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APPLICATION NUMBER:

761143Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of BLA 761143

Application Type	BLA
Application Number(s)	761143
Priority or Standard	Priority
Submitted and Received Date	July 8, 2019
Office	Office of New Drugs
Reviewer Name(s)	Wiley A. Chambers, MD
Review Completion Date	January 13, 2020
Name	Tepezza (teprotumumab-trbw)
Applicant	Horizon Pharma Ireland, Ltd.
Dosage Form(s)	Lyophilized powder for intravenous infusion
Applicant Proposed Dosing Regimen(s)	Intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks. The recommended course of therapy is 8 infusions.
Applicant Proposed Indication(s)	Treatment of Thyroid Eye Disease
Recommendation on Regulatory Action	Approval

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Executive Summary

1.1. Product Introduction

Teprotumumab (HZN-001), a fully human monoclonal antibody (mAb), is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor developed for the treatment of Thyroid Eye Disease.

Thyroid Eye Disease (TED), also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy or Graves' orbitopathy, is a rare, serious, debilitating and painful autoimmune disease associated with major comorbidities that can lead to blindness. TED is more common in women than men (16 per 100,000 versus 3 per 100,000, respectively), with no significant ethnic predisposition. Median age at diagnosis is 43 years. Risk factors for TED include female gender, middle age and smoking. The risk of TED increases 7 to 8 times in smokers. In addition, a positive family history of TED is observed in 61% of TED patients.

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Thyroid Eye Disease (TED) is a rare, serious, debilitating and painful autoimmune disease associated with major comorbidities that can lead to visual disability. The natural history of TED involves an initial progressive worsening of signs and symptoms. Effective therapy has been lacking. Efficacy with teprotumumab, as demonstrated by a reduction in proptosis, has been demonstrated in two adequate and well controlled studies. Eighty-two percent (82%) of patients treated with 8 doses of teprotumumab had at least a two-millimeter reduction in ptosis compared to only 16 percent of patients treated with placebo. A two-millimeter reduction is considered clinically significant because it is expected to reduce the incidence of diplopia and improve the lid coverage over the cornea. The systemic treatment also had an effect on the non-study eye, reducing ptosis in 68% of non-study eyes compared to only 9% of patients treated with placebo. The submitted studies are limited in size with only 120 thyroid patients being treated to date. The most frequently associated adverse events associated with the administration of teprotumumab were muscle spasms, alopecia, nausea, diarrhea, dry skin, dysgeusia and temporary hearing loss. The reported adverse events were generally of limited duration and able to be managed without interruption of therapy.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Thyroid Eye Disease (TED) is a rare, serious, debilitating and painful autoimmune disease associated with major comorbidities that can lead to visual impairment. • The natural history of TED involves an initial progressive worsening of signs and symptoms.	Patients may present with orbital pain, periorbital inflammation, proptosis, eyelid retraction, strabismus and diplopia. Over time, there is a progressive increase in the severity of TED, with an increase in proptosis, increased eyelid aperture, compromised eye motility, diplopia and, in severe cases, dysthyroid optic neuropathy. Sight-threatening disease affects approximately 6% of TED patients.
Current Treatment Options	• There are currently no United States (U.S.) FDA-approved medical treatments available for patients with TED.	Corticosteroids, orbital irradiation and orbital surgery have been used with generally poor results.
Benefit	• Approximately 80% of patients treated with teprotumumab had a reduction in proptosis of at least 2 millimeters.	Proptosis reduction by 2 millimeters or more is expected to reduce diplopia and improve corneal epithelial health by allowing the lids to fully cover the cornea.
Risk and Risk Management	• The most frequently associated adverse events associated with the administration of teprotumumab were muscle spasms, alopecia, nausea, diarrhea, dry skin, dysgeusia and temporary hearing loss.	The reported adverse events were generally of limited duration and able to be managed without interruption of therapy.

1.4 Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[Sec 6 Study endpoints]
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Current Treatment Options

There are no approved drug or biologic products for the proposed indication.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Teprotumumab was originally developed by F. Hoffman-La Roche Ltd., for the treatment of a variety of solid tumors; however, the program was terminated due to lack of efficacy. River Vision Development Corporation initiated a study of teprotumumab for the treatment of diabetic macular edema, but this program was terminated without demonstrating significant efficacy. River Vision initiated a program in Active Thyroid Eye Disease in June 2013. Horizon Pharma USA, Inc. acquired River Vision and continued the program.

3.2. Summary of Presubmission/Submission Regulatory Activity

Teprotumumab infusion was submitted as IND 112952. Teprotumumab was granted orphan designation for the treatment of Active Thyroid Eye Disease on June 19, 2019 [12-3878/DRU-201203878]. Teprotumumab received Fast Track designation in April 2015, and Breakthrough Therapy designation in July 2016.

3.3. Foreign Regulatory Actions and Marketing History

Each of the teprotumumab studies in Thyroid Eye Disease was conducted in the U.S. and Europe (Germany, Italy and the United Kingdom). Of the 171 subjects randomized in the adequate and well-controlled studies of teprotumumab, 57% participated at sites located in the U.S. and 43% participated at sites in Europe. Teprotumumab is not approved for any indication anywhere in the world.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Routine inspections of clinical investigators and the applicant have been completed. Two clinical investigators, Drs. Fowler and Dailey, were inspected in support of this BLA. An inspection of the sponsor, Horizon Pharma, was also conducted. Based on the results of the inspections of the clinical sites and the preliminary results of the inspection of the sponsor, the studies (Protocols HZNP-TEP-301 and TED01RV) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

4.2. Product Quality

The drug product (DP) is a sterile, preservative-free, lyophilized powder for reconstitution and dilution for infusion, which is presented as a white to off-white powder cake. Each vial delivers

500 mg of teprotumumab formulated in (b) (4) histidine, (b) (4) trehalose and (b) (4) polysorbate 20, pH 5.5. The composition of the drug product is provided in Table 1. At time of use, the product is reconstituted with 10 mL of water for injection, which is supplied by the clinical pharmacy, to a final teprotumumab concentration of 47.6 mg/mL. The reconstituted solution for infusion is a clear to opalescent, nearly colorless to slightly brown liquid and practically free of visible particles.

Drug Product Composition

Material	Concentration after reconstitution (per mL)	Amount per Vial	Function
Teprotumumab	50 mg/mL	500 mg	Active
L-Histidine, USP/Ph. Eur./JP	(b) (4)	7.45 mg	Buffer
L-Histidine hydrochloride, monohydrate, Ph. Eur.		31.8 mg	Buffer
α, α – Trehalose dihydrate, NF/Ph. Eur./JP		946 mg	Bulking agent, tonicity agent
Polysorbate 20, NF/Ph. Eur./JPE		1 mg	Surfactant

NF=National Formulary; Ph. Eur.=European Pharmacopeia; USP=United States Pharmacopeia; JP = Japanese Pharmacopeia: JPE = Japanese Pharmaceutical Excipients

4.3. Nonclinical Pharmacology/Toxicology

The nonclinical program consisted primarily of primary and safety pharmacology studies, intravenous toxicity studies in monkeys (up to 39 weeks), and a non-GLP embryo-fetal dose range-finding study in monkeys. Drug administration was associated with cessation of weight gain, decreased serum alkaline phosphatase, and thymic atrophy. Genetic toxicity and carcinogenicity studies with teprotumumab were not conducted or considered necessary for approval.

Teprotumumab was associated with reduced fetal growth and was teratogenic in the non-GLP monkey study. The published literature is mixed regarding the potential for IGF1R inhibition to adversely affect fertility. No adverse signals were identified regarding reproductive tissues in general toxicity studies. The product label will address the potential for fetal harm based on the observed findings and mechanism of action.

4.4. Clinical Pharmacology

Rationale for Dose Selection
The Applicant's rationale for the proposed teprotumumab dosing regimen is that this regimen is expected to produce > 90% saturation of target-mediated clearance of teprotumumab in TED patients. This is based on PK analysis of data from a dose-ranging Phase 1 study (Study BO19373) in oncology patients (dose range: 1 to 16 mg/kg). Overall, the collective findings from a Pop PK analysis conducted by the Applicant from Study B019373 suggest that the proposed teprotumumab regimen is expected to produce > 90% saturation of target-mediated clearance of teprotumumab in TED patients. However, the Applicant has not submitted IGF-1 levels or estimated IGF-1R saturation levels in TED patients. In addition, the Applicant has not provided any IGF-1R/IGF-1 levels vs. efficacy response analysis that suggest a link between the saturation levels of IGF-1R by teprotumumab and its efficacy in TED patients.

Regarding the proposed initial dose of 10 mg/kg, the Applicant indicated that this dose was selected for patient tolerability. At the time of this review, during the clinical development program for TED, the Applicant did not conduct any dose-ranging studies nor evaluated the efficacy, safety, tolerability, and PK of teprotumumab following re-treatment with the proposed dosing regimen (i.e., more than 8 IV injections beyond 24 weeks). In addition, the Applicant did not provide justification for the proposed weight-based dosing regimen nor the treatment duration in TED patients. However, the proposed teprotumumab dosing regimen was evaluated in one Phase 2 Study TED01RV and one Phase 3 Study HZNP-TEP-301 conducted in TED patients and the efficacy and safety findings from these studies were deemed to support the proposed regimen (see the Medical Officer's review).

Characterization of Systemic PK
Characterization of systemic PK of teprotumumab in TED patients was derived by the Applicant based on a Pop PK approach. The Pop PK analyses relied on pooled sparse teprotumumab PK data from 84 patients enrolled in two aforementioned clinical studies in TED patients (Phase 2 Study TED01RV and Phase 3 Study HZNP-TEP-301) and intensive PK data from 36 patients with advanced solid tumors, non-Hodgkin's lymphoma, or Hodgkin's lymphoma enrolled in the Phase 1 Study BO19373. However, the review of the supporting bioanalytical methods for Study TED01RV indicated that the PK samples collected from Study TED01RV were analyzed outside the established long-term stability period. Therefore, the PK data from this study were excluded from the Pop PK analyses by the Clinical Pharmacology review team for purposes of deriving the post-hoc PK parameter estimates for product labeling. The Applicant conducted their Pop PK and E-R analyses using the PK data from Study TED01RV. To further investigate the potential consequence of the PK sample stability related issue, additional Pop PK analyses were performed by the Clinical Pharmacology review team with and without the PK data from Study TED01RV. The findings from this additional analysis suggested no significant impact (<6% difference) on the PK estimates. Therefore, for the purposes of only conducting E-R analyses, the PK data from Study TEDRV01 were retained by the Clinical Pharmacology review team. Systemic teprotumumab PK in TED patients are summarized below.

Post-hoc mean (± standard deviation) PK exposure estimates at steady-state (week 21 to week 24) in 40 patients who were enrolled in Study HZNP-TEP-301 and received an initial intravenous infusion of 10 mg/kg teprotumumab, followed by infusions of 20 mg/kg teprotumumab Q3W are:

Area under the concentration curve (AUC_ss)= 138 (± 34) mg*hr/mL
Peak teprotumumab concentrations (Cmax_ss) = 632 (± 139) µg/mL
Trough teprotumumab concentrations (Cmin_ss) = 176 (± 56) µg/mL

Distribution: From the Pop PK analysis, the mean (± SD) of simulated estimates for the central volume of distribution, peripheral volume of distribution, and inter-compartment clearance at steady-state were 3.26 (± 0.87) L, 4.32 (± 0.67) L, and 0.74 (± 0.16) L/day, respectively.

Elimination: From the Pop PK analysis, the mean (± SD) of simulated estimates for teprotumumab clearance and the elimination half-life were 0.27 (± 0.08) L/day and 20 (± 5) days, respectively.

Metabolism: Metabolism of teprotumumab has not been fully characterized. However, teprotumumab is expected to undergo metabolism via proteolysis.

Specific Populations
Age, Gender, Racial Groups, and Weight: Pop PK analysis suggests that age (18-80 years old), race (103 White patients, 10 Black patients and 3 Asian patients), and weight (45.8-168.7 kg) had no effect on teprotumumab PK. Simulated C_{max} estimates were 15% higher in female patients compared to male patients, however, simulated AUC estimates were similar.

Patients with Hepatic or Renal Impairment: Pop PK analysis in TED patients with mild or moderate renal impairment (measured based on creatinine clearance (CL_{CR}) estimates from 30 to 89 mL/min estimated by Cockcroft-Gault Equation) showed no significant change in the teprotumumab PK compared to TED patients with normal renal function (CL_{CR} > 89 mL/min). Teprotumumab PK has not been evaluated in patients with hepatic impairment and the effect of hepatic impairment on the PK of teprotumumab is unknown.

Immunogenicity
Immunogenicity testing was performed by screening anti-teprotumumab antibodies (ADAs) in serum samples collected from Studies TED01RV and HZNP-TEP-301. However, the ADA assay used for evaluating samples from Study TED01RV was deemed unacceptable by the CMC/OBP review team due to a drug tolerance issue, i.e., drug tolerance level was not adequate. In Study HZNP-TEP-301, none of the 41 teprotumumab treated patients had detectable anti-teprotumumab antibodies in serum; however, one of the 42 patients treated with placebo had detectable anti-teprotumumab antibodies in all collected serum samples from that patient.

Exposure-Response Analysis for Efficacy and Safety
The primary efficacy endpoint for the Phase 2 and Phase 3 studies was proptosis of the eye(s). Overall, there appears to be no conclusive trend of exposure-PRR (proptosis responder rate) relationship in 83 patients with TED from clinical studies HZNP-TEP-301 and TED01RV. The primary adverse events of teprotumumab in TED patients were hyperglycemia and muscle spasm. No exposure-safety relationships were observed for hyperglycemia and muscle spasm using data collected from clinical studies HZNP-TEP-301 and TED01RV (n=84). The exposure-response relationships for efficacy and safety should be interpreted with caution as it is based on a small number of patients from only one dosing regimen that was evaluated. The Applicant did not conduct any dose ranging studies.

