CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761143Orig1s000

SUMMARY REVIEW

Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review of BLA 761143

Date	January 21, 2020
From	Peter Stein, M.D., Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review
BLA	761143
Applicant	Horizon Pharma Ireland, Ltd.
Date of Submission	July 8, 2019
PDUFA Goal Date	March 8, 2020
Proprietary Name	Tepezza
Established or Proper Name	teprotumumab-trbw for injection
Dosage Form(s)	Lyophilized powder for intravenous infusion
Recommendation on Regulatory Action	Approval
Recommended Indication	Indicated for the treatment of Thyroid Eye Disease
Recommended Dosing Regimen	Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions

Material Reviewed/Consulted **OND Action Package, including:**	**Names of Discipline Reviewers**
Medical Officer Review	Wiley A. Chambers
Statistical Review	Yunfan Deng
Pharmacology Toxicology Review	Andrew J. McDougal
OPQ Review • Drug Substance/Drug Product Immunogenicity/Analytical Method Validation • Labeling • Facility • Microbiology • Application Lead	Eric Hales Chia-Wen Hsu Vicky Borders-Hemphill Ashley Queen/Zhong Li/Thuy Thanh Nguyen Reyes Candauchacon/Bo Chi/Jessica Hankins Kristen Nickens
Clinical Pharmacology Review	Abhay Joshi
Office of Prescription Drug Promotion	Carrie Newcomer
Office of Scientific Investigations	Roy Blay
Cross-Discipline Team Leader	William M. Boyd
Division of Medication Error Prevention and Analysis	Nasim Roosta
Division of Risk Management	Courtney Cunningham

1. Summary

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 (TED).

Thyroid Eye Disease, 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.

Efficacy with teprotumumab, as demonstrated by a reduction in proptosis, has been demonstrated in two adequate and well controlled studies. The submitted studies are limited in size with only 120 thyroid patients being treated to date.

The clinical studies contained in this submission support the use of Tepezza (teprotumumab-trbw) for injection for the treatment of Thyroid Eye Disease. BLA 761143 Tepezza (teprotumumab-trbw) for injection is recommended for approval with the revised labeling identified in this review.

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 proptosis 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.

3. Background

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.

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.

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.

Teprotumumab has been granted Fast Track, Breakthrough Therapy, and Orphan Drug designations by the FDA for the proposed indication, Active Thyroid Eye Disease.

4. Product Quality

From the Office of Biotechnology Products (OBP) Executive Summary dated 12/16/19 and the OBP CMC review dated 12/16/19:

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761143 for teprotumumab-trbw manufactured by Horizon Therapeutics Ireland, DAC. The data submitted in this application are adequate to support the conclusion that the manufacture of teprotumumab-trbw is well-controlled and leads to a product that is safe, pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Teprotumumab-trbw drug product (DP) is supplied at 500 mg/vial as a sterile, lyophilized powder for intravenous infusion. Upon reconstitution with 10 mL of sterile water for injection, the reconstituted protein concentration of teprotumumab-trbw DP is 47.6 mg/mL. Teprotumumab-trbw is indicated for the treatment of Thyroid Eye Disease (TED).

Drug Substance

Teprotumumab-trbw is a recombinant, human IgG1κ monoclonal antibody produced in genetically engineered Chinese Hamster Ovary (CHO) cells. Teprotumumab-trbw binds to the alpha-subunit of the insulin-like growth factor-1 receptor (IGF-1R) and inhibits the ligand-receptor binding interaction between IGF-1 and IGF-2 with IGF-1R. This inhibition is believe to lead to the inhibition of autophosphorylation of IGF-1R and prevention of the activation of downstream signaling pathways that promote cell proliferation.

Teprotumumab consists of (b) (4) an intact molecular weight of 148 kDa. (b) (4) (b) (4)

Source: BLA 761143 OBP Product Quality Review

Drug Product

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

Dating Period and Storage Conditions

The dating period for teprotumumab-trbw DP is 18 months when stored at 2-8°C, protected from light. Storage conditions at room temperature for no more than 4 hours or at 2-8°C for no more than 48 hours are proposed for the reconstituted and diluted drug product in the sterile water for injection.

