Summary Report of Benefit-Risk Assessment

TEPEZZA POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 500 MG/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Teprotumumab
Product Registrant	Amgen Biotechnology Singapore Pte Ltd
Product Registration Number	SIN17539P
Application Route	Abridged evaluation
Date of Approval	15 May 2026

Table of Contents

A INTRODUCTION

Tepezza is indicated in adults for the treatment of moderate to severe thyroid eye disease (TED).

The active substance, teprotumumab, is a fully human IgG monoclonal antibody that targets the insulin-like growth factor-1 receptor (IGF-1R). IGF-1R is over expressed in orbital fibroblasts in patients with TED and plays a central role in disease pathophysiology through activation of inflammatory pathways, hyaluronan production, adipogenesis and tissue remodelling. By inhibiting IGF-1R signalling, teprotumumab reduces orbital fibroblast activation, leading to reductions in orbital inflammation, extra ocular muscle and fat expansion, and associated clinical manifestations such as proptosis and diplopia.

Tepezza is available as powder for concentrate for solution for infusion containing 500 mg/vial of teprotumumab. Other ingredients in the vial are L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20, and trehalose dihydrate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, teprotumumab, is manufactured at AGC Biologics A/S, Soeborg, Denmark. The drug product, Tepezza powder for concentrate for solution for infusion 500 mg/vial, is manufactured at Patheon Italia S.p.A., Ferentino, Italy and Patheon Italia S.p.A, Monza, Italy.

Drug substance:

Adequate controls have been presented for the cell banks and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice standard. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support commercial drug substance shelf-life of 60 months at storage of -80 ± 10°C. The packaging are 5 L and 2 L polycarbonate square bottles.

Drug product:

The manufacturing process involves thawing, pooling and mixing of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored between 2ºC and 8ºC. The combined storage duration of the reconstituted drug product and diluted solution in the infusion bag containing 0.9% sodium chloride is up to 4 hours at 20°C to 25°C or up to 48 hours at 2°C to 8°C. The container closure system is a 20 mL Type I glass vial, closed with a 20mm coated chlorobutyl stopper and a crimped aluminium seal.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of teprotumumab in the treatment of TED was based primarily on data from three randomised, double-masked, placebo-controlled studies in acute TED — the Phase 2 study TED01RV, the Phase 3 OPTIC study (HZNP-TEP-301), and the OPTIC-J study (HZNP-TEP-303). Efficacy in chronic TED was evaluated in one pivotal Phase 4, randomised, double-masked, placebo-controlled study (HZNP-TEP-403).

Acute TED studies

The acute TED studies were multicentre, randomised, double-masked, placebo-controlled trials conducted in adult patients with moderate to severe active TED. Patients were randomised in a 1:1 ratio to receive intravenous teprotumumab or placebo. Teprotumumab was administered at an initial dose of 10 mg/kg, followed by 20 mg/kg every three weeks for a total of 8 infusions over 24 weeks.

The primary efficacy endpoint differed across the acute TED studies. In the Phase 2 study TED01RV, the primary endpoint was the overall responder rate at Week 24, defined as the proportion of patients with a ≥2-point reduction in Clinical Activity Score (CAS) and a ≥2 mm reduction in proptosis in the study eye, without corresponding deterioration in the fellow eye. In the pivotal Phase 3 studies OPTIC and OPTIC-J, the primary efficacy endpoint was the proptosis responder rate at Week 24, defined as the proportion of patients with a ≥2 mm reduction in proptosis in the study eye without a corresponding deterioration in the fellow eye. Key secondary endpoints included overall responder rate, change from baseline in proptosis, CAS categorical responder rate, and complete and overall binocular diplopia responder rate at Week 24.

A total of 225 patients were randomised in the acute TED studies, including TED01RV (teprotumumab, n=43; placebo, n=45), OPTIC (teprotumumab, n=41; placebo, n=42), and OPTIC-J (teprotumumab, n=27; placebo, n=27). The majority of patients (66.7% to 80.0%) were female. Patients aged from 18 to 79 years with active, moderate-to-severe TED and symptom onset of ≤9 months were enrolled in the studies. Mean disease duration ranged from 4.3 to 6.4 months, mean baseline CAS ranged from 4.0 to 5.3, and mean baseline proptosis ranged from 20.4 mm to 23.4 mm. OPTIC-J enrolled Japanese patients, while TED01RV and OPTIC enrolled patients from multiple countries.