5. Sources of Clinical Data and Review Strategy

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
TED01RV	01868997	Randomized, double-masked, placebo-controlled, parallel-group	Teprotumumab or placebo. 10 mg/kg for first infusion; 20 mg/kg for subsequent Q3W IV infusions	24-week treatment followed by 48 week follow-up	Teprotumumab: 42 Placebo: 45	Active Thyroid Eye Disease
HZNP-TEP-301	03298867	Randomized, double-masked, placebo-controlled, parallel-group	Teprotumumab or placebo. 10 mg/kg for first infusion; 20 mg/kg for subsequent Q3W IV infusions	24-week treatment followed by 48 week follow-up and phone/email at Month 6, 12 and 15	Teprotumumab: 41 Placebo: 42	Active Thyroid Eye Disease
HZNP-TEP-302		Open-label, uncontrolled extension study	24-Week treatment period for non-responders or relapsed subjects	24-week treatment with 6 and 12 months phone/email contact	Ongoing	
DME01RV		Open-label, Phase 1, single arm	Teprotumumab 20 mg/kg Q3W	9-week treatment and 24-week follow-up	5	Diabetic macular edema
BO19373		Open-label, Phase 1, Multiple ascending dose	Teprotumumab manufactured in CHO cell line Teprotumumab manufactured in SP2/0 cell lines	6 infusions	61 SP2/0 36 CHO	Advanced solid tumors, non-Hodgkin's and Hodgkin's lymphoma
NO21200		Open-label, Phase 1, pediatric (2-17 years) dose finding	Teprotumumab 3 and 9 mg/kg QW or a PK-derived dose (not to exceed 16 mg/kg) 16 mg/kg Q3W or a PK-derived dose (not to exceed 25 mg/kg)	Limited number of infusions	34	Advanced solid tumors
NO21157/ SARC011		Open-label, Phase 2, single-arm, 2-stage design for each sub-type cohort	9 mg/kg IV QW 27 mg/kg Q3W (Expanded Ewing's Sarcoma cohort)	Repeated infusions until disease progression	317	Recurrent or refractory sarcoma

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
NO22068		Open label, Phase 1, 12 regimens in combination with different standard chemotherapy therapies, 13th regimen of monotherapy of R1507 was added in amendment.	Variable regimens	Repeated infusions until disease progression	104	Advanced malignancies
NO21160		Placebo controlled Phase 2, in combination with erlotinib	16 mg/kg q3W or 9 mg/kg QW in combination with erlotinib	Repeated infusions until disease progression	Teprotumumab: 116 Placebo: 55	NSCLC stage IIIB/IV
NO21746		Open-label, single-arm, Phase 2 in combination with erlotinib	9 mg/kg QW in combination with erlotinib	Up to 24 months	34	NSCLC stage IIIB/IV
NO21161		Open-label, Phase ½, in combination with letrozole	16 mg/kg q3W in combination with letrozole	Up to 24 weeks	6	Postmenopausal with ER+ HER2- advanced letrozole nonresponsive breast cancer
NO21884		Open-label, Phase ½, multiple ascending dose in combination with mTOR inhibitor	16 mg/kg IV q3W in combination with RAD001	Repeated infusions until disease progression	11	Advanced solid tumors
NO2202		Open-label, single-arm, single dose, Phase 1 study	16 mg/kg single IV dose	Single dose	8	Operable breast cancer

Investigators:

HZNP-TEP-301			TED01RV		
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HZNP-TEP-301			TED01RV		
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HZNP-TEP-301			TED01RV		
Principal Investigator (Site No.) Phone e-mail	Study Location	# Subjects Randomized	Principal Investigator (Site No.) Phone e-mail	Study Location	# Subjects Randomized
N/A	N/A	N/A	Maarten Soeters, MD (056) Phone: 3120 566 9111 Email:m.r.soeters @amc.uva.nl	AMC Medical Research BV Dept of Endocrinology and Metabolism – Internal Medicine F5-161, Academico Medical Center Meibergdreef 9 Amsterdam Zuidoost, 1105 AZ The Netherlands	0

Reviewer's Comments: *While there is some overlap in investigators, the overlap is insufficient to preclude the studies from being considered independent of each other.*

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1 Review Study #1

A Multicenter, Double-masked, Placebo-controlled, Efficacy and Safety Study of Teprotumumab (HZN-001), an Insulin-like Growth Factor-1 Receptor (IGF-1R) Antagonist Antibody (fully human), administered every 3 weeks (Q3W) by Intravenous (IV) infusion in patients suffering from active Thyroid Eye Disease – TED01RV

6.1.1. Study Design

Trial Design- Randomized, double-masked, placebo-controlled, parallel-group

Plan-
1) A Screening Phase of 4 weeks (± 2 weeks) with no treatment. Subjects attended the clinic once or twice, or as required, during the screening period.

2) A double-masked Treatment Phase of 24 weeks. Subjects attended clinic visits at Week 0 (baseline visit, 1st infusion), Weeks 1 and 3 (2nd infusion), 4 and 6 (3rd infusion), 9 (4th infusion), 12 (5th infusion), 15 (6th infusion), 18 (7th infusion), 21 (8th infusion), and 24 (final assessment visit). Research staff telephoned subjects focusing on safety and tolerability aspects the day after infusion for the 1st and 2nd infusions, and thereafter as required. Research staff also contacted subjects who experienced an infusion-related event the day after the infusion.

3) A Follow-up Phase of 48 weeks with no additional treatment during at least the first 12 weeks. Subjects attended clinic visits at Week 28, 36, 48, 60, and 72.

Eligible subjects who met study entry criteria were randomly assigned to the double-masked treatment phase in a 1:1 ratio to receive a starting dose of 10 mg/kg of HZN-001 or placebo once every 3 weeks (q3W) by IV. At Week 3, the dose was escalated to 20 mg/kg IV q3W. Following dose escalation, subjects continued at this dose level for all subsequent infusions.

In the case of an intolerable adverse event (AE), subjects were to be withdrawn from the study. The active treatment phase of the study was 24 weeks (8 infusions) in duration. Randomization was stratified by smoking status. During the treatment period, subjects were evaluated at clinic visits every 3 weeks and, if appropriate, by telephone contact by research staff. Measurements for efficacy, tolerability, safety, biomarkers, and pharmacokinetics were performed according to the assessment schedule.

Subjects were to be withdrawn from the study if they developed optic neuropathy or any condition that required surgical intervention. An independent data and safety monitoring board (DSMB) was chartered to review safety data on a regular basis; the DSMB was masked to efficacy data.

Key Inclusion Criteria:

1. Age 18 to 75 years.
2. Clinical diagnosis of Grave's disease associated with active TED with a clinical activity score of ≥4 for the most severely affected eye.
3. Fewer than 9 months from onset of TED.
4. Euthyroid or with mild hypo- or hyperthyroidism defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits.

Key Exclusion Criteria:

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision within the last 6 months of 2 lines, new visual field defect or color defect.
2. Improvement in CAS of ≥2 points between screening and baseline.
3. Treatment with oral or IV steroids within the previous 3 months (except doses less than 1g methylprednisolone or equivalent)
4. Previous orbital irradiation.
5. Poorly controlled diabetes.

Clinical Activity Score (CAS)

Subjects were assessed at screening and predose at Visit 1 (Week 0, baseline assessment) and at Weeks 6, 12, 18, 24, 28, and 72 using the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS [Mourits et al. 1989; Mourits et al. 1997]. The 7-point CAS scale is comprised of 2 patient-reported outcomes and 5 clinician-reported outcomes. For each item present, 1 point was given. The sum of these points was the total score.

1. Spontaneous orbital pain.
2. Gaze-evoked orbital pain.
3. Eyelid swelling that was considered to be due to active (inflammatory phase) Graves Ophthalmopathy.
4. Eyelid erythema.
5. Conjunctival redness that was considered to be due to active (inflammatory phase) Graves Ophthalmopathy (ignore "equivocal" redness).
6. Chemosis.
7. Inflammation of caruncle or plica.

Reviewer's Comments: *The Agency disagreed with the construction of the CAS score. The CAS score is a composite with equal weighting of a number of factors. However, FDA's clinical team does not consider these factors to be of equal weight either to the patients or to physician's treating these patients.*

Proptosis
For assessment of proptosis, the same Hertel instrument and intercanthal distance was to be used at each time point. Every effort was made for the same observer to conduct the assessment on each occasion. The Hertel values were measured for each eye at all time points.

Graves' Ophthalmopathy Quality of Life Scale
The Graves' Ophthalmopathy Quality of Life (GO-QOL) scale [Terwee 1998] was completed at screening, Weeks 6, 12, 24, 28, 48, 72, and early withdrawal. The GO-QOL is a 16-item self-administered questionnaire used to assess the perceived effects of TED by subjects on their daily physical and psychosocial functioning.

Clinical Measures of Severity Score (CSS)

CSS Item and Assessment Scale	Minimum change required for classifying overall response
Lid aperture (distance between the lid margins (mm) with the subject looking in the primary position sitting relaxed and with distant fixation)	Decrease ≥2 mm
Swelling of the eyelids (absent, mild, moderate, or severe)	Decrease ≥1 grade
Redness of the eyelids (absent, present)	Decrease ≥1 grade
Redness of the conjunctiva (absent, present)	Decrease ≥1 grade
Conjunctival edema (absent, present)	Decrease ≥1 grade
Inflammation of the caruncle or plica (absent, present)	Decrease ≥1 grade
Exophthalmos (measured in mm using the same Hertel ophthalmometer and same intercanthal distance for each individual subject)	Decrease ≥2 mm
Subjective diplopia score (0=no diplopia; 1=intermittent, i.e., diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e., diplopia at extremes of gaze; 3=constant, i.e., continuous diplopia in primary or reading position)	Decrease ≥1 grade
Eye muscle involvement (ductions in degrees)	Increase ≥8° in at least one direction of gaze
Corneal involvement (absent/punctate keratopathy/ulcer)	Decrease ≥1 grade
Optic nerve involvement (best corrected visual acuity, color vision, optic disc, relative afferent pupillary defect (absent, present), plus visual fields if optic nerve compression is suspected.	Change of best corrected visual acuity by ≥2 lines on Snellen chart, or substantial color vision change, or significant change of visual fields, or significant change in optic disc appearance, or (Dis-)appearance of relative afferent pupillary defect

Ophthalmic Examination
The ophthalmic examination included best-corrected visual acuity, pupil examination and color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure, and slit lamp examination. If significant abnormalities were noted compared with

previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including afferent pupillary defect, rise in intraocular pressure, development of corneal infiltrates, or other abnormalities that were of concern to the ophthalmologist, further investigations of visual function were conducted according to the ophthalmologist's decision.

Clinical Laboratory Evaluations

The following laboratory tests were performed at screening, baseline (Week 0), Weeks 3, 6, 9, 12, 18, 24, 36, 72, and early withdrawal. All sampling was performed prior to dosing (at infusion visits). Results for blood glucose and platelets from the previous visit were evaluated prior to dosing.

- Hematology: hemoglobin, platelet count, white blood cells and differential (also at Weeks 1, 4, 15, and 21)
- Renal Function: serum creatinine and blood urea nitrogen
- Hepatic function: total bilirubin, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transferase, SGOT/AST, and alanine aminotransferase SGPT/ALT
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium, and phosphate
- Blood glucose: fasting at Weeks 1 and 4 and non-fasting at other study time points
- Hemoglobin A1c: at screening and Weeks 12, 24, 36, and 72
- Thyroid function tests: FT4, FT3 and TSH (TSH Germany only – Site 50)
- Human anti-human antibodies (HAHA): serum sample prior to dosing at Weeks 0, 3, and 9, and at Weeks 24, 36, and 72. Analysis of HAHA was performed only when all subjects had completed the masked treatment phase of the study. Any subject with treatment emergent positive HAHA titer, which was still present at Week 72, was followed. This included subjects with HAHA detected post-dose and those with positive baseline HAHA if there was an important increase in titer post-dose.
- Serum pregnancy test (for women of childbearing potential) at screening only. Urine pregnancy test at all other time points (Weeks 0, 3, 6, 9, 12, 15, 18, 21, 24, 28, 36, and early withdrawal)
- Complete urinalysis (including specific gravity, protein, blood, ketones, glucose, etc.) Hematology and blood glucose were performed for all subjects at Weeks 1, 4, 15, and 21. Subjects were fasting at Weeks 1 and 4.

Biomarker Assessments

Blood for plasma and serum was collected at baseline (Week 0) and at Weeks 12, 24, 28 and 72. Samples used for biomarker assays included thyroid stimulating immunoglobulin (TSI) and TBII; anti-thyroid peroxidase (TPO) and anti-thyroglobulin antibodies; T and B cell and fibrocyte flow cytometry for IGF-1R (Weeks 0 and 28 only) and TSHR levels; serum IL-6, IL-16, and RANTES (Weeks 0, 12, 24, and 72 only).

Treatment
HZN-001 or placebo was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All subjects were started at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and remained there for the rest of the study. The first and second infusions were administered over 90 minutes. Subsequent infusions were administered over a 60-minute period, providing there were no significant infusion-related events. Subjects with intolerable AEs were to be withdrawn from the study.

Review Study #1 Primary Efficacy Endpoint
The primary efficacy endpoint was whether the subject was a responder or not (yes or no) at Week 24. A responder was defined as a subject with the following:

- A decrease in overall CAS ≥2 points AND
- A reduction in proptosis ≥2 mm, AND
- No deterioration of CAS in the Non-Study Eye (i.e., increase of CAS ≥2 points OR increase in proptosis ≥2 mm) at the 24-week evaluation.

Reviewer's Comments: *The Agency disagreed with the inclusion of the CAS score in the primary endpoint. The CAS score is a composite with equal weighting of a number of factors. However, FDA's clinical team does not consider these factors to be of equal weight either to the patients or to physician's treating these patients. The primary hallmark of patient symptoms and concerns is proptosis and therefore the Agency considered proptosis to be the primary endpoint.*

Review Study #1 Follow-up
To evaluate subjects off-treatment following the masked 24-Week Treatment Phase with teprotumumab or placebo in subjects diagnosed with active TED. The off-treatment Follow-up Period was designed to assess safety, including evaluation of the possibility of an acute disease activity rebound effect off treatment, during the 30-day Follow-up Period (Week 24 to Week 28), and evaluate continued short-term response of teprotumumab after 4 weeks of treatment discontinuation at Week 28. Continued teprotumumab treatment effect as well as worsening of disease requiring additional treatment was evaluated in the long-term follow-up at Week 72.

The off-treatment follow-up period was for 48 weeks, with no additional treatment for TED during at least the first 12 weeks, unless medically indicated. Subjects attended clinic visits at Weeks 28, 36, 48, 60, and 72 for safety assessments; efficacy was only measured at Weeks 28 and 72.

For responder/non-responder analyses, any subject who received additional treatment for thyroid eye disease (TED) was considered a non-responder from the time of TED treatment forward. A proptosis relapse/non-relapse analysis was performed for Weeks 28 and 72 based on if a subject was a proptosis responder at Week 24 (relapse was defined as an increase in proptosis of ≥2 mm from Week 24).

6.1.2. Review Study #1 Results

Patient Disposition

There were 88 subjects enrolled in the study. Of these, 87 subjects took at least 1 dose of study drug and were included in the ITT and mITT Populations.

	Placebo (N=45) n (%)	HZN-001 (N=43) n (%)
Enrolled (Informed Consent Signed)	45	43
ITT Population	45 (100%)	42 (98%)
MITT Population	45 (100%)	42 (98%)
PP Population	36 (80%)	33 (77%)
Safety Population	44 (98%)	43 (100%)
Completed the Study Treatment Reason for Early	39 (87%)	37 (86%)
Termination		
Adverse Event	1 (2%)	5 (12%)
Lack of Efficacy	2 (4%)	0
Pregnancy	0	0
Protocol Violation	0	0
Study Terminated by Sponsor	0	0
Death	0	0
Other – see Note below	3 (7%)	1 (2%)

Abbreviations: ITT = intent to treat, MITT=modified intent to treat, PP=per protocol.

Note: All subjects who signed informed consent were considered enrolled in the study. The percentages presented in this table are based on the ITT Population. Three subjects received the wrong treatment; these 3 subjects were excluded from the PP Population and analyzed under the first treatment actually received for the Safety Population. One subject (Subject (b) (6)), randomized to HZN-001, terminated early, and never received any study drug.

Demographic and Baseline Characteristics (Safety Population)

Review Study #1	Placebo (N=44)	HZN-001 (N=43)
Age (years) Mean (SD)	54.2 (13.0)	51.6 (10.7)
Median	55.4	50.5
(Min, Max)	(20.4, 77.0)	(22.3, 72.6)
<65 years old	36 (80%)	39 (91%)
≥65 years old	9 (20%)	4 (9%)
Gender, n (%)		
Female	36 (82%)	28 (65%)
Ethnicity, n (%)		
Hispanic or Latino	4 (9%)	2 (5%)
Not Hispanic or Latino	40 (91%)	41 (95%)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	2 (5%)	1 (2%)
Black or African–American	4 (9%)	4 (9%)
Native Hawaiian or Other Pacific Islander	0	1 (2.3)
White	38 (86%)	37 (86%)
Weight (kg), N	44	43
Mean (SD)	78.8 (16.88)	82.5 (23.73)
Median	73.3	75.0
(Min, Max)	(53.6, 122.0)	(47.6, 168.7)
Study Eye, n(%)		
Right Eye	20 (45%)	27 (63%)
Smoking Status, n(%)		
Smoker	18 (41%)	11 (26%)
CAS Score in Study Eye at Baseline n (%)		
0 or 1	0	0
2	0	1 (2%)
3	0	0
4	6 (14%)	10 (23%)
5	23 (52%)	18 (42%)
6	13 (30%)	12 (28%)
7	2 (5%)	2 (5%)
Exophthalmos (mm), N	44	43
Mean (SD)	22.91 (2.67)	23.57 (3.36)
Median	22.5	23.0
Min, Max	(16.0, 29.0)	(17.0, 33.0)

Abbreviation: CAS=Clinical Activity Score; CSS = Clinical Measures of Severity Score; ITT=intent-to-treat; N = number; SD =standard deviation

[a] Baseline was the last predose measurement.