Container Closure

The primary container closure system for teprotumumab-trbw DP consists of a (b) (4) vial (b) (4)

Inspections

Adequate descriptions of the facilities, equipment, environmental controls, process equipment cleaning, and contamination control strategy were provided (b) (4) (b) (4) and (b) (4) proposed for teprotumumab DP and DS manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

Establishment Information – DS and DP

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
[redacted]	[redacted]	[redacted] (b) (4)	Approve – Based on PAI/PLI conducted on [redacted] (b) (4)	FDA Form-483 issued (8-items), VAI	Approve
[redacted]	[redacted]	[redacted]	Approve- Based on Previous History	N/A	Approve
[redacted]	[redacted]	[redacted]	Approve- Based on Previous History	N/A	Approve
[redacted]	[redacted]	[redacted]	Approve- Based on Previous History	N/A	Approve

(b) (4)					
			No Evaluation Necessary	N/A	Approve
			No Evaluation Necessary	N/A	Approve
			Approve- Based on Previous History	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Approve – Based on PAI/PLI conducted on (b) (4)	FDA Form-483 issued (5-item), VAI	Approve
			Approve- Based on Previous History	N/A	Approve

OPQ Post-Marketing Commitments

Post-marketing commitments, with the timetable submitted by the Applicant on January 6, 2020, state that they will conduct these studies according to the following schedules:

3780-1 Establish an in-house qualification program for the IGF-1R AlphaLISA commercial kit used to control the potency of teprotumumab drug substance and drug product at release and during storage. Submit the description of the qualification program, information and data to support the adequacy of the qualification program with respect to the assurance of consistent performance of the AlphaLISA commercial kit in final study report.

Final Report Submission: 03/2020

3780-2 Re-validate the potency assay using the IGF-1R AlphaLISA commercial kit to ensure proper implementation of an internal assay control. Submit the updated potency assay description, information and data to support the validation of the updated potency assay in a PAS to the BLA.

Final Report Submission: 02/2020

3780-3 Develop, validate, and implement an in-house biological activity assay to control the potency for lot release and stability testing of teprotumumab drug substance and drug product. Submit the analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion for the in-house potency assay to the BLA in a PAS.

Final Report Submission: 07/2021

3780-4 Perform (b) (4) testing (b) (4) of three consecutive commercial batches to confirm the consistency of the protein concentration values for the filled vials throughout (b) (4). Submit the (b) (4) testing results in a final study report.

Final Report Submission: 05/2020

3780-5 Perform real-time drug product container closure system leachable studies using appropriate methods to detect, identify, and quantify organic non-volatile, volatile, and semi-volatile species and metals through the end of shelf life. Submit the complete data set and toxicology risk evaluation for the levels of leachables detected in the drug product in a final study report.

Final Report Submission: 12/2020

3780-6 Develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay for teprotumumab drug substance release. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

Final Report Submission: 06/2021

3780-7 Validate the [redacted] (b) (4) teprotumumab drug product [redacted] (b) (4) [redacted] (b) (4) and submit the validation data.

Final Report Submission: 06/2020

5. 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 IGF-1R 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.

From a nonclinical perspective, P/T recommends approval of BLA 761143 for Tepezza (teprotumumab-trbw) for injection.

6. Clinical Pharmacology

From the original Clinical Pharmacology Review dated 12/18/19:

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).

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. 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

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.