The key efficacy results from the individual acute TED studies and the combined analysis are summarised in the tables below.

Summary of key efficacy results — individual acute TED studies

Endpoint	TED01RV			OPTIC			OPTIC-J		
	Tepro (N=43)	Placebo (N=45)	p-value	Tepro (N=41)	Placebo (N=42)	p-value	Tepro (N=27)	Placebo (N=27)	p-value
Primary efficacy endpoint									
Proptosis responder rate[a] at Week 24, n (%)	31 (72.1%)	9 (20.0%)	<0.0001	34 (82.9%)	4 (9.5%)	<0.0001	24 (88.9%)	3 (11.1%)	<0.0001
Secondary efficacy endpoints									
Mean change from baseline in proptosis[b] at Week 24 (mm), LS mean (SE)	−2.95 (0.263)	−0.29 (0.252)	<0.0001	−3.32 (0.233)	−0.53 (0.235)	<0.0001	−2.36 (0.302)	−0.37 (0.303)	<0.0001
Overall responder rate[c] at Week 24, n (%)	30 (69.8%)	9 (20.0%)	<0.0001	32 (78.0%)	3 (7.1%)	<0.0001	21 (77.8%)	1 (3.7%)	<0.0001
CAS categorical responder rate[d] at Week 24, n (%)	28 (65.1%)	10 (22.2%)	<0.0001	24 (58.5%)	9 (21.4%)	0.0002	16 (59.3%)	6 (22.2%)	0.0031
Binocular diplopia responder rate[e] at Week 24, n (%)	27/38 (71.1%)	10/31 (32.3%)	0.0004	19/28 (67.9%)	8/28 (28.6%)	0.0012	14/22 (63.6%)	9/20 (45.0%)	0.2430
Complete binocular diplopia responder rate[f] at Week 24, n (%)	19/38 (50.0%)	8/31 (25.8%)	0.0261	16/28 (57.1%)	7/28 (25.0%)	0.0094	11/22 (50.0%)	4/20 (20.0%)	0.0430[g]

Tepro = teprotumumab; LS = least squares; SE = standard error

a. Proptosis responders were defined as participants 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.

b. Mean change from baseline in proptosis was calculated using participants with available baseline and Week 24 assessments. The analysis population (tepro/placebo) was n = 39/40 for TED01RV, n = 40/40 for OPTIC, and n = 27/27 for OPTIC-J.

c. Overall responders were defined as participants with a ≥2 mm reduction in proptosis and a ≥2-point reduction in CAS from baseline in the study eye, without deterioration (≥2 mm increase in proptosis or ≥2-point increase in CAS) in the fellow eye at Week 24. This was the primary efficacy endpoint in Study TED01RV.

d. CAS categorical responders were defined as participants with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) in the study eye as a categorical response variable at Week 24.

e. Binocular diplopia responders were defined as participants with baseline binocular diplopia >0 who had a reduction of ≥1 grade at Week 24.

f. Complete binocular diplopia responders were defined as participants with baseline binocular diplopia >0 and a score of 0 at Week 24.

g. Statistical significance could not be claimed in the hierarchy analysis in the Optic-J study.

Summary of key efficacy results — combined analysis

Endpoint	Combined Teprotumumab (N=111)	Combined Placebo (N=114)	p-value
Primary efficacy endpoint			

Proptosis responder rate at Week 24, n (%)	89 (80.2%)	16 (14.0%)	<0.0001
Secondary efficacy endpoints			
Mean change from baseline in proptosis at Week 24 (mm), LS mean (SE)	−2.96 (0.152)	−0.38 (0.149)	<0.0001
Overall responder rate at Week 24, n (%)	83 (74.8%)	13 (11.4%)	<0.0001
CAS categorical responder rate at Week 24, n (%)	68 (61.3%)	25 (21.9%)	<0.0001
Complete binocular diplopia responder rate at Week 24, n (%)	46/88 (52.3%)	19/79 (24.1%)	<0.0001
Binocular diplopia responder rate at Week 24, n (%)	60/88 (68.2%)	27/79 (34.2%)	<0.0001