Efficacy Results – Review Study #1 Primary Endpoint

Responder (CAS+Proptosis)

	Placebo	Teprotumumab	Difference (95% conf)	p-value
Week 6 Study Eye	2/42 (5%)	18/39 (46%)	41% (24,58)	<0.001
Week 12 Study Eye	2/41 (5%)	23/40 (58%)	53% (36,69)	<0.001
Week 18 Study Eye	2/41 (5%)	30/39 (77%)	72% (57,87)	<0.001
Week 24 Study Eye	9/39 (23%)	29/38 (76%)	53% (34,72)	<0.001
Week 28 Study Eye*	6	31		
Week 6 Non-Study Eye	2/42 (5%)	8/39 (21%)	16% (2,30)	0.031
Week 12 Non-Study Eye	1/41 (2%)	13/40 (33%)	30% (15,45)	<0.001
Week 18 Non-Study Eye	1/41 (2%)	17/39 (44%)	41% (25,57)	<0.001
Week 24 Non-study Eye	6/39 (13%)	22/38 (58%)	42% (23,62)	<0.001
Week 28 Non-study Eye*	5	20		

p-value based on chi square
* Off treatment for 4 weeks

Reviewer's Comments: *The Agency disagreed with the Primary endpoint due to the inclusion of the CAS portion of the endpoint. The CAS assigns equal weight to a number of components which have different clinical value to both patients and clinicians. The Agency requested an endpoint which included only Proptosis.*

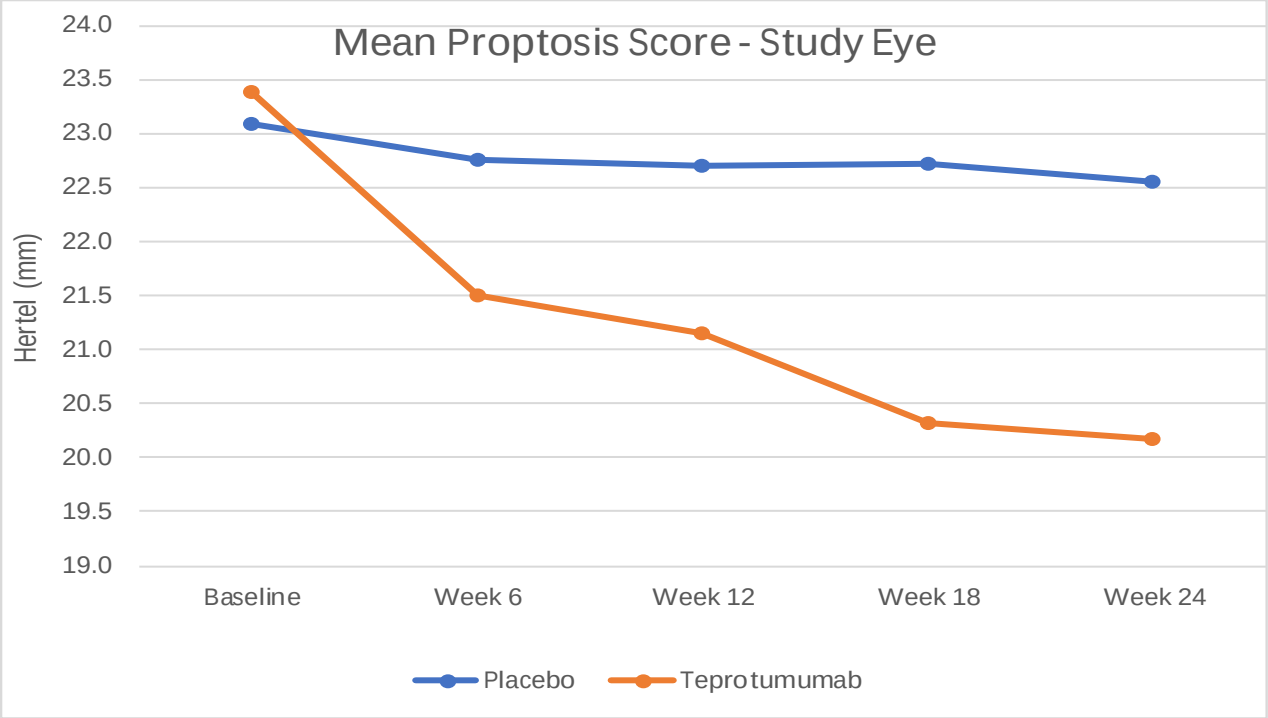
Agency's Requested – Primary Endpoint: % patients with 2 mm or more decrease in Proptosis

Proptosis	Placebo	Teprotumumab	Difference (95% conf)	p-value
Week 6 Study Eye	4/42 (10%)	22/40 (55%)	45%	<0.001
Week 12 Study Eye	2/41 (5%)	24/40 (60%)	55%	<0.001
Week 18 Study Eye	4/41 (10%)	32/39 (82%)	72%	<0.001
Week 24 Study Eye	9/39 (23%)	30/38 (79%)	56%	<0.001
Week 28 Study Eye*	6	31		
Week 6 Non-study Eye	3/42 (7%)	9/40 (23%)	16%	<0.001
Week 12 Non-study Eye	3/41 (7%)	15/40 (38%)	31%	<0.001
Week 18 Non-study Eye	4/41 (10%)	21/39 (54%)	44%	<0.001
Week 24 Non-study Eye	6/39 (15%)	26/38 (68%)	53%	<0.001

* Off treatment for 4 weeks

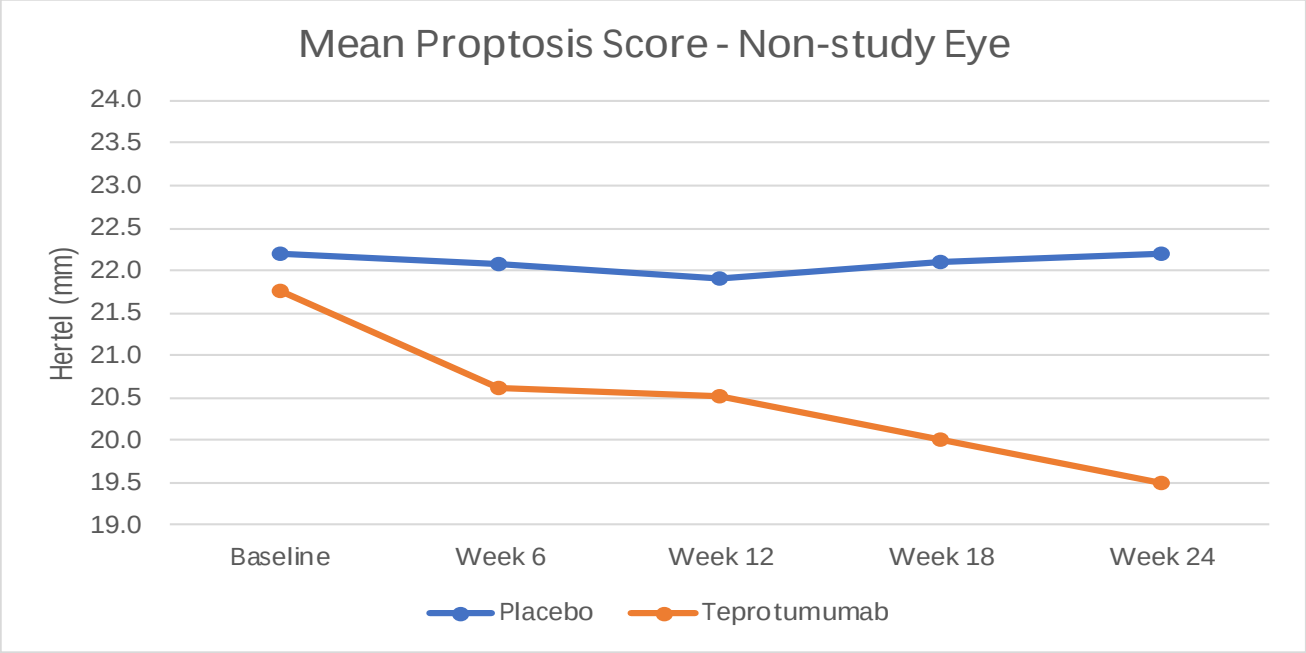
Reviewer's Comments: *By the first evaluation period at Week 6, there is a clinically significant reduction in proptosis (i.e., greater than 2 mm) in both eyes which continues through the treatment period.*

Review Study #1



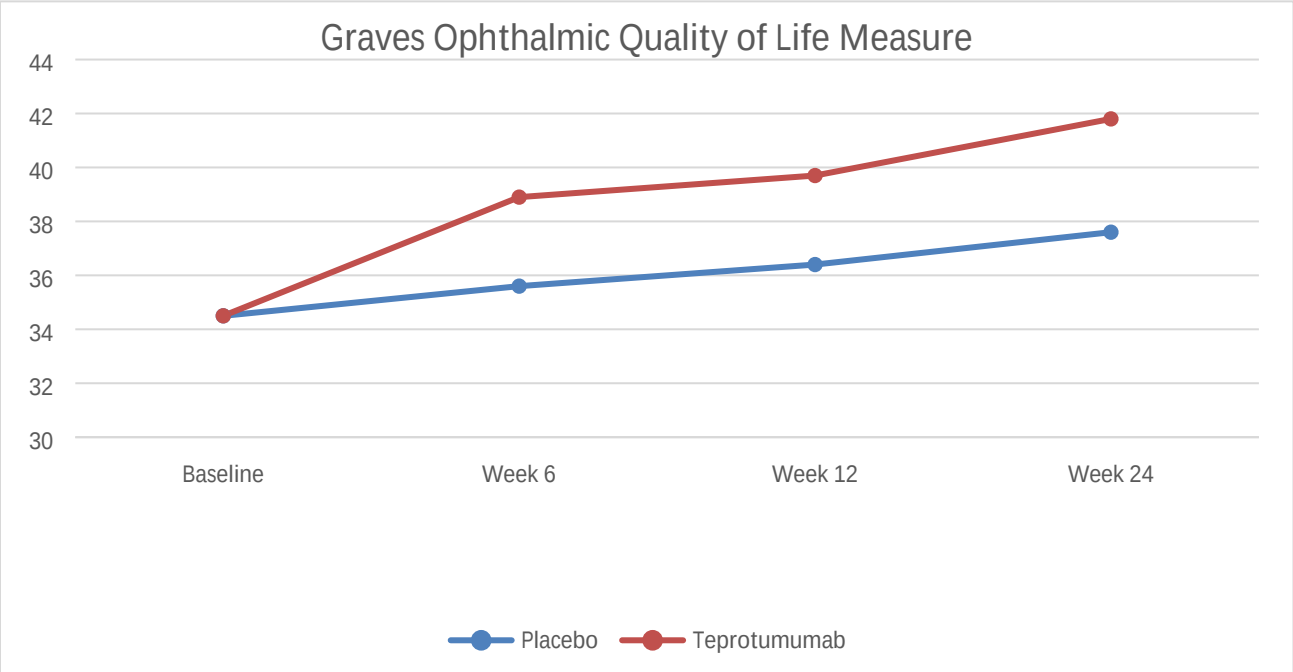
Reviewer's Comments: *By the first evaluation period at Week 6, there is a reduction in proptosis which continues through the treatment period.*

Review Study #1



Reviewer's Comments: *By the first evaluation period at Week 6, there is a reduction in proptosis in both eyes which continues through the treatment period.*

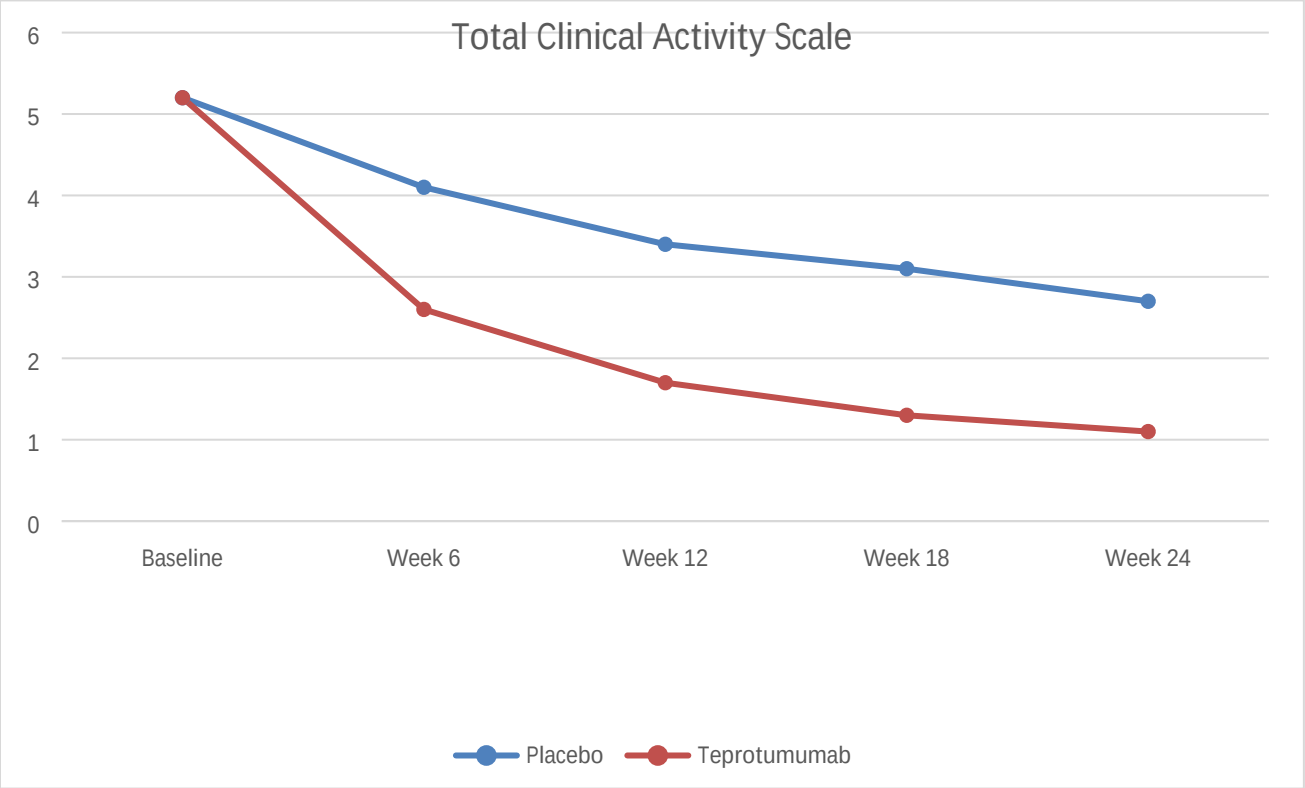
Review Study #1: Secondary Endpoints



Grave's Ophthal Quality of Life Score	Placebo	Teprotumumab	Difference
Baseline	34.5 (6.8)	34.5 (7.4)	0
Week 6	35.6 (6.3)	38.9 (7.2)	3.3
Week 12	36.4 (6.9)	39.7 (6.2)	3.3
Week 24	37.6 (6.9)	41.8 (6.4)	4.2

Reviewer's Comments: *Validation information for the Grave's Ophthalmology Quality of Life Score has not been submitted and therefore interpretation of the scores is not possible.*