7. Clinical Microbiology

This product is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 1/13/20:

Sources of Clinical Data

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 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

Evidence of effectiveness is derived from one Phase 2 study (Study TED01RV) and one Phase 3 study (Study HZNP-TEP-301). Both studies were randomized placebo-controlled studies that evaluated the safety and efficacy of the proposed teprotumumab dosing regimen in patients with active TED. The entry criteria in both clinical studies allowed for the assessment of efficacy of teprotumumab in a relevant population of adult subjects with TED. Male or female subjects, 18 to 75 years of age in Study TED01RV and 18 to 80 years of age in
Study HZNP-TEP-301, with a clinical diagnosis of Graves' disease associated with TED were eligible to participate if they met the protocol-specified inclusion/exclusion criteria.

Primary Efficacy Results - Study TED01RV (Study 1)

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 clinical activity score (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.

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 did 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.

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 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

p-value based on chi square

Because the Agency disagreed with the Primary endpoint due to the inclusion of the CAS portion of the endpoint because 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 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

There is a clinically significant reduction in proptosis (i.e., greater than 2 mm) in both eyes which continues through the treatment period by the first evaluation period at Week 6.

Primary Efficacy Results - Study HZNP-TEP-301 (Study 2)

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

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.

9. Safety

From the original Medical Officer Review dated 1/13/20:

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

Deaths – none

Treatment Emergent Common Adverse Reactions

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%)
Infections and Infestations	9 (21%)	10 (24%)	13 (30%)	16 (40%)
Upper respiratory tract infection	4 (9%)		0	
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%)
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%)
Dysgeusia	0	0	3 (7%)	4 (10%)
Metabolism and Nutrition Disorders	2 (5%)		10 (23%)	
Hyperglycemia	2 (5%)	0	5 (12%)	2 (5%)

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] 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

Interpretation of these findings 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 disorder.

Immunogenicity

No clinically significant changes were reported.

Study Limitations leading to Post-Marketing Requirements:
The submitted studies are limited in size with only 120 thyroid patients being treated to date.
Two post-marketing requirements are needed:

I. PMR 3780-8: An adequate and well-controlled clinical trial to evaluate the safety, efficacy and need for retreatment of three different teprotumumab treatment durations for the treatment of Thyroid Eye Disease

The results of this PMR will address the very limited safety data available from patients with extended treatment periods and/or retreatments following relapse of proptosis by evaluating a population of subjects with shorter, standard, or longer treatments periods along with a standard re-treatment for subjects who are inadequately treated or relapse within a year after completing their initial treatment course.

II. PMR 3780-9: Completion of ongoing trial, HZNP-TEP-302 (OPTIC-X)

The results of this PMR will address the very limited safety data available from patients who need retreatment by evaluating a population of subjects who are non-responsive or relapsing at Week 24 after initial treatment.

10. 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.

11. Advisory Committee Meeting

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.

12. Other Relevant Regulatory Issues

Biostatistics

Per the original Biostatistics review dated 12/10/19:

For Study TED01RV, the primary outcome measure was the overall responder rate in the study eye at week 24, which was defined as the percentage of patients with ≥2 mm reduction in proptosis (bulging of the eye) in the study eye from baseline and with a ≥2-point reduction in clinical activity score (CAS), without deterioration in the non-study eye (≥2 mm increase in proptosis or a ≥2-point increase in CAS). CAS is a 7-point scale used to measure the signs and symptoms of TED including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis and inflammation, where lower scores indicate fewer symptoms. For Study HZNP-TEP-301, the primary outcome measure was the proptosis responder rate in the study eye at week 24, defined as the percentage of patients with a ≥2 mm reduction from baseline in proptosis in the study eye without deterioration of ≥2 mm increase in proptosis in the non-study eye; the overall responder rate was the first secondary efficacy outcome in this study. It should be noted that the proptosis responder rate is the Agency's clinical review team preferred primary efficacy measure.