Across the acute TED programme, teprotumumab demonstrated consistent and statistically significant superiority over placebo across all efficacy endpoints. In the combined analysis (N=225), the proptosis responder rate at Week 24 was 80.2% with teprotumumab vs 14.0% with placebo (p<0.0001), with a mean reduction in proptosis of 2.96 mm vs 0.38 (p<0.0001). Treatment effects were observed as early as Week 6, with proptosis responder rates in the teprotumumab group increasing from 52.3% at Week 6 to 80.2% at Week 24, and were sustained through the end of treatment.

All secondary endpoints were statistically significant. The overall responder rate at Week 24 was 74.8% with teprotumumab vs 11.4% with placebo (p<0.0001), and the CAS categorical responder rate was 61.3% vs 21.9% (p<0.0001). Diplopia outcomes also favoured teprotumumab, with a complete binocular diplopia responder rate of 52.3% vs 24.1% (p<0.0001) and a binocular diplopia responder rate of 68.2% vs 34.2% (p<0.0001). Among patients without baseline diplopia, none of the teprotumumab-treated patients developed new diplopia compared with 24.2% in the placebo group. Results were consistent across individual studies and prespecified subgroups.

Chronic TED study

Efficacy in chronic TED was evaluated in the pivotal Phase 4 study HZNP-TEP-403, a multicentre, randomised, double-masked, placebo-controlled trial conducted in adult patients with long-standing TED and low disease activity (CAS ≤1). Patients were randomised in a 2:1 ratio to receive teprotumumab or placebo over 24 weeks. Teprotumumab was administered at the same dosing regimen as in the acute TED studies.

The primary efficacy endpoint was the change from baseline in proptosis at Week 24. Secondary endpoints included proptosis responder rate, change in Graves' Ophthalmopathy Quality of Life (GO-QoL) appearance and visual functioning subscales, and change in diplopia from baseline at Week 24.

A total of 62 patients were randomised in the study (teprotumumab, n=42; placebo, n=20). The mean age was 48.7 years (range: 18–75 years) and the majority of patients (80.6%) were female. Patients enrolled in the study had inactive, chronic TED with a mean disease duration of 62.2 months. Mean baseline CAS was 0.4 and mean baseline proptosis was 24.4 mm.

The key efficacy results are summarised in the table below.

Summary of key efficacy results — chronic TED study (HZNP-TEP-403)

Endpoint	Teprotumumab (N=42)	Placebo (N=20)	p-value
Primary efficacy endpoint			
Mean change from baseline in proptosis at Week 24 (mm), LS mean (SE)	−2.41 (0.228)	−0.92 (0.323)	0.0004
Secondary efficacy endpoints			
Proptosis responder rate[a] at Week 24, n (%)	26 (61.9%)	5 (25.0%)	0.0134
GO-QoL visual functioning subscale[b] change from baseline, LS mean (SE)	+8.73 (1.661)	+2.41 (2.329)	0.0318
GO-QoL appearance subscale[b] change from baseline, LS mean (SE)	+10.03 (3.592)	+7.19 (5.069)	0.6494
Diplopia improvement at Week 24[c], n (%)	6 (14.3%)	2 (10.0%)	0.3815

a. Proptosis responders were defined as participants 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.
b. The GO-QoL subscale scores range from 0 to 100, with lower scores representing poorer health status. GO-QoL subscale scores were calculated using participants with available baseline and Week 24 assessments. The analysis population (teprotumumab/placebo) was n = 39/20.
c. Severity of diplopia was defined as follows: 0 = no diplopia; 1 = intermittent (diplopia in the primary position of gaze when tired or when first awakening); 2 = inconsistent (diplopia at extremes of gaze); 3 = consistent (continuous diplopia in primary or reading position). Change from baseline was categorised into 5 categories: significant worsening if change score was 2 or 3; worsening if change score was 1; no change if change score was 0; improvement if change score was -1; significant improvement if change score was -2 or -3.