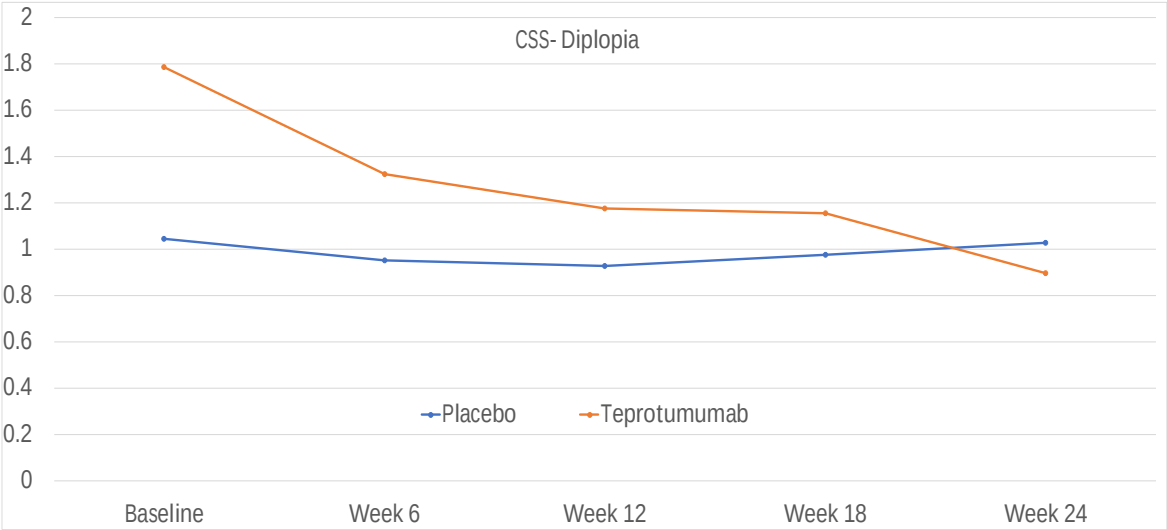
Review Study #1



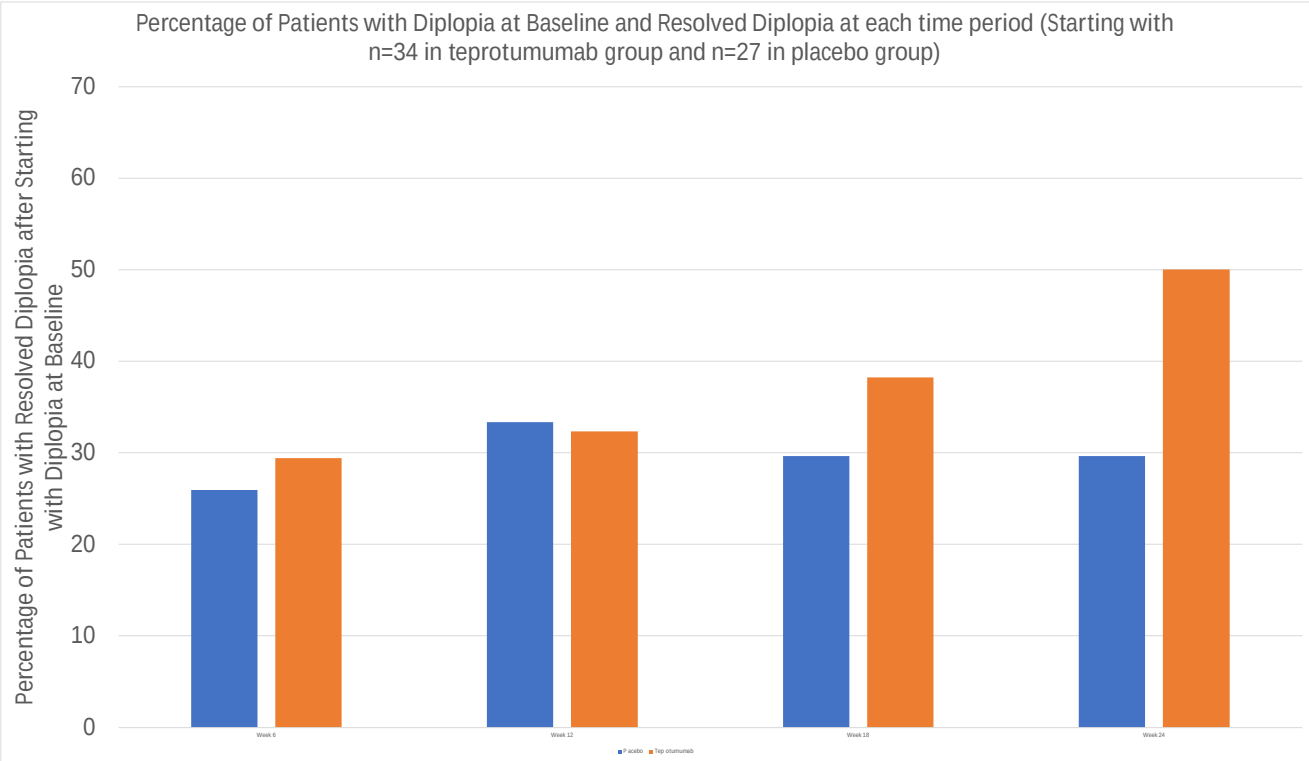
CAS Change from Baseline	Placebo	Teprotumumab	Difference
Baseline	5.2	5.1	0.1
Week 6	-1.1	-2.5	-1.5
Week 12	-1.8	-3.4	-1.6
Week 18	-2.1	-3.8	-1.7
Week 24	-2.5	-4.0	-1.6

Reviewer's Comments: *Clinical Activity Scale is not accepted because there is not necessarily equal weight for each component.*

Review Study #1 Subjective Diplopia measured on CSS Score (ITT Population)



Resolved Diplopia



	Placebo (N=45)	Teprotumumab (N=42)
Baseline		
0, no diplopia	14 (31.1)	4 (9.5)
1, intermittent	19 (42.2)	16 (38.1)
2, inconstant	8 (17.8)	7 (16.7)
3, constant	4 (8.9)	15 (35.7)
Week 6, n (%)		
0, no diplopia	18 (40.0)	13 (31.0)
1, intermittent	12 (26.7)	11 (26.2)
2, inconstant	8 (17.8)	6 (14.3)
3, constant	4 (8.9)	10 (23.8)
CSS responder, n (%)	9 (21.4)	17 (42.5)
Week 12, n (%)		
0, no diplopia	20 (44.4)	16 (38.1)
1, intermittent	9 (20.0)	8 (19.0)
2, inconstant	7 (15.6)	9 (21.4)
3, constant	5 (11.1)	7 (16.7)
CSS responder, n (%)	10 (24.4)	24 (60.0)
Week 18, n (%)		
0, no diplopia	19 (42.2)	16 (38.1)
1, intermittent	9 (20.0)	8 (19.0)
2, inconstant	8 (17.8)	8 (19.0)
3, constant	5 (11.1)	7 (16.7)
CSS responder, n (%)	11 (26.8)	23 (59.0)
Week 24, n (%)		
0, no diplopia	18 (40.0)	21 (50.0)
1, intermittent	8 (17.8)	4 (9.5)
2, inconstant	7 (15.6)	9 (21.4)
3, constant	6 (13.3)	4 (9.5)
CSS responder, n (%)	10 (25.6)	26 (68.4)

Reviewer's Comments: *As a single question about diplopia, the response demonstrates an improvement in diplopia.*

6.1.3 Subject Disposition from Week 24 to Week 72 (All Subjects)

	Placebo, N=45 n (%)	Teprotumumab, N=42 n (%)
ITT Population	45	42
Completed Study Treatment (Week 24)	39	37
Completed Extended Follow-up (Week 72)	38	36
Reason for Extended Follow-up Termination		
Adverse Event	2	5
Lack of Efficacy	2	0
Other[a]	3	1

Source: Table 14.1.1 Abbreviations: ITT = intent-to-treat; TED = thyroid eye disease

a. Placebo group: left eye optic disc edema (b) (6); incorrect treatment given (b) (6); and subject decision to withdraw (b) (6). Teprotumumab group: elective TED surgery (b) (6)

Subjects who received additional TED treatment during the off-treatment follow-up period

Subject	Group	Study Week	Corticosteroids	Rituximab	Orbital Decompression
(b) (6)	Placebo	26	Yes		Yes
	Placebo	25	Yes		
	Placebo	28	Yes		Yes
	Placebo	29	Yes	Yes	Yes
	Placebo	60			Yes
	Placebo	57			Yes
a	Teprotumumab	47	Yes		
a	Teprotumumab	50	Yes		
a	Teprotumumab	62	Yes		Yes
a	Teprotumumab	70			Yes[b]

Source: Listing 16.2.3.7.3
a. Responder at Week 24
b. Elective TED surgery at Week 70; no proptosis data collected at Week 72

Proportions of Proptosis Responders Who Relapsed **(≥2** mm) from Week 24 through Week 72

	Placebo	Teprotumumab
Week 28, n		
Relapse[a]	1 (11%)	0
No Relapse	8 (89%)	29 (97%)
Missing[b]	0	1 (3%)
Week 72, n		
Relapse[a]	3 (33%)	11 (37%)
No Relapse	6 (67%)	18 (60%)
Missing[c]	0	1 (3%)

Source: Table 14.2.2.2.2.6
Includes Week 24 proptosis responders. Subjects who received TED treatment in the off-treatment Follow-up Period were treated as relapsed from the time of TED treatment forward.

a. Relapse was defined as an increase in proptosis of ≥2 mm from Week 24 in the Study Eye only.
b. Subject (b) (6) Week 28 proptosis value is missing.
c. Subject had elective TED surgery at Week 70; therefore, the Week 72 proptosis value is missing.

Reviewer's Comments: *Relapses occur in the follow-up period after treatment. However, approximately 60% of patients did not relapse in the year following treatment.*

6.2 Review Study #2 Protocol

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

Short title: Treatment of Graves' **O**rbitopathy to Reduce **P**roptosis with **T**eprotumumab **I**nfusions in a Randomized, Placebo-Controlled, **C**linical Study (OPTIC)

6.2.1 Review Study #2 Study Design

Trial Design- Same as Review Study #1
Plan- Same as Review Study #1
Key Inclusion Criteria: Same as Review Study #1 except maximum age of 80.
Key Exclusion Criteria: Same as Review Study #1
Clinical Activity Score (CAS)- Same as Review Study #1
Proptosis- Same as Review Study #1
Graves' Ophthalmopathy Quality of Life Scale- Same as Review Study #1
Clinical Measures of Severity Score (CSS)- Same as Review Study #1
Treatment- Same as Review Study #1

Ophthalmic Examination
The ophthalmic examination included pupil examination, color vision assessment, intraocular pressure, and slit lamp examination. If significant abnormalities were noted compared with previous visits, including a loss of 2 lines or more of vision.

Clinical Laboratory Evaluations- see Schedule of Events Table

Criteria for Responders Who Relapse
Subjects who met the response criteria at Week 24, but subsequently experience a disease relapse
during the 48-week Follow-up Period will have the option to enter the open-label extension study
(HZNP-TEP-302) and receive 8 infusions of teprotumumab. Determination of relapse is based on the following criteria:

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

Review Study #2 Schedule of Events: Screening, Treatment and Follow-up Periods

	Screening[1]	Treatment Period[2]										Follow-Up Period[3]						Follow-Up Contact[4]	
Study Visit	S1/S2/ S3	1	2	3	4	5	6	7	8	9	10	11/ PW1[5]	12	13	14	15	16/ PW2[6]	17	18
Week (W)/Month(M)	-42 to -14 days	Day 1[7]	W1	W3	W4/M 1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M24	W120/ M30
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
Informed consent	X																		
Review inc/exc criteria	X	X																	
Demographics	X																		
Medical history 8	X[9]	X																	
Weight [10]	X							X				X		X	X	X	X		
Randomization 11		X[7]																	
Study drug infusion		X		X		X	X	X	X	X	X								
Phone (email) contact for		X		X															
Safety 24 hours postdose [12]																			
Efficacy assessments																			
Clinical Activity Score[13]	X	X[14]				X		X		X		X	X	X	X	X	X		
Clinical Measures of Severity - includes proptosis, diplopia and motility restriction	X	X[15]				X		X		X		X	X	X	X	X	X		
Pregnancy test[16]	X	X		X		X	X	X	X	X	X	X	X	X	X		X[17]		
Physical examination[18]	X[19]	X[18]	X			X		X		X		X[18]			X		X[18]		
Ophthalmic examination[20]	X[21]	X	X			X		X		X		X			X		X		
Vital signs[22]	X	X[22]	X	X[22]	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X	X		X		X		X				X					X		
Clinical laboratory tests[23]																			
Chemistry (excl. glucose)	X[24]	X		X		X	X	X		X		X		X			X		
Thyroid (F3, FT4,TSH)[25]	X	X		X		X	X	X		X		X		X			X		
Hematology	X	X	X		X	X	X	X	X	X	X	X		X			X		
Glucose[23]	X	X	X	X	X	X	X	X	X	X	X	X		X			X		
HbA1c [26]	X							X				X		X			X		
Urinalysis	X	X		X		X	X	X		X		X		X			X		
ADA/NAb samples[27]		X		X			X					X[28]		X			X		
AE/ SAE assessment [29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
GO-QoL Questionnaire		X				X		X				X	X		X		X		

	Screening[1]	Treatment Period[2]										Follow-Up Period[3]						Follow-Up Contact[4]	
Study Visit	S1/S2/ S3	1	2	3	4	5	6	7	8	9	10	11/ PW1[5]	12	13	14	15	16/ PW2[6]	17	18
Week (W)/Month(M)	-42 to -14 days	Day 1[7]	W1	W3	W4/M 1	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W36/ M9	W48/ M12	W60/ M15	W72/ M18	W96/ M24	W120/ M30
Visit Window (± days)		(±3)	(±1)	(±3)	(±1)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)
Biomarker samples[30]		X						X				X							
Pharmacokinetic samples[31]		X	X	X	X		X					X[28]							
Contact (phone/ email) to assess additional TED Treatment[32]																		X	X

ADA = anti-drug antibody; AE = adverse event; CAS = Clinical Activity Score; ECG = electrocardiogram; exc = exclusion; FT3 = free triiodothyronine; FT4 = free thyroxine; GO-QoL = Graves' Ophthalmopathy Quality of Life; HbA1c = glycated hemoglobin; IL = interleukin; inc = inclusion; INFγ = interferon gamma; micRNA = microribonucleic acid; NAb = neutralizing antibody; PW = premature withdrawal; q3W = every 3 weeks; S = Screening; SAE = serious adverse event; sIL-1RA = secretory interleukin-1 receptor antagonist;
TED = thyroid eye disease; TGFβ = transforming growth factor beta; TNFα = tumor necrosis factor alpha; TSH = thyroid-stimulating hormone; TSH-R-Ab = thyroid-stimulating-hormone-receptor stimulating, blocking and binding antibody; ULN = upper limit of normal.

1. Screening procedures could have taken place over more than 1 day/clinic visit provided consent was obtained first and all assessments were completed within the designated window.
2. Double-Masked Treatment Period. Subjects who were proptosis non-responders at Week 24 were eligible to enroll in an open-label extension study in which all subjects receive teprotumumab 20 mg/kg (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions).
3. Proptosis responders and non-responders who chose not to enroll in the open-label extension study participated in a Follow-Up Period.
4. Subjects who completed the Week 72 Visit were contacted via phone or email by research staff to enquire if any treatment for TED had been received since last study contact.
5. If a subject prematurely discontinued study drug during the Double-Masked Treatment Period, they returned for a clinic visit and underwent the Week 24 assessments, with the exception of the collection of blood samples for pharmacokinetic and ADA evaluations. Subjects were encouraged to continue study participation in the Follow-Up Period.
6. If a subject prematurely discontinued from the study during the Follow-Up Period, they returned for a clinic visit and underwent the Week 72 assessments prior to discharge.
7. On Day 1 (Baseline), subjects were randomized and received the first dose of study drug; however, Baseline assessments were performed prior to dosing.
8. Medical history included tobacco use history and Graves' disease and treatment history.
9. TED must have been moderate to severe in intensity (non-sight threatening but appreciable impact on daily life) with an onset of symptoms (as determined by subject records) within 9 months prior to the Baseline Visit for study enrollment.
10. Dosing was adjusted if there was a change in weight during the Double-Masked Treatment Period. The weight obtained at Week 12 could have been used in dose calculations beginning at Week 12 or Week 15.
11. Subjects were randomized in a 1:1 ratio (stratified by tobacco use status) to receive either: a) teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) or b) placebo (q3W for all 8 infusions).
12. Phone (or email) contact by research staff focusing on safety and tolerability aspects was made the day after infusion for the first and second infusions, and thereafter as deemed appropriate. In addition, subjects who experienced an infusion-associated event after any subsequent infusion were also contacted by phone (or email) by research staff the day after the infusion, and thereafter as deemed appropriate.
13. CAS must have been ≥4 for enrollment and randomization.
14. Subjects whose CAS in the study eye decreased 2 or more points from Screening were not eligible for randomization.
15. Subjects who had a ≥2 mm decrease in proptosis in the study eye from Screening were not eligible for randomization.
16. Serum pregnancy test at Screening and urine pregnancy tests prior to dosing at all other visits, as applicable. Performed for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Screening,

non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]).