For both studies, compared with placebo, significantly more patients treated with teprotumumab had an improvement in both proptosis responder rate and the overall responder rate. In Study TED01RV, the proptosis responder rate was 71.3% in teprotumumab vs. 20.0% of placebo, the treatment difference was 51.1% with 95% CI of (32.5%, 69.7%); the overall responder rate was 69.1% in teprotumumab vs. 20.0% in placebo, the treatment difference was 49.1% with 95% CI of (30.8%, 67.3%). In Study HZNP-TEP-301, the proptosis responder rate was 82.9% in teprotumumab vs. 9.5% of placebo, the treatment difference was 73.4% with 95% CI of (58.9%,88.0%); the overall responder rate was 78.0% in teprotumumab vs. 7.1% in placebo, the treatment difference was 70.8% with 95% CI of (55.9%, 85.6%).

Table 1: Study TED01RV and Study HZNP-TEP-301 Primary Efficacy Results at Week 24 (ITT)

	Study TED01RV			Study HZNP-TEP-301		
	Teprotumumab	**Placebo**	**Difference (95% CI)[1]**	**Teprotumumab**	**Placebo**	**Difference (95% CI)[1]**
Proptosis Response Rate	30/42 (71.3%)	9/45 (20.0%)	51.1% (32.5%, 69.7%)	34/41 (82.9%)	4/42 (9.5%)	73.4% (58.9%, 87.9%)
Overall Response Rate	29/42 (69.1%)	9/45 (20.0%)	48.9% (30.2%, 67.6%)	32/41 (78.1%)	3/42 (7.1%)	70.9% (56.0%, 85.8%)

[1] Difference and its corresponding 95% CI is based on a weighted average of the difference within each randomization stratum (tobacco user, tobacco non-use) using CMH weights. Missing responses were imputed as non-responders.
Source: Statistical reviewer's analysis for Study TED01RV and Tables 14.2.1.3.1 and 14.2.2.1.3 of Study 301 Report

The two studies demonstrated that teprotumumab was efficacious in treating active TED; and the treatment effects were relatively consistent across the two studies. Therefore, the statistical reviewer recommends the approval of teprotumumab for the treatment of active thyroid eye disease.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

The only investigator/sub-investigator with financial interests was (b) (6) who participated in Study TED01RV (b) (6). During the course of the study, (b) (6) did not receive any tangible products, goods or compensation. (b) (6) (b) (6) (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. (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.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. 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.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, TEPEZZA, and granted conditional acceptance on 2/22/19 under the IND 112952. Their proprietary name risk assessment at that time did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional. In a correspondence dated 7/2/19, DMEPA notified the Horizon Pharma that the name TEPEZZA was no longer acceptable because it could result in medication errors due to confusion with another product under review by DMEPA. The ultimate acceptability of TEPEZZA would be dependent upon which underlying application was approved first. DMEPA requested that an alternate proprietary name be submitted.

DMEPA completed a labeling review of the originally submitted USPI and carton/container labeling (TEPEZZA) on 10/30/2019. DMEPA notified the applicant that the nonproprietary name, teprotumumab-trbw, was conditionally acceptable for the product on 11/25/19.

DMEPA granted conditional acceptance to the alternate name, (b) (4) on 11/26/19.

DMEPA notified the applicant that the proprietary name, TEPEZZA, was conditionally acceptable for the product on 1/14/20. BLA 761143 will receive an approval action prior to another product under review by DMEPA with a similar name; thus TEPEZZA is again conditionally acceptable.

OBP LABELING

The Office of Biotechnology (OBP) Labeling Reviewer completed a review of the labels and labeling submitted on 12/13/19 (carton/container) and 1/13/20 (PI) and found the carton/container labeling to be **not** acceptable from a labeling perspective. The OBP reviewer made several recommendations for the proposed labeling (see review). The Division did not agree with some of recommendations because they were not required by regulation and conflicted with the clinical reviewer's labeling recommendations. Other recommendations were conveyed to the applicant and incorporated into the labeling. The carton/container labeling submitted on 1/14/20 was not reviewed by OBP in the 1/13/20 review. The 1/14/20 submitted labeling contained the quantitative information for active and inactive ingredients on the carton.