The study demonstrated a statistically significant improvement in proptosis with teprotumumab compared with placebo, with a mean reduction of 2.41 mm in the teprotumumab group vs 0.92 mm in the placebo group at Week 24 (p=0.0004). The observed mean reduction from baseline in the teprotumumab group met the ≥2 mm threshold for clinical meaningfulness as defined by the European Group on Graves' Orbitopathy (EUGOGO) guidelines. Clinically meaningful proptosis reduction was achieved from Week 18 onwards in the chronic TED population. Although the magnitude of effect was numerically smaller than that observed in the acute TED studies, the reduction remained clinically relevant. The proptosis responder rate at Week 24 was also significantly higher in the teprotumumab group compared with placebo (61.9% vs 25.0%; p=0.0134).

The GO-QoL visual functioning subscale showed a statistically significant improvement with teprotumumab vs placebo (LS mean change: +8.73 vs +2.41; p=0.0318), although the appearance subscale did not achieve statistical significance (LS mean change: +10.03 vs +7.19; p=0.6494). Diplopia improvement at Week 24 was observed in 14.3% of teprotumumab-treated patients vs 10.0% of placebo patients (odds ratio 2.13; p=0.3815), which did not reach statistical significance. The study was not powered to detect differences in diplopia, and baseline diplopia prevalence was lower in this chronic population (33.3% teprotumumab, 20.0% placebo) than in studies of acute TED.

Overall, the clinical efficacy data demonstrated that treatment with teprotumumab achieved statistically significant and clinically relevant improvements with respect to the primary efficacy endpoint of proptosis compared to placebo in acute and chronic TED, supporting its role as a disease-modifying therapy across different stages of TED.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of teprotumumab was based primarily on pooled safety data derived from the pivotal randomised, double-masked, placebo-controlled studies in acute and chronic TED, including the Phase 2 study TED01RV, the Phase 3 OPTIC (HZNP-TEP-301) and OPTIC-J (HZNP-TEP-303) studies and the Phase 4 chronic TED study (HZNP-TEP-403). The overall pooled safety population comprised a total of 285 patients, including 224 patients in the acute TED studies and 61 patients in the chronic TED studies. Most patients completed all 8 planned infusions (87.5% teprotumumab, 90.2% placebo).

Overview of safety profile

Adverse event (AE)	Acute TED		Chronic TED		Overall	
	Teprotumumab (N=111) n (%)	Placebo (N=113) n (%)	Teprotumumab (N=41) n (%)	Placebo (N=20) n (%)	Teprotumumab (N=152) n (%)	Placebo (N=133) n (%)
Any AE	94 (84.7)	81 (71.7)	33 (80.5)	16 (80.0)	127 (83.6)	97 (72.9)
Treatment-related AE	64 (57.7)	31 (27.4)	31 (75.6)	12 (60.0)	95 (62.5)	43 (32.3)
Serious adverse event (SAE)	8 (7.2)	1 (0.9)	1 (2.4)	1 (5.0)	9 (5.9)	2 (1.5)
Treatment-related SAE	3 (2.7)	0	1 (2.4)	1 (5.0)	4 (2.6)	1 (0.8)
Grade 3 or higher AE	6 (5.4)	1 (0.9)	1 (2.4)	1 (5.0)	7 (4.6)	2 (1.5)
AE leading to treatment interruption	6 (5.4)	1 (0.9)	2 (4.9)	2 (10.0)	8 (5.3)	3 (2.3)
AE leading to treatment discontinuation	6 (5.4)	3 (2.7)	1 (2.4)	1 (5.0)	7 (4.6)	4 (3.0)
Treatment-related AE leading to treatment discontinuation	3 (2.7)	0	1 (2.4)	0	4 (2.6)	0
AE leading to death	0	0	0	0	0	0

Across the controlled studies, treatment-emergent AEs were more frequently reported in patients receiving teprotumumab compared with placebo (83.6% vs 72.9%). The majority of AEs were mild to moderate in severity. The most frequently reported AEs (≥10%) in teprotumumab-treated patients were muscle spasms (27.6% vs 6.0%), diarrhoea (14.5% vs 9.0%), hearing impairment (13.8% vs 2.3%), alopecia (13.2% vs 5.3%), hyperglycaemia (13.2% vs 3.0%), fatigue (12.5% vs 6.0%), nausea (10.5% vs 6.8%), and headache (10.5% vs 7.5%). The overall safety profile was consistent across acute and chronic TED populations. However, the relative impact of hearing impairment was more notable in the chronic TED setting.