17. Pregnancy test only performed for female subjects of childbearing potential who entered the Follow-Up Period but discontinued study participation prior to Week 48.
18. Physical examination included assessment of presence or absence of pretibial myxedema on Day 1 and Week 24 (or PW) of the Double-Masked Treatment Period and Week 72 (or PW) of the Follow-Up Period. If present, measurements of instep and calf were taken.
19. Height was measured at Screening only.
20. Ophthalmic examination: best corrected visual acuity, pupil examination, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure and slit lamp examination. If significant abnormalities, including a loss of 2 lines or more of vision, development of pupil abnormalities including afferent pupillary defect, rise in intraocular pressure, development of corneal infiltrates or other abnormalities not specified here but of concern to the ophthalmologist, were noted compared to previous visits, further investigations of visual function were conducted according to the ophthalmologist's decision.
21. Subjects who had 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) were not eligible for randomization.
22. Vital signs (heart rate, blood pressure, respiratory rate, temperature) were measured at all clinic visits. Vital signs were measured pre- and post-infusion on Day 1 and Week 3, and predose on all other infusion days. Additional vital signs were monitored if infusion-associated AEs occurred.
23. Non-diabetic subjects were fasting at Weeks 1 and 4 only. Diabetic subjects were fasting at each visit blood glucose was evaluated.
24. Alanine aminotransferase/aspartate aminotransferase was to be ≤3 × ULN and serum creatinine was to be <1.5 × ULN according to age to be eligible for randomization.
25. Hypothyroidism (defined as FT4 and FT3 levels <50% above or below the normal limits). Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the clinical trial.
26. HbA1c was <9.0% for randomization. If the HbA1c was elevated and considered clinically significant at any time point after Screening, it was repeated approximately every 45 days until it returned to normal or Baseline value.
27. If a sample was positive in the ADA test, after confirmatory and reactive titer testing, the sample was then tested for NAb. If the subject tested positive for NAb, he/she was followed until levels either reverted to Baseline or the subject's value decreased or remained stable. Any subject with a positive NAb test at Week 72 (or PW) during the Follow-Up Period continued to be followed until the subject's value decreased or remained stable.
28. Not collected for subjects who prematurely discontinued from the Double-Masked Treatment Period.
29. AEs that occurred within 2 weeks prior to Day 1 and prior to dosing on Day 1 were considered Baseline signs/symptoms. AEs occurring or worsening after the first dose on Day 1 through the end of the Double-Masked Treatment Period were considered treatment-emergent. AEs occurring or worsening during the Follow-Up Period were considered postdose AEs. All SAEs that occurred from the signing of informed consent through 30 days after study discontinuation were recorded.
30. Serum was obtained on Day 1 and Weeks 12 and 24 of the Double-Masked Treatment Period for possible analysis of IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-1β, sIL-1RA, INFγ, TGFβ, TNFα, micRNA and TSH-R-Ab. Based on the results of the assays, other similar serum biomarkers may have been assayed to further explore drug and disease mechanisms.
31. Pharmacokinetic samples were collected prior to and at the end of the infusion on Day 1 and Weeks 3 and 9 of the Double-Masked Treatment Period; additional single samples were collected at Weeks 1, 4 and 24.
32. If TED treatment had been received since last contact, the subject was questioned regarding type of treatment and outcome/response.

Review Study #2 Primary Efficacy Endpoint- The primary efficacy endpoint was the proptosis responder rate (percentage of subjects with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration [≥2 mm increase] of proptosis in the fellow eye) at Week 24.

Reviewer's Comments: *The Agency was in agreement with the primary endpoint.*

Secondary Efficacy Endpoints (hierarchical testing)

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

Reviewer's Comments: *The Agency disagreed with the inclusion of the CAS score as an endpoint. The CAS score is a composite with equal weighting of a number of factors. However, FDA's clinical team does not consider these factors to be of equal weight either to the patients or to physician's treating these patients.*

6.2.2 Review Study #2 Study Results

Patient Disposition
There were 83 subjects enrolled in the study.

	Placebo (N=42) n (%)	HZN-001 (N=41) n (%)
Enrolled (Informed Consent Signed)	42	41
ITT Population	42 (100%)	41 (100%)
MITT Population	42 (100%)	40 (98%)
PP Population	34 (81%)	33 (81%)
Safety Population	42 (100%)	41 (100%)
Completed the Study Treatment Reason for Early	40 (95%)	39 (95%)
Termination		
Adverse Event	1 (2%)	1 (2%)
Lack of Efficacy	0	0
Pregnancy	0	0
Protocol Violation	0	0
Study Terminated by Sponsor	0	0
Death	0	0
Withdrawal by Subject	1 (2%)	1 (2%)

Review Study #2 Demographic and Baseline Characteristics (Safety Population)

Review Study #2	Placebo (N=42)	Teprotumumab (N=41)
Age (years) Mean (SD)	48.9 (13.0)	51.6 (12.6)
Median	51.5	53
(Min, Max)	(20, 73)	(31,79)
<65 years old	38 (90%)	32 (78%)
≥65 years old	4 (10%)	9 (22%)
Gender, n (%)		
Female	31 (74%)	29 (71%)
Ethnicity, n (%)		
Hispanic or Latino	1 (2%)	2 (5%)
Not Hispanic or Latino	41 (98%)	39 (95%)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	1 (2%)	2 (5%)
Black or African–American	2 (5%)	4 (10%)
Native Hawaiian or Other Pacific Islander	0	0
White	37 (88%)	35 (85%)
Mixed	2 (5%)	0
Weight (kg)		
Mean (SD)	75.8 (18.5)	75.0 (16.5)
Median	74.5	73.9
(Min, Max) Kilograms	45.0, 122.9	49.4, 110.0
Study Eye, n(%)		
Right Eye	20 (48%)	22 (54%)
Smoking Status, n(%)		
Smoker (current or former)	8 (19%)	9 (22%)
Time since diagnosis of Active TED (months)		
Mean (SD)	6.4 (2.4)	6.2 (2.3)
Median	6.8	6.3
Min, Max	1.1, 10.3	0.9, 9.7

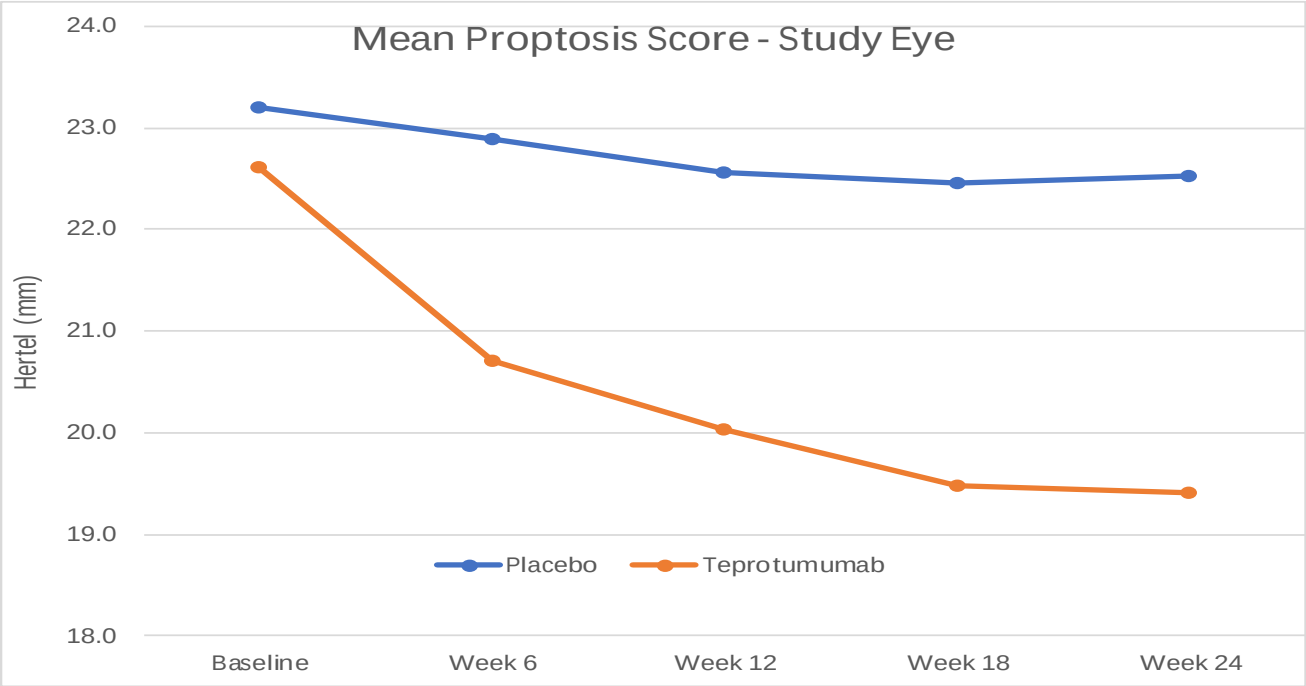
Abbreviation: CAS=Clinical Activity Score; CSS = Clinical Measures of Severity Score; ITT=intent-to-treat; N = number; SD =standard deviation

[a] Baseline was the last predose measurement.

Review Study #2 Efficacy Results – Primary Endpoint: % patients with 2 mm or more decrease in Proptosis

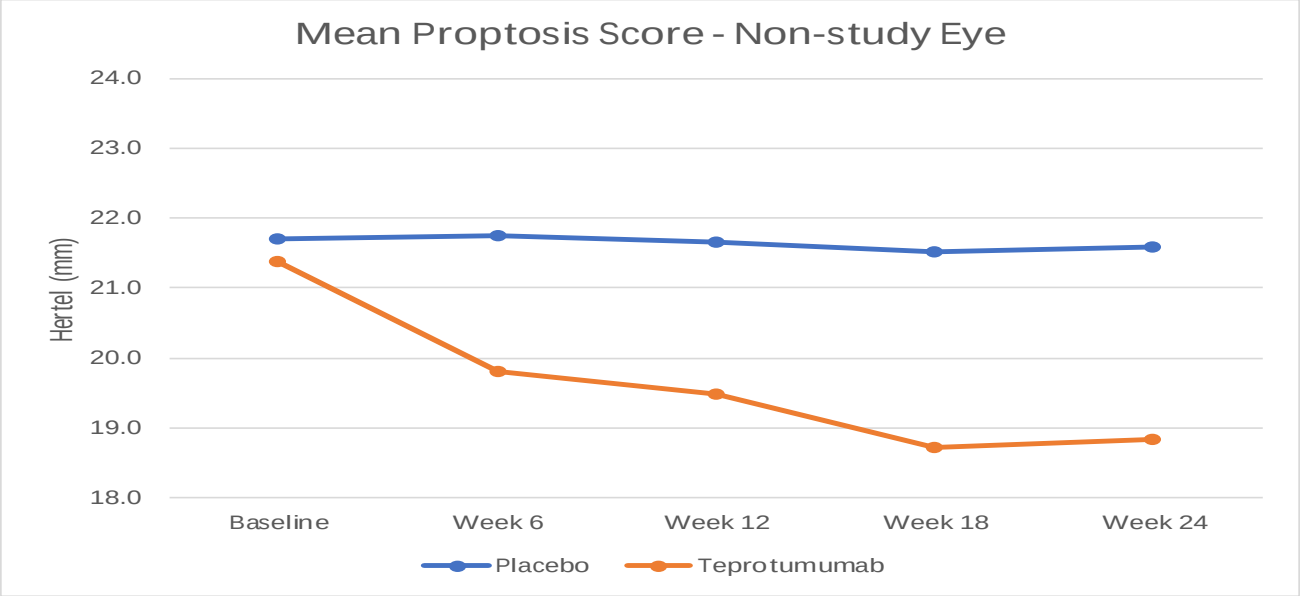
Proptosis	Placebo	Teprotumumab	Difference	p-value
Week 6 Study Eye	3/42 (7%)	23/40 (58%)	51%	<0.001
Week 12 Study Eye	6/41 (15%)	31/39 (80%)	65%	<0.001
Week 18 Study Eye	6/40 (15%)	34/39 (87%)	72%	<0.001
Week 24 Study Eye	4/40 (10%)	34/40 (85%)	75%	<0.001
Week 6 Non-study Eye	0/42	22/39 (55%)	55%	<0.001
Week 12 Non-study Eye	2/41 (5%)	24/39 (62%)	57%	<0.001
Week 18 Non-study Eye	2/40 (5%)	29/39 (74%)	69%	<0.001
Week 24 Non-study Eye	1/40 (3%)	27/40 (68%)	65%	<0.001

Reviewer's Comments: *By the first evaluation period at Week 6, there is a clinically significant reduction in proptosis (i.e., greater than 2 mm) in both eyes which continues through the treatment period.*



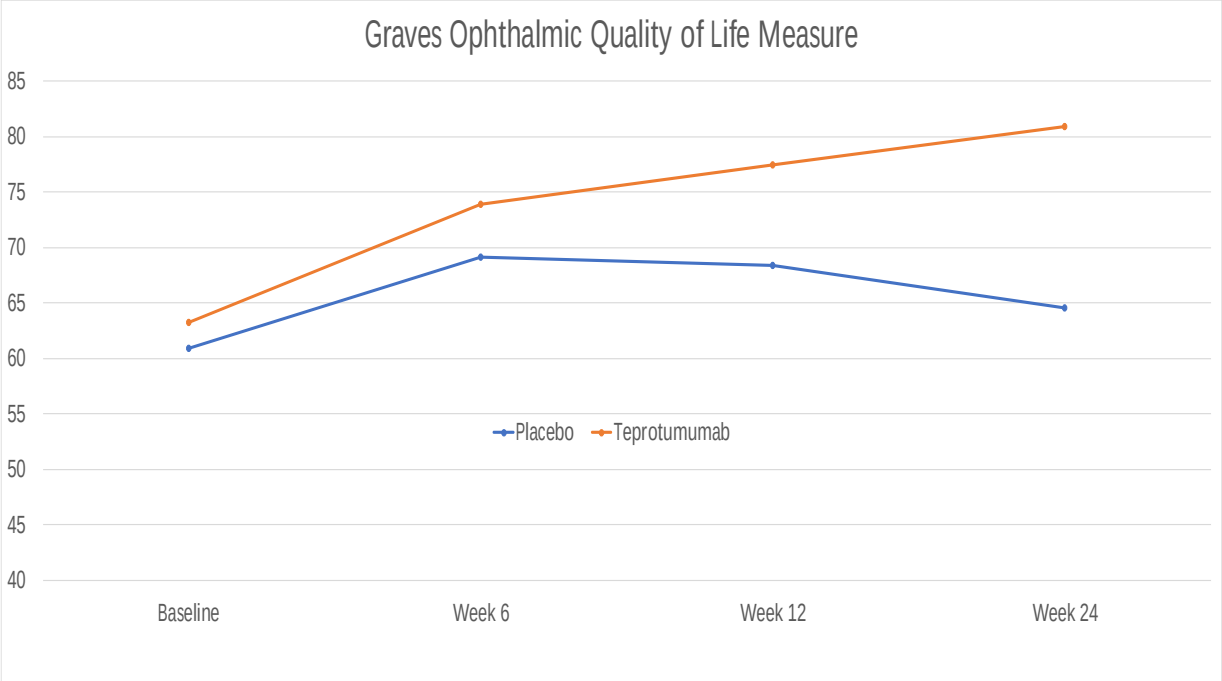
Reviewer's Comments: *The clinical effect continues to improve over the course of treatment.*