A meeting was held between the Division and representatives from OBP on 1/21/20. The statement, "After reconstitution , the final concentration is 47.6 mg/mL." was added to Section 2.2 of the Package Insert at the request of OBP.

OPDP

Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete labeling on 1/13/20. The labeling subsequently continued to be edited by the Division and the applicant.

DRISK

The Clinical Team met with Division of Risk Management (DRISK) during the review of the application. DRISK raised no new safety issues related to the application and concurred with the Clinical Team that no post-marketing risk evaluation and management strategies (i.e., REMS) were needed for this drug product.

13. Patient Experience Data

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.		

14. Regulatory Action

BLA 761143 Tepezza (teprotumumab-trbw) for injection will be approved for the treatment of Thyroid Eye Disease. There are no recommended post-marketing risk evaluation and management strategies (i.e., REMS) for this drug product.

However, in addition to the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product, there are seven (7) Post-marketing Commitments (PMCs) and two (2) Post-marketing Requirements (PMRs):

Post-marketing Requirements (PMRs) and Commitments (PMCs)

I. Post-marketing commitments, with the timetable submitted by the Applicant on January 6, 2020, which states that they will conduct these studies according to the following schedules:

3780-1 Establish an in-house qualification program for the IGF-1R AlphaLISA commercial kit used to control the potency of teprotumumab drug substance and drug product at release and during storage. Submit the description of the qualification program, information and data to support the adequacy of the qualification program with respect to the assurance of consistent performance of the AlphaLISA commercial kit in final study report.

Final Report Submission: 03/2020

3780-2 Re-validate the potency assay using the IGF-1R AlphaLISA commercial kit to ensure proper implementation of an internal assay control. Submit the updated potency assay description, information and data to support the validation of the updated potency assay in a PAS to the BLA.

Final Report Submission: 02/2020

3780-3 Develop, validate, and implement an in-house biological activity assay to control the potency for lot release and stability testing of teprotumumab drug substance and drug product. Submit the analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion for the in-house potency assay to the BLA in a PAS.

Final Report Submission: 07/2021

3780-4 Perform (b) (4) testing (b) (4) of three consecutive commercial batches to confirm the consistency of the protein concentration values for the filled vials (b) (4). Submit the (b) (4) testing results in a final study report.

Final Report Submission: 05/2020

3780-5 Perform real-time drug product container closure system leachable studies using appropriate methods to detect, identify, and quantify organic non-volatile, volatile, and semi-volatile species and metals through the end of shelf life. Submit the complete data set and toxicology risk evaluation for the levels of leachables detected in the drug product in a final study report.

Final Report Submission: 12/2020

3780-6 Develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay for teprotumumab drug substance release. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

Final Report Submission: 06/2021

3780-7 Validate the (b) (4) teprotumumab drug product (b) (4) in three media fill runs and submit the validation data.

Final Report Submission: 06/2020

II. Post-marketing requirements, with the timetable submitted by the Applicant on January 14, 2020, which states that they will conduct these studies according to the following schedules:

3780-8 A descriptive clinical trial to evaluate the safety, efficacy and need for retreatment of three different teprotumumab treatment durations for the treatment of Thyroid Eye Disease.

Final Protocol Submission: 08/2020
First Patient Enrolled: 01/2021
Study Completion: 05/2026
Final Report Submission: 11/2026

3780-9 Completion of the ongoing study, HZNP-TEP-302 (OPTIC-X).

Study Completion: 07/2020
Final Report Submission: 01/ 2021

15. Labeling

BLA 761143 Tepezza (teprotumumab-trbw) for injection will be approved for the treatment of Thyroid Eye Disease with the following labeling submitted to the application on 1/14/20.

13 Pages of Draft Labeling Have Been Withheld In Full As B4 (CCI/TS)
Immediately Following This Page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
01/21/2020 09:31:24 AM

WILEY A CHAMBERS
01/21/2020 09:39:14 AM

PETER P STEIN
01/21/2020 01:28:11 PM