SAEs were reported in 5.9% of teprotumumab-treated patients and 1.5% of placebo-treated patients across the pooled TED studies. Across the acute studies, 8 SAEs were reported in teprotumumab-treated patients, including diarrhoea, inflammatory bowel disease, *Escherichia coli* sepsis, Hashimoto's encephalopathy, urinary retention, infusion reaction, pneumothorax, and COVID-19. In the chronic TED study, 1 SAE of conductive deafness was reported in a teprotumumab-treated patient and led to treatment discontinuation. An SAE of diabetic

ketoacidosis was reported in the placebo group in a participant who had inadvertently received teprotumumab as the first infusion. No deaths were reported in the acute or chronic TED studies.

AEs leading to treatment discontinuation were reported in 4.6% of teprotumumab-treated patients and 3.0% of placebo-treated patients across the pooled TED studies. In the acute TED studies, AEs leading to treatment discontinuation in teprotumumab-treated patients included diarrhoea, inflammatory bowel disease, *Escherichia coli* sepsis, neurosensory hypoacusis, and infusion reaction. In the placebo group, treatment discontinuation was reported following optic neuropathy. In the chronic TED study, conductive deafness and an infusion-related reaction led to treatment discontinuation in 1 patient each in the teprotumumab and placebo groups, respectively.

The predefined adverse events of special interest (AESIs) included hearing impairment, hyperglycaemia, infusion-related reactions (IRRs), and exacerbation of inflammatory bowel disease (IBD). No cases of IBD exacerbation were reported across the controlled studies.

Hearing impairment was the most notable safety signal, encompassing events reported as hypoacusis, tinnitus, hyperacusis, autophony, eustachian tube dysfunction, and deafness. Hearing-related events occurred in 13.8% of teprotumumab-treated patients vs 2.3% of placebo patients in the overall controlled study population, and in 16.3% (40/246) of teprotumumab-treated participants across the entire clinical programme. The incidence was higher in the chronic TED population (22.0% vs 10.0%) compared with the acute TED population (10.8% vs 0.9%). The mean time to first hearing impairment event from initial teprotumumab dose was 77.9 days (range: 3–153 days), occurring on average after 4.2 infusions. The majority of events were mild to moderate in severity and no cases of complete hearing loss were reported; however, approximately one-third of events remained unresolved at study completion and irreversibility cannot be excluded. Hearing impairment was therefore identified as the key risk associated with teprotumumab treatment.

Hyperglycaemia occurred in 13.2% of teprotumumab-treated patients vs 3.0% with placebo, with comparable rates across the acute TED (12.6% vs 1.8%) and chronic TED (14.6% vs 10.0%) populations. Rates were particularly elevated when compared with placebo in patients with pre-existing diabetes (69.2% vs 9.1%) or prediabetes (18.4% vs 0.0%). Most events were Grade 1 or 2 in severity and manageable with standard glycaemic control medications. Post-marketing data identified cases of diabetic ketoacidosis and hyperosmolar hyperglycaemic state.

IRRs were infrequent and occurred at similar rates between teprotumumab and placebo in the overall population (3.9% vs 3.0%). The reactions were generally mild to moderate in severity, and could be managed with antihistamines and/or corticosteroids. No IRR was reported as anaphylactic reactions.

The key safety risks, particularly hearing impairment which represents a clinically significant safety concern, have been highlighted through strengthened warnings and precautions in the package insert, including recommendations for baseline, during-treatment, and post-treatment audiometric assessments, glucose monitoring in patients at risk of hyperglycaemia, and guidance on treatment discontinuation where clinically indicated. Additional risk-minimisation measures, including Physician Educational Material (PEM) and Patient Medication Guide (PMG), have been implemented to support early detection and management of hearing impairment and other key risks.