Review Study #2 – Non-study Eye Proptosis



Reviewer's Comments: *By the first evaluation period at Week 6, there is a reduction in proptosis in both eyes which continues through the treatment period.*

Review Study #2 Secondary Endpoints
Graves Ophthalmic Quality of Life Measure

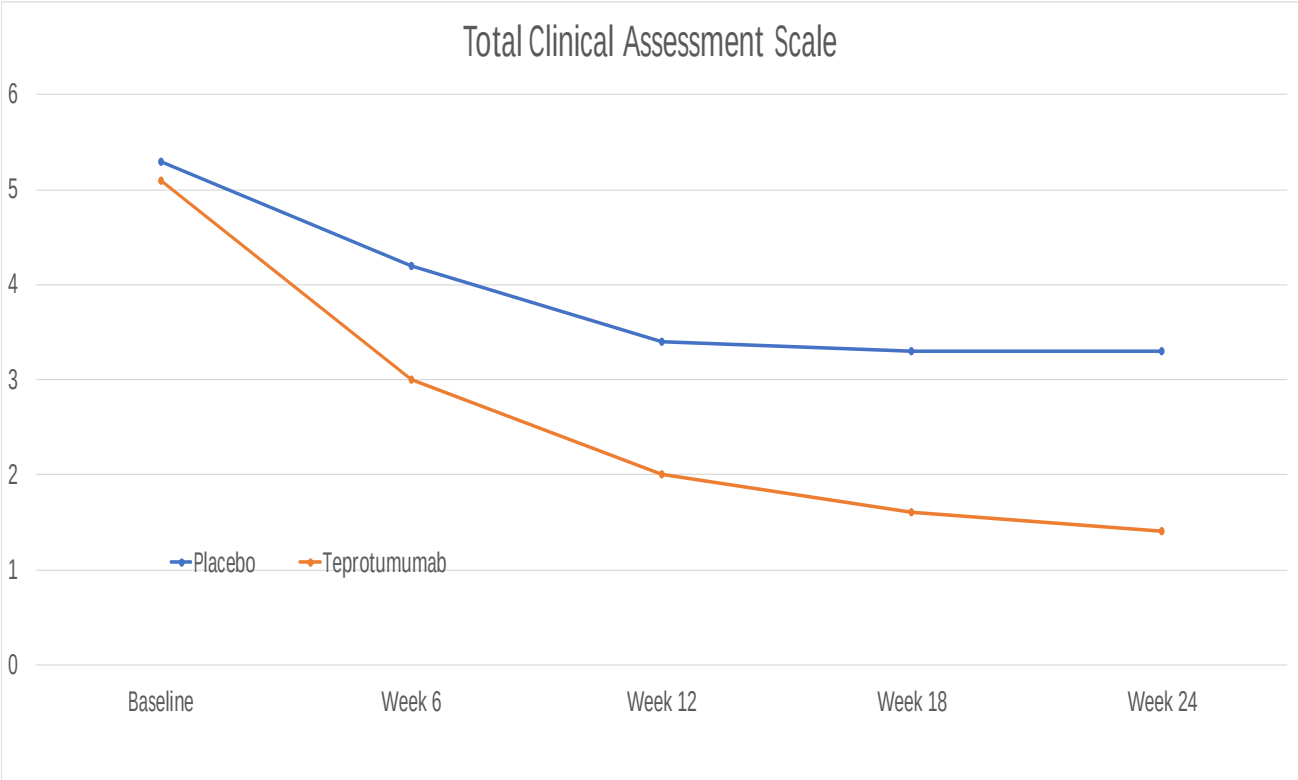


Transformed score = [(sum of each score – number of completed items) / (2 * number of completed items)] * 100.

Grave's Ophthal Quality of Life Score	Placebo	Teprotumumab	Difference
Baseline	60.9 (19.4)	63.3 (22.1)	2.4
Week 6	69.1 (16.3)	73.9 (21.0)	4.8
Week 12	68.4 (16.5)	77.5 (21.9)	9.1
Week 24	64.6 (18.7)	80.9 (17.6)	16.3

Reviewer's Comments: *Validation information for the Grave's Ophthalmology Quality of Life Score has not been submitted and therefore interpretation of the scores is not possible.*

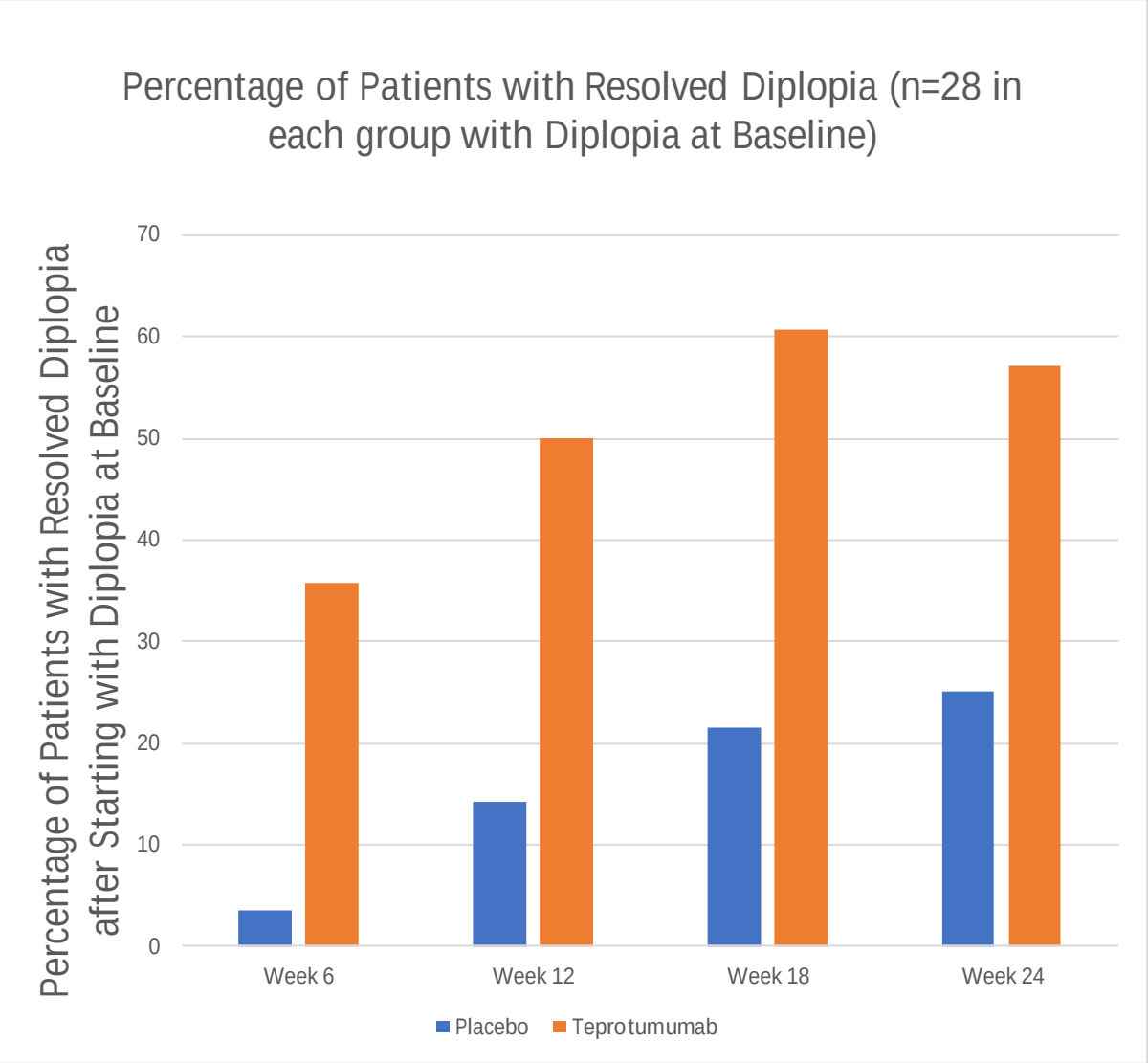
Review Study #2 – Clinical Assessment Scale



CAS Change from Baseline	Placebo	Teprotumumab	Difference
Baseline	5.3 (1.0)	5.1 (0.9)	0.2
Week 6	4.2 (1.5)	3.0 (1.7)	1.2
Week 12	3.4 (1.6)	2.0 (1.5)	1.4
Week 18	3.3 (1.9)	1.6 (1.7)	1.7
Week 24	3.3 (1.9)	1.4 (1.4)	1.9

Reviewer's Comments: *Clinical Activity Scale is not accepted because there is not necessarily equal weight for each component.*

Review Study #2- Resolution of Diplopia



Reviewer's Comments: *Diplopia was resolved in approximately 57% of patients with diplopia at the start of the clinical trial.*

6.2.3 Extension Period – From Safety Update

The analysis presented in the initial submission included data collected from 2 randomized, double-masked, placebo-controlled, parallel-group studies (Phase 2 Study TED01RV (Review Study #1) and Phase 3 Study HZNP-TEP-301; OPTIC (Review Study #2)); both study designs included a 24-Week Treatment Period and a Follow-up Period with no additional study treatment. The Treatment and Follow-up Periods of Study TED01RV had been completed; however, the Follow-up Period of Study HZNP-TEP-301 was ongoing and safety data through 19 February 2019, were included in the submission. In addition, safety data from an ongoing open-label extension study (Study HZNP-TEP-302; OPTIC-X) through 27 February 2019, were also included in the initial submission.

Among the 121 subjects in the All Teprotumumab Population, 97 (80.2%) had received at least 8 doses of teprotumumab at the time of the data cutoff. Among the 9 subjects who received teprotumumab in Study HZNP-TEP-301 and in Study HZNP-TEP-302, the total number of teprotumumab doses received across both studies was 9 for 2 subjects, 10 for 1 subject, 11 for 1 subject, 12 for 1 subject, 14 for 1 subject, 15 for 1 subject, and 16 for 2 subjects. Among the 121 subjects in the All Teprotumumab Population, 63 (52.1%) have been followed for at least 24 weeks off treatment and 29 (24.0%) have been followed for at least 48 weeks off treatment.

Since the initial submission, 1 additional subject experienced a serious adverse event during the Treatment Period (life-threatening *Cerebral hemorrhage*) and 2 additional subjects experienced serious adverse events severe *Intercostal neuralgia* and severe *Optic neuropathy* during the Follow-up Period.

7. Review of Safety

8.1 Deaths – none

8.2 Serious Adverse Events

Listing of Serious Treatment-Emergent Adverse Events

Review Study #1

Subject ID	Preferred Term	Day of Onset	Outcome	Study Medication Action Taken	Other Action Taken
Teprotumumab					
(b) (6)	Hashimoto's encephalopathy	130	Unknown	Drug interrupted	Hospitalization, (b) (6)
	Urinary retention		Resolved	Dose not changed	Medication and hospitalization
	Diarrhoea[b]	253	Resolved	Drug withdrawn	Hospitalization
	Escherichia sepsis	45	Unknown	Drug	Hospitalization
	Inflammatory bowel disease	169	Resolved with Sequelae	Drug withdrawn	Medication and hospitalization
Placebo					
(b) (6)	Optic neuropathy		Resolved	Not applicable	Medication

a (b) (6).

b Subject had medical history of colitis with abdominal cramping and bloody diarrhea in the 7 months preceding randomization. After 3 months on study, subject had a colonoscopy and was diagnosed with ulcerative colitis. Source: Appendix 16.2, Listing 16.3.1.2.

Review Study #2

Subject ID	Preferred Term	Day of Onset	Outcome	Study Medication Action Taken	Other Action Taken
Teprotumumab					
(b) (6)	Infusion related reaction	1	Resolved	Drug withdrawn	Concomitant medication discontinued study
	Pneumothorax	113	Recovering	Dose not changed	Hospitalization
Placebo					
(b) (6)	Visual field defect	64	Recovering	Drug withdrawn	Orbital decompression surgery

Source: Listing 16.2.4.1 and 16.2.7.2.

8.3 Dropouts and/or Discontinuations

No treatment – Review Study #1

(b) (6)

Subject voluntarily withdrew from the study due to difficulties with placing an IV and withdrawing blood at the baseline visit. No infusions were administered to the patient.

Teprotumumab

Review Study #1

(b) (6)

Day	
130	AE Hospitalized for altered mental status. Suspect Hashimoto's Encephalopathy
43	AE Facial flushing, heart palpitations, elevated BP & Heart rate
253	AE Diarrhea
79	The subject was dispensed the incorrect treatment assignment at Week 3 in error and an administrative decision on the part of the sponsor was made to discontinue the subject
45	AE Hospitalization for systemic E. Coli Sepsis and dehydration
169	AE Inflammatory bowel disease

Review Study #2

(b) (6)

1	AE Infusion Reaction
43	AE Skin itchy and red after 3rd dose, concerned about the risk of allergy

Placebo

Review Study #1

(b) (6)

47	Left eye, Optic disc edema
170	Lack of Efficacy
64	Lack of Efficacy
1	AE Vasovagal Attack
302	Patient decision to withdraw
127	Back pain, back surgery

Review Study #2

(b) (6)

43	Worsening Visual Field
85	Subject Decision

8.4 Treatment Emergent Adverse Events and Adverse Reactions in at least 5%

System Organ Class	Study 1 Placebo (N=44)	Study 2 Placebo (N=42)	Study 1 Teprotumumab (N=43)	Study 2 Teprotumumab (N=41)
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any TEAE[a]	32 (73%)	29 (69%)	32 (74%)	35 (85%)
Gastrointestinal Disorders	6 (14%)	9 (21%)	16 (37%)	18 (44%)
Nausea	4 (9%)	4 (10%)	8 (19%)	6 (15%)
Diarrhea	2 (5%)	5 (12%)	6 (14%)	4 (10%)
Abdominal pain upper		3 (7%)		2 (5%)
Stomatitis		1 (2%)		3 (7%)
Infections and Infestations	9 (21%)	10 (24%)	13 (30%)	16 (40%)
Upper respiratory tract infection	4 (9%)		0	
Influenza		3 (7%)		1 (2%)
Respiratory, thoracic and mediastinal disorders		4 (10%)		6 (15%)
Cough		3 (7%)		2 (5%)
Skin and Subcutaneous Tissue Disorders	9 (20%)	11 (26%)	11 (26%)	15 (37%)
Alopecia	2 (5%)	5 (12%)	3 (7%)	8 (20%)
Dry skin	0	0	3 (7%)	4 (10%)
Rash	4 (9%)		3 (7%)	
Musculoskeletal and Connective Tissue Disorders	7 (16%)	5 (12%)	12 (28%)	16 (39%)
Muscle spasms	2 (5%)	4 (10%)	8 (19%)	13 (32%)
Nervous System Disorders	9 (20%)	8 (19%)	10 (23%)	14 (34%)
Dizziness	4 (9%)	0	0	3 (7%)
Dysgeusia	0	0	3 (7%)	4 (10%)
Headache	2 (5%)	4 (10%)	3 (7%)	4 (10%)
Paresthesia	0		3 (7%)	
Somnolence	3 (7%)		0	
Investigations	7 (16%)		9 (21%)	
Weight decreased	0		3 (7%)	
Metabolism and Nutrition Disorders	2 (5%)		10 (23%)	
Hyperglycemia	2 (5%)	0	5 (12%)	2 (5%)
Reproductive system and breast disorders		0		4 (10%)
Amenorrhea		0		3 (7%)
General Disorders and Site Conditions	10 (23%)	4 (10%)	6 (14%)	8 (20%)
Fatigue	6 (14%)	1 (2%)	3 (7%)	5 (12%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event. Note: The denominator for the percentages is the number of subjects in each treatment group. At each level of summarization, subjects who experienced more than 1 TEAE were counted only once. All TEAEs were coded using MedDRA, Version 14.0. [a] A TEAE was defined as an AE with onset at the time of or following the start of treatment with study drug or an AE starting before the start of treatment but increasing in severity following the start of treatment. Table 14.3.1.1

Reviewer's Comments: *Interpretability is difficult because of the low number of subjects enrolled in the clinical trials. There appear to be increased trends in the teprotumumab groups for gastrointestinal disorders, infections, muscle spasms, hyperglycemia and reproductive system and breast disorders.*

Studies in Safety Database

Study 1	42	Thyroid Eye Disease	
Study 2	41	Thyroid Eye Disease	
DME01RV	5	Diabetic Macular Edema	3 infusions
NO21161	6	Breast Cancer	Up to 24 weeks
NO2202	8	Breast Cancer	Single dose
NO21884	11	Advanced Solid Tumors	Repeated until progression
NO21746	34	Lung Cancer	Up to 24 months
NO21200	34	Advanced Solid Tumors	Limited number of infusions
BO19373	97	Solid tumors and lymphoma	Various schedules
NO22068	104	Advanced malignancies	Repeated until progression
NO21160	116	Lung Cancer	Repeated until progression
NO21157	317	Recurrent/refractory sarcomas	Repeated until progression

8.5 Laboratory Findings

With the exception of elevated glucose and hemoglobin A1c levels in some patients, no significant shifts in laboratory findings were noted.

