline compared to each postbaseline visit.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by treatment group and visit. A shift table for vital signs by NCI-CTCAE grade and visit will be generated by treatment group.

Safety laboratory (hematology and fasting chemistry [including thyroid panel and HbA1c]) values and change from Baseline will be summarized by visit and treatment group using descriptive statistics. The laboratory assessment will be categorized as low, normal or high based on normal ranges and graded using the NCI-CTCAE grading scale, when available. Shift tables using categories of low, normal and high from Baseline to each visit will be generated by treatment group. Additionally, a shift table for glucose by NCI-CTCAE grade and visit will be generated by treatment group. Summaries will be provided separately for hyperglycemia.

The rate and titer of positive ADA samples will be summarized by visit and treatment group using descriptive statistics. Teprotumumab peak and trough (i.e., prior to dose) concentrations will also be summarized by visit using descriptive statistics.

9.6.6 Interim Analyses

No interim analyses are planned.

9.6.7 Sample Size and Power Considerations

A total of 57 patients (38 in the TEPEZZA group and 19 in the placebo group) will be enrolled in the trial to detect at least a 2-mm mean difference between the 2 treatment groups in the change from Baseline of proptosis values at Week 24 in order to have 81% power at the 2-sided 0.05 level of significance. The sample size was determined assuming that the mean difference in proptosis change between the 2 groups is at least 2.0 mm (clinically relevant) and the standard deviation of proptosis change values is 2.5 for both groups (larger than observed in Phase 2 and Phase 3 active TED trials).

9.7 Changes in the Conduct of the Trial

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

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

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

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

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

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

- Medical history/physical condition and diagnosis of the patient before involvement in the trial sufficient to verify that the patient meets protocol entry criteria.
- Trial number, assigned patient number and verification that written informed consent(s) was(were) obtained (each recorded in dated and signed progress notes).
- Progress notes or equivalent source documentation for each patient visit and contact (each dated and signed).
- Records of each trial visit including each trial assessment and the identity of the staff member performing the assessment.
- Trial drug dispensing and return.
- Review by the Investigator or qualified personnel of laboratory test results.
- AEs (start and stop date, description, relationship to trial drug, action taken and resolution).
- Investigator or sub-investigator's signed assessment of each AE.
- Concomitant medications (start and stop dates, reason for use).
- Condition of patient upon completion of, or PW from, the trial.

11 CASE REPORT FORMS

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

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

12 TRIAL MONITORING

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

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

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

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

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

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

Every effort will be made to maintain the anonymity and confidentiality of patients participating in this trial. However, the Investigator agrees to allow representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this trial and to have direct access to inspect, for purposes of verification, the

hospital or clinical records of all patients enrolled in this trial. A statement to this effect should be included in the ICF.

13 DATA MANAGEMENT

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

The coding of AE, medical history and concomitant medication terms will be performed by a qualified medical coder and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary and AE/medical history/surgery/non-drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities.

14 RETENTION OF RECORDS

No trial documents at the site should be destroyed without prior written agreement between the Sponsor and the Investigator. All patient medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, IRB correspondence and correspondence with the Sponsor must be kept by the Investigator for at least 2 years or as required by local law following the date of the last approval of a marketing application in an ICH region (including the US) and until there are no pending or contemplated marketing applications in any other ICH region. The Sponsor must be notified prior to the disposal of any trial-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the trial was conducted.

15 PUBLICATION

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

16 REFERENCES

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17 APPENDICES

17.1 Administrative Appendix

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

Medical Monitor	PPD 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: PPD Email: PPD
Sponsor Representative	PPD 1 Horizon Way Deerfield, IL 60015 Office telephone number: PPD Mobile telephone number: PPD Email: PPD
Sponsor Contact for SAE Reporting	Horizon Therapeutics U.S.A., Inc. Fax: PPD Email: PPD

17.2 CCI

17.3 Sampson Criteria for Anaphylactic Reaction

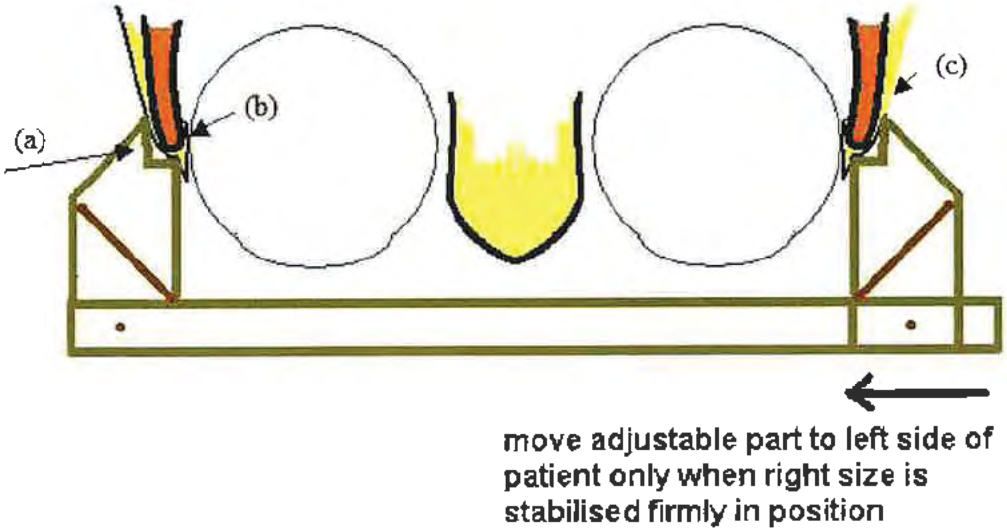
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, cramp, abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

17.4 Proptosis (Exophthalmometry) Method

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



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

9. The distance along the horizonal bar, as defined by the location of the feet on the lateral canthi, is also recorded as the base so that the carriers will be set at the same base at subsequent readings for comparison of the forward protrusion of each eye in relation to the bony orbit.

17.5 CCI [redacted]

Directions:

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

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