8.6 Vital Signs

No clinically significant changes were reported.

8.7 Electrocardiograms (ECGs)

No clinically significant changes were reported.

8.8 QT

Monoclonal antibodies would not be expected to have a significant risk of inducing QT changes. A traditional thorough QT study (based on International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use Guidance: E14) was considered unnecessary and was not conducted. In Review Studies #1 and #2, all of the teprotumumab-treated subjects had electrocardiogram (ECG) results at Baseline and throughout the Treatment Period. None demonstrated clinically significant findings.

8.9 Immunogenicity

No clinically significant changes were reported.

9. Pediatrics

Teprotumumab was granted orphan drug designation for the treatment of Active Thyroid Eye Disease (Orphan Drug Designation 12-3878). Submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication. In addition, Thyroid Eye Disease occurs very rarely, if at all in pediatric patients.

10. Safety Update Summary of Reported Adverse Events

Teprotumumab N=121

System Organ Class or Verbatim Term	Subjects	(%)	Events
Any TEAEs	101	(83%)	553
Musculoskeletal and connective tissue disorders	49	(40%)	94
Gastrointestinal disorders	43	(36%)	88
Skin and subcutaneous tissue disorders	43	(36%)	72
Infections and infestations	40	(33%)	49
Nervous system disorders	32	(26%)	55
Ear and labyrinth disorders	21	(17%)	25
General disorders and administration site conditions	20	(17%)	31
Metabolism and nutrition disorders	17	(14%)	20
Respiratory, thoracic and mediastinal disorders	15	(12%)	23
Investigations	13	(11%)	16
Injury, poisoning and procedural complications	11	(9%)	11
Reproductive system and breast disorders	10	(8%)	14
Eye disorders	10	(8%)	15
Psychiatric disorders	7	(6%)	8
Renal and urinary disorders	7	(6%)	8
Vascular disorders	6	(5%)	7
Cardiac disorders	4	(3%)	5
Blood and lymphatic system disorders	4	(3%)	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(2.5%)	4
Endocrine disorders	2	(2%)	2
Muscle spasms	39	(32%)	75
Alopecia	18	(15%)	21
Nausea	15	(12%)	24
Diarrhea	15	(12%)	20
Fatigue	12	(10%)	15
Dry skin	12	(10%)	12
Dysgeusia	10	(8%)	15
Headache	8	(7%)	10
Rash	8	(7%)	10

Ear discomfort	8	(7%)	9
Urinary tract infection	7	(6%)	7
Amenorrhea	6	(5%)	7
Hyperglycaemia	6	(5%)	7
Abdominal pain upper	6	(5%)	6
Influenza	5	(4%)	6
Pain in extremity	5	(4%)	6
Bronchitis	5	(4%)	5
Hypoacusis	5	(4%)	5
Onychoclasis	5	(4%)	5
Epistaxis	4	(3%)	7
Sinusitis	4	(3%)	5
Abdominal pain	4	(3%)	4
Cystitis	4	(3%)	4
Dizziness	4	(3%)	4
Rhinorrhea	4	(3%)	4
Tremor	4	(3%)	4
Weight decreased	4	(3%)	4
Madarosis	3	(2.5%)	4
Tinnitus	3	(2.5%)	4
Blood glucose increased	3	(2.5%)	3
Blood pressure increased	3	(2.5%)	3
Cough	3	(2.5%)	3
Decreased appetite	3	(2.5%)	3
Depression	3	(2.5%)	3
Dry mouth	3	(2.5%)	3
Feeling hot	3	(2.5%)	3
Gastroesophageal reflux disease	3	(2.5%)	3
Hypertension	3	(2.5%)	3
Nasopharyngitis	3	(2.5%)	3
Noninfective gingivitis	3	(2.5%)	3
Palpitations	3	(2.5%)	3
Paresthesia	3	(2.5%)	3
Stomatitis	3	(2.5%)	3
Vomiting	3	(2.5%)	3
Asthenia	2	(2%)	4
Abdominal distension	2	(2%)	2
Arthralgia	2	(2%)	2
Chest pain	2	(2%)	2
Deafness	2	(2%)	2
Dry eye	2	(2%)	2
Dysuria	2	(2%)	2
Gingival pain	2	(2%)	2
Gingival recession	2	(2%)	2
Glossodynia	2	(2%)	2
Hair growth abnormal	2	(2%)	2
Ingrown nail	2	(2%)	2
Localized infection	2	(2%)	2
Myalgia	2	(2%)	2

Nail disorder	2	(2%)	2
Nasal congestion	2	(2%)	2
Nasal dryness	2	(2%)	2
Nightmare	2	(2%)	2
Osteopenia	2	(2%)	2
Rash pruritic	2	(2%)	2
Tachycardia	2	(2%)	2
Thrombocytopenia	2	(2%)	2
Vertigo	2	(2%)	2
Muscle contractions involuntary	1	(1%)	4
Butterfly rash	1	(1%)	2
Disturbance in attention	1	(1%)	2
Inflammatory bowel disease	1	(1%)	2
Metrorrhagia	1	(1%)	2
Nail discoloration	1	(1%)	2
Rectal hemorrhage	1	(1%)	2
Trichiasis	1	(1%)	2
Abnormal feces	1	(1%)	1
Abnormal sensation in eye	1	(1%)	1
Acarodermatitis	1	(1%)	1
Acne	1	(1%)	1
Adverse drug reaction	1	(1%)	1
Aphasia	1	(1%)	1
Arthropod sting	1	(1%)	1
Bacterial vaginosis	1	(1%)	1
Balance disorder	1	(1%)	1
Biotin deficiency	1	(1%)	1
Blepharospasm	1	(1%)	1
Blood bilirubin increased	1	(1%)	1
Blood creatinine increased	1	(1%)	1
Blood urine present	1	(1%)	1
Cerebral hemorrhage	1	(1%)	1
Chills	1	(1%)	1
Chronic kidney disease	1	(1%)	1
Confusional state	1	(1%)	1
Contusion	1	(1%)	1
Corneal abrasion	1	(1%)	1
Corneal erosion	1	(1%)	1
Dehydration	1	(1%)	1
Dermal cyst	1	(1%)	1
Dermatitis	1	(1%)	1
Diabetes mellitus	1	(1%)	1
Diplopia	1	(1%)	1
Dysarthria	1	(1%)	1
Dysmenorrhea	1	(1%)	1
Dyspepsia	1	(1%)	1
Ear infection	1	(1%)	1
Erectile dysfunction	1	(1%)	1
Erythema of eyelid	1	(1%)	1

Escherichia sepsis	1	(1%)	1
Eustachian tube dysfunction	1	(1%)	1
Eustachian tube patulous	1	(1%)	1
Eye irritation	1	(1%)	1
Eye pain	1	(1%)	1
Eyelid retraction	1	(1%)	1
Feeling cold	1	(1%)	1
Flushing	1	(1%)	1
Gastroenteritis	1	(1%)	1
Gingival bleeding	1	(1%)	1
Gout	1	(1%)	1
Hemangioma of skin	1	(1%)	1
Hematochezia	1	(1%)	1
Hematoma	1	(1%)	1
Hematuria	1	(1%)	1
Hemoglobin decreased	1	(1%)	1
Hashimoto's encephalopathy	1	(1%)	1
Heart rate increased	1	(1%)	1
Helicobacter infection	1	(1%)	1
Hyperacusis	1	(1%)	1
Hypersensitivity	1	(1%)	1
Hyperthyroidism	1	(1%)	1
Hypogeusia	1	(1%)	1
Hypokalemia	1	(1%)	1
Hyposmia	1	(1%)	1
Hypotension	1	(1%)	1
Hypothyroidism	1	(1%)	1
Immune system disorders	1	(1%)	1
Increased appetite	1	(1%)	1
Influenza like illness	1	(1%)	1
Infusion related reaction	1	(1%)	1
Inguinal hernia	1	(1%)	1
Iron deficiency	1	(1%)	1
Joint stiffness	1	(1%)	1
Jugular vein distension	1	(1%)	1
Lenticular opacities	1	(1%)	1
Ligament sprain	1	(1%)	1
Limb injury	1	(1%)	1
Loss of consciousness	1	(1%)	1
Lymphadenopathy	1	(1%)	1
Medial tibial stress syndrome	1	(1%)	1
Memory impairment	1	(1%)	1
Migraine	1	(1%)	1
Migraine with aura	1	(1%)	1
Migraine without aura	1	(1%)	1
Muscle injury	1	(1%)	1
Muscle rupture	1	(1%)	1
Muscle strain	1	(1%)	1
Muscular weakness	1	(1%)	1

Musculoskeletal pain	1	(1%)	1
Musculoskeletal stiffness	1	(1%)	1
Nail infection	1	(1%)	1
Nasal discomfort	1	(1%)	1
Night sweats	1	(1%)	1
Edema peripheral	1	(1%)	1
Oral herpes	1	(1%)	1
Oropharyngeal pain	1	(1%)	1
Osteoporosis	1	(1%)	1
Otitis media	1	(1%)	1
Paranasal sinus discomfort	1	(1%)	1
Pelvic discomfort	1	(1%)	1
Periodontitis	1	(1%)	1
Peripheral swelling	1	(1%)	1
Petechiae	1	(1%)	1
Pneumonia chlamydial	1	(1%)	1
Pneumothorax	1	(1%)	1
Pollakiuria	1	(1%)	1
Polydipsia	1	(1%)	1
Polyuria	1	(1%)	1
Procedural nausea	1	(1%)	1
Pruritus	1	(1%)	1
Pruritus generalized	1	(1%)	1
Pyogenic granuloma	1	(1%)	1
Rhinitis	1	(1%)	1
Seborrheic keratosis	1	(1%)	1
Sinusitis bacterial	1	(1%)	1
Sleep disorder	1	(1%)	1
Sneezing	1	(1%)	1
Spontaneous hematoma	1	(1%)	1
Squamous cell carcinoma	1	(1%)	1
Strabismus	1	(1%)	1
Subcutaneous abscess	1	(1%)	1
Tendonitis	1	(1%)	1
Tension	1	(1%)	1
Thirst	1	(1%)	1
Tonsillitis	1	(1%)	1
Tooth abscess	1	(1%)	1
Tooth development disorder	1	(1%)	1
Tooth infection	1	(1%)	1
Toothache	1	(1%)	1
Trichorrhexis	1	(1%)	1
Type 2 diabetes mellitus	1	(1%)	1
Urinary retention	1	(1%)	1
Urine odor abnormal	1	(1%)	1
Vaginal discharge	1	(1%)	1
Vaginal hemorrhage	1	(1%)	1
Vascular injury	1	(1%)	1
Vision blurred	1	(1%)	1

Visual field defect	1	(1%)	1
Vitamin D deficiency	1	(1%)	1
Weight increased	1	(1%)	1

Reviewer's Comments: *Using the verbatim term for the reported adverse event has served to separate terms which may otherwise refer to a very similar adverse event. For example, Tooth abscess, Tooth infection and Toothache should be included as the same adverse event.*

8. Advisory Committee Meeting and Other External Consultations

The Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 13, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Horizon Pharma Ireland, Ltd. The meeting was called to order by James Chodosh, MD (Chairperson). The conflict of interest statement was read into the record by Jay Fajiculay, PharmD (Acting Designated Federal Officer). There were approximately 100 people in attendance. There were 11 Open Public Hearing (OPH) speaker presentations.

The committee unanimously voted “Yes”, that the potential benefits of using teprotumumab as recommended outweigh the potential risks associated with the use of the drug product for the intended population. The committee acknowledged that there are currently no products available on the market to treat thyroid eye disease, and that the benefits of teprotumumab use outweigh the adverse events observed in clinical trials. Some committee members suggested that the Applicant conduct a clinical trial with a greater number of subjects to identify any additional adverse event that may have not been identified from the limited data presented. The committee also recommended that the Applicant work with the Agency to identify post-marketing commitments such as appropriate labeling or use of a registry.

9. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies have been considered necessarily to monitor the observed adverse events.

10. Financial Disclosure

Covered Clinical Study (Name and/or Number): Review Studies #1 and #2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐

The only investigator/sub-investigator with financial interests was [redacted] (b) (6) who participated in Study TED01RV [redacted] (b) (6) [redacted] (b) (6). During the course of the study, [redacted] (b) (6) did not receive any tangible products, goods or compensation. [redacted] (b) (6) [redacted] (b) (6) [redacted] (b) (6). Study TED01RV enrolled 88 patients at 15 centers with recruitment ranging from 1 to 19 patients per active site. The study design included aspects to minimize bias including randomization, double-masking and placebo-control. [redacted] (b) (6) [redacted] (b) (6) enrolled 7 patients which does not make a significant contribution to the overall evaluation of safety and efficacy from this study in 88 patients.

11. Application Issues:

1. Efficacy

   Efficacy, as demonstrated by a reduction in proptosis, has been demonstrated in two adequate and well controlled studies. Eighty-two percent (82%) of patients treated with 8 doses of teprotumumab had at least a two-millimeter reduction in ptosis compared to only 16 percent of patients treated with placebo. A two-millimeter reduction is considered clinically significant because it is expected to reduce the incidence of diplopia and improve the lid coverage over the cornea. The systemic treatment also had an effect on the non-study eye, reducing proptosis in 68% of non-study eyes compared to only 9% of patients treated with placebo.

2. Onset and Duration

   The onset of ptosis reduction was evident in some patients at the first evaluation examination, 6 weeks after the first infusion (three weeks after the second infusion). The duration of the effect is still under study. An extension of Review Study #1 demonstrated that the effect continued for at least 4 weeks after the last infusion. At week 72 approximately 60% of patients who had an effective reduction in ptosis had not relapsed (lost 2 millimeter of ptosis). The extension of Review Study #2, as well as the open label treatment period for patients who had not previously responded (placebo or teprotumumab) is still ongoing. Safety and efficacy of repeated courses of treatment will be included in a post-marketing requirement by the Agency.

3. Limited number of subjects studied to date

   Less than 90 subjects treated with infusions of teprotumumab have been enrolled in controlled clinical trials. This is a considerably smaller database than the common safety database of greater than 300 patients treated with a course of therapy. Based on the rule of 3's, with a safety database of 90 subjects, adverse events may be expected to occur at rates of 3% without the event being observed in the prior clinical trials. In view of the limited number of patients with this condition, the database is considered adequate for approval. An additional study will be required in a post-marketing requirement. The additional study will compare dosing for 3 months, 6 months and 12 months and included a retreatment for both initial failures and patients in which efficacy is not sustained.

4. Hyperglycemia

   The drug product is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor. It has the potential to interfere with glucose regulation in the body, particularly in individuals with diabetes. Some patients receiving Teprotumumab required additional amounts of insulin to maintain glycemic control.

   A total of 22 placebo subjects and 21 teprotumumab subjects had fasting glucose values available at Baseline and at other time points during the treatment period. All of the

subjects in the placebo group and 17 (81.0%) of the 21 subjects in the teprotumumab group had normal fasting glucose values at Baseline with no shifts from the normal range noted during treatment. Three teprotumumab subjects with normal fasting glucose values at Baseline demonstrated elevated fasting glucose values for at least 1 visit during the treatment period. None of these 3 subjects had a history of diabetes mellitus however, 2 of the 3 subjects had somewhat elevated HbA1c values at baseline. The need for glucose monitoring will be included as a Warning/Precaution in the Tepezza labeling.

6. Muscle Spasms

The overall incidence of *Muscle spasms* was higher in the teprotumumab group (32%) compared to the placebo group (9.5%). In the teprotumumab group, a total of 27 TEAEs of *Muscle spasms* were reported among 13 subjects. The most common sites specified involved the lower extremities (leg: 9 events; calf: 5 events; feet/toes: 5 events); other sites included hands (2 events), back (1 event), chest (1 event) and side of body (1), and no site specified for 3 events. None of the events resulted in discontinuation of study drug. No clinically significant abnormality in electrolytes (including calcium) or aspartate aminotransferase (AST) values were noted for subjects who experienced *Muscle spasms*. A total of 6 subjects requested and received treatment for the muscle spasms including magnesium (5 subjects), calcium (1 subject), vitamins B6, B12, and folic acid (1 subject) and cyclobenzaprine hydrochloride (1 subject). Seven (7) of the 13 subjects had at least 1 adverse event of *Muscle spasms* that began either on the day of an infusion (4 subjects; 11 events) or the day following an infusion (3 subjects; 3 events).

The mechanism of action for the muscle spasms remains unknown. Physician labeling will include muscle spasms as the first most common adverse reaction.

7. Hearing Impairment

At least five patients reported hypoacusis/loss of hearing. In addition, patients have reported tinnitus. Subject (b) (6), a 32-year-old female, experienced an adverse event of *Hypoacusis* on Day 75 that spontaneously resolved the following day. In other subjects, the event did not resolve until after completion of treatment with teprotumumab. The mechanism of action for hypoacusis remains unknown. The adverse reaction section of the labeling will include potential hearing impairment.

8. Diarrhea/Irritable Bowel Syndrome

Gastrointestinal complaints were reported in clinical trials by 36% of patients. Nausea and diarrhea were each reported in 12% of patients. Abdominal pain was reported in 5% of patients. None of these events resulted in discontinuation of study drug. However, one patient discontinued teprotumumab following hospitalization for systemic *E. Coli* sepsis and dehydration and another discontinued due to an episode of inflammatory bowel disease. Any potential causal association between teprotumumab and

inflammatory bowel disease is uncertain at this time. The Warnings/Precautions will include the potential for an exacerbation of inflammatory bowel disease and nausea and diarrhea will be included as adverse events.

9. Infection Rate

The reported infection rate associated with teprotumumab was 33%, and higher than that of the placebo control in both studies. No specific site of infection was identified and the potential contribution of teprotumumab to this infection rate is not known. Monitoring of infection rates in the post-marketing setting will continue.

12. Labeling Recommendations

The following text is recommended to be included as the package insert:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEPEZZA safely and effectively. See full prescribing information for TEPEZZA.

TEPEZZA (teprotumumab-trbw) for injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

----------DOSAGE AND ADMINISTRATION----------
- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Infusion reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)
- Exacerbation of Preexisting Inflammatory Bowel Disease (IBD) : Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)
- Hyperglycemia: Monitor glucose levels in all patients; treat hyperglycemia with glycemic control medications (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 5%) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TEPEZZA is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks for 7 additional infusions.

2.2 Reconstitution and Preparation

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dosage based on patient weight. Each TEPEZZA vial contains 500 mg of the teprotumumab antibody.

Step 2: Using appropriate aseptic technique, reconstitute each TEPEZZA vial with 10 mL of Sterile Water for Injection, USP. Ensure that the stream of diluent is not directed onto the lyophilized powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilized powder is dissolved. The reconstituted solution has a volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg.

Step 3: The reconstituted TEPEZZA solution must be further diluted in 0.9% Sodium Chloride Injection, USP prior to infusion. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the volume equivalent to the amount of the reconstituted TEPEZZA solution to be placed into the infusion bag. Discard the 0.9% Sodium Chloride, USP volume withdrawn.

Step 4: Withdraw the required volume from the reconstituted TEPEZZA vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing 0.9% Sodium Chloride Solution, USP to prepare a diluted solution with a total volume of 100 mL (for less than 1800 mg dose) or 250 mL (for 1800 mg and greater dose). Mix diluted solution by gentle inversion. Do not shake.

The product does not contain any preservative. 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.

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 which is free of foreign particulate matter. Discard the solution if any particulate matter or discoloration are observed.

Do not freeze the reconstituted or diluted solution.

Discard vial(s) and all unused contents.

No incompatibilities between TEPEZZA and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

2.3 Administration

Administer the diluted solution intravenously over 90 minutes for the first two infusions. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes.

Do not administer as an intravenous push or bolus. TEPEZZA should not be infused concomitantly with other agents.

3 DOSAGE FORMS AND STRENGTHS

For injection (intravenous infusion): 500 mg of teprotumumab as a white to off-white lyophilized powder in a single-dose vial for reconstitution and dilution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

5.2 Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

5.3 Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if needed.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with pre-existing diabetes should be under appropriate glycemic control before receiving TEPEZZA.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Exacerbation of Inflammatory Bowel Disease *[see Warnings and Precautions (5.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

[a] Fatigue includes asthenia
[b] Hyperglycemia includes blood glucose increase
[c] Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of

TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data
In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

8.2 Lactation

Risk Summary
There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

8.3 Females and Males of Reproductive Potential

Contraception
Females
Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

10 OVERDOSAGE

No information is available for patients who have received an overdosage.

11 DESCRIPTION

Teprotumumab-trbw, an insulin-like growth factor-1 receptor inhibitor (IGF-1R), is a fully human IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO-DG44) cells. It has a molecular weight of approximately 148 kilodaltons.

TEPEZZA (teprotumumab-trbw) for injection is supplied as a sterile, preservative-free, white to off-white, lyophilized powder for intravenous infusion. Each single-dose vial contains 500 mg of teprotumumab-trbw, L-histidine (7.45 mg), L-histidine hydrochloride monohydrate (31.8 mg), polysorbate 20 (1 mg), and trehalose dihydrate (946 mg). After reconstitution with 10 mL of Sterile Water for Injection, USP, the final concentration is 47.6 mg/mL with a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teprotumumab-trbw's mechanism of action in patients with Thyroid Eye Disease has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with teprotumumab-trbw.

12.3 Pharmacokinetics

The pharmacokinetics of teprotumumab-trbw was described by a two compartment population PK model based on data from 40 patients with Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg TEPEZZA every 3 weeks in two clinical trials. Following this regimen, the mean (± standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (Cmax), and trough (Ctrough) concentrations of teprotumumab-trbw were 138 (± 34) mg•hr/mL, 632 (± 139) mcg/mL, and 176 (± 56) mcg/mL, respectively.

Distribution
Following the recommended TEPEZZA dosing regimen, the population PK estimated mean (± standard deviation) for central and peripheral volume of distribution of teprotumumab-trbw were 3.26 (±0.87) L and 4.32 (± 0.67) L, respectively. The mean (± standard deviation) estimated inter-compartment clearance was 0.74 (± 0.16) L/day.

Elimination
Following the recommended TEPEZZA dosing regimen, the population PK estimated mean (± standard deviation) for the clearance of teprotumumab-trbw was 0.27 (± 0.08) L/day and for the elimination half-life was 20 (± 5) days.

Metabolism
Metabolism of teprotumumab-trbw has not been fully characterized. However, teprotumumab-trbw is expected to undergo metabolism via proteolysis.

Specific Populations
No clinically significant differences in the pharmacokinetics of teprotumumab-trbw were observed following administration of TEPEZZA based on patient's age (18-80 years), gender, race/ethnicity (103 White, 10 Black, and 3 Asian), weight (46-169 kg), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min estimated by Cockcroft-Gault Equation), bilirubin levels (2.7-24.3 mcmol/L), aspartate aminotransferase (AST) levels (11-221 U/L), or alanine aminotransferase (ALT) levels (7-174 U/L). The effect of hepatic impairment on the pharmacokinetics of teprotumumab-trbw is unknown.

Drug Interactions
No studies evaluating the drug interaction potential of TEPEZZA have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies.

Mutagenesis
The genotoxic potential of TEPEZZA has not been evaluated.

Impairment of Fertility
Fertility studies have not been performed with TEPEZZA.

14 CLINICAL STUDIES

TEPEZZA was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with Thyroid Eye Disease: Study 1 (NCT01868997) and Study 2 (NCT03298867). Patients were randomized to receive TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of Thyroid Eye Disease with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for Thyroid Eye Disease was not permitted. Proptosis ranged from 16 to 33 mm and 125 patients (73%) had diplopia at baseline.

A total of 84 patients were randomized to TEPEZZA and 87 patients were randomized to placebo. The median age was 52 years (range 20 to 79 years), 86% were White, 9% were Black or African-American, 4% were Asian and 1% identified as Other. The majority (73%) were female. At baseline, 27% of patients were smokers.

The proptosis responder rate at week 24 was defined as the percentage of patients with ≥2 mm reduction in proptosis in the study eye from baseline, without deterioration in the non-study eye (≥2 mm increase) in proptosis. Additional evaluations included signs and symptoms of Thyroid Eye Disease including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis inflammation clinical activity score and assessments of functional vision and patient appearance. Results for proptosis are found in Table 2.

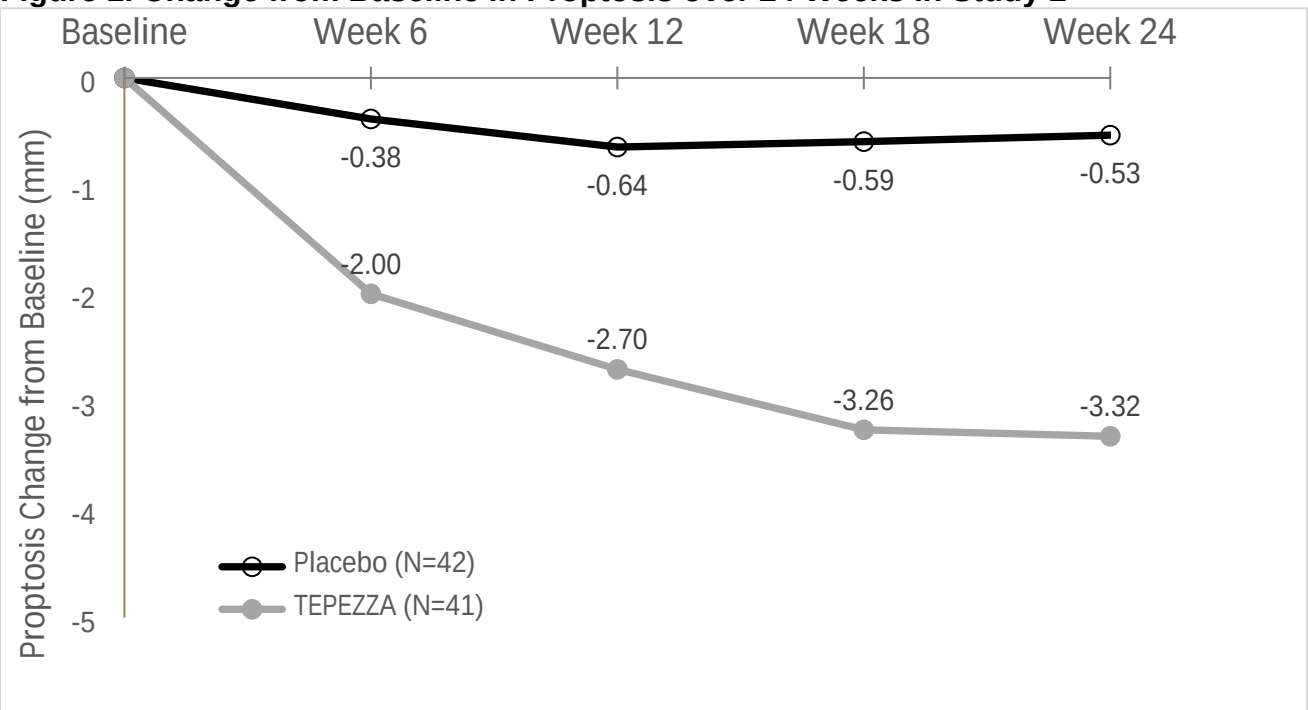
Table 2. Efficacy Results in Patients with Thyroid Eye Disease in Study 1 and 2

	Study 1			Study 2		
	Teprotumumab (N=41)	Placebo (N=42)	Difference (95% CI)	Teprotumumab (N=42)	Placebo (N=45)	Difference (95% CI)
Proptosis responder rate at week 24, % (n) [1]	71% (30)	20% (9)	51% (33, 69)	83% (34)	10% (4)	73% (59, 88)
Proptosis (mm) average change from baseline through week 24, LS Mean (SE) [2]	-2.5 (0.2)	-0.2 (0.2)	-2.3 (-2.8, -1.8)	-2.8 (0.2)	-0.5 (0.2)	-2.3 (-2.8, -1.8)

[1] Difference and its corresponding 95% Confidence Interval (CI) is based on a weighted average of the difference within each randomization stratum (tobacco user, tobacco non-use) using CMH weights.
[2] Results were obtained from an MMRM with an unstructured covariance matrix and including treatment, smoking status, baseline value, visit, treatment by visit, and visit by baseline value interaction as fixed effects. A change from Baseline of 0 was imputed at the first post-Baseline visit for any subject without a post-Baseline value.

In Study 2, improvement of proptosis as measured by mean change from Baseline was observed as early as 6 weeks and continued to improve through week 24 as shown in Figure 1. Similar results were seen in Study 1.

Figure 1. Change from Baseline in Proptosis over 24 Weeks in Study 2



P<0.01 at each timepoint

TEPEZZA also led to improvement in the less severely impacted "fellow" eye**.**

Diplopia (double vision) was evaluated in a subgroup of patients that had diplopia at baseline in Study 1 and 2. Results are shown in Table 3.

Table 3. Diplopia in Patients with Active Thyroid Eye Disease in Study 1 and 2

Parameter	TEPEZZA (n=66)	Placebo (n=59)
Diplopia Responder rate[a] at week 24, % (n)	53% (35)	25% (15)

P<0.01
[a] Diplopia was evaluated on a 4-point scale where scores ranged from 0 for no diplopia to 3 for constant diplopia. A diplopia responder was defined as a patient with baseline diplopia >0 and a score of 0 at week 24.

Following discontinuation of treatment in Study 1, 53% of patients (16 of 30 patients) who were proptosis responders at week 24 maintained proptosis response 51 weeks after the last TEPEZZA infusion. 67% of patients (12 of 18) who were diplopia responders at week 24 maintained diplopia response 51 weeks after the last TEPEZZA infusion.

Subgroups
Examination of age and gender subgroups did not identify differences in response to TEPEZZA among these subgroups. Reduction in proptosis was similar between smokers and non-smokers in both studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

TEPEZZA (teprotumumab-trbw) for injection is a sterile, preservative-free, white to off-white lyophilized powder available as follows:

Carton containing one 500 mg single-dose vial	NDC 75987-130-15

Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton until time of use to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity
- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions
- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease
- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia
- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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