The overall safety profile of teprotumumab is considered acceptable for the intended use when the risk mitigation measures are implemented.

E ASSESSMENT OF BENEFIT-RISK PROFILE

TED is a debilitating autoimmune orbital disease that can cause significant visual morbidity and adversely impact the quality of life. The current standard of care for acute TED includes systemic corticosteroids, immunosuppressive therapies, and orbital radiotherapy, while management of chronic TED relies largely on surgical intervention such as orbital decompression. While these approaches may provide symptomatic relief, they are associated with limitations in terms of durability of response, tolerability, and invasiveness, and do not directly target key disease mechanisms. As such, there remains a place in therapy for disease-modifying medical therapies across different stages of TED.

In acute TED, teprotumumab demonstrated consistent efficacy across three randomised, placebo-controlled clinical trials. Proptosis responder rates exceeded 80% with teprotumumab compared with approximately 10–15% with placebo, with a clinically meaningful mean reduction in proptosis of approximately 2.96 mm. These effects were observed early and sustained through Week 24, reflecting the ability of teprotumumab to modify disease progression driven by active inflammation.

In chronic TED, the pivotal Phase 4 study (HZNP-TEP-403) demonstrated a statistically significant and clinically relevant improvement in proptosis, with a mean reduction of 2.41 mm in the teprotumumab group compared with 0.92 mm for placebo, corresponding to a treatment difference of 1.48 mm (p=0.0004), together with a significantly higher proptosis responder rate (61.9% vs 25.0%). Although the effect size was smaller than that observed in acute TED, the mean reduction from baseline observed in the teprotumumab group meets the ≥2 mm threshold for clinical meaningfulness as defined by EUGOGO guidelines. The secondary endpoint assessing change in diplopia did not achieve statistical significance; however, a numerical improvement favouring teprotumumab was observed (14.3% vs 10.0%; odds ratio 2.13). In the context of chronic TED, where fibrotic and structurally remodelled tissues limit treatment responsiveness, functional improvements in patients with significant impairment may be clinically relevant.

In terms of safety, hearing impairment is a clinically significant concern which occurred more frequently with teprotumumab than placebo, particularly in the chronic TED population. While most events were mild to moderate in severity, and no cases of complete hearing loss were reported, irreversibility cannot be excluded. In view of this, precautionary information on hearing impairment has been strengthened in the package insert to emphasise the need for individualised benefit-risk assessment for each patient. Specifically in the context of chronic TED, considering the smaller magnitude of proptosis reduction observed in the chronic TED study, the potential risk of hearing loss must be carefully weighed against the expected clinical benefit. Because of this risk, structured audiometric monitoring and additional risk-minimisation measures including physician and patient educational materials are required. Other identified risks, including hyperglycaemia and embryofoetal toxicity, are similarly highlighted in the package insert and routine clinical monitoring is recommended.

Overall, the demonstrated efficacy in both acute and chronic TED when weighed against the identified safety risks and the availability of appropriate risk mitigation measures, is considered

favourable in the benefit-risk assessment of teprotumumab for the treatment of moderate to severe TED in adults.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tepezza for the treatment of moderate to severe thyroid eye disease in adults was deemed favourable and approval of the product registration was granted on 15 May 2026.

APPROVED PACKAGE INSERT AT REGISTRATION

FULL PACKAGE INSERT

TEPEZZA® POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 500 MG/VIAL

1 INDICATIONS AND USAGE

TEPEZZA is indicated in adults for the treatment of moderate to severe Thyroid Eye Disease (TED).

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 total volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted TEPEZZA solution must be further diluted in 0.9% Sodium Chloride Injection, USP prior to infusion. To prepare the diluted solution, use 100 mL infusion bags for a dose less than 1800 mg, and 250 mL for a dose equal to or greater than 1800 mg. 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 volume of 0.9% Sodium Chloride Injection, USP withdrawn.

Step 4: Withdraw the required volume from the reconstituted TEPEZZA vial(s) based on the patient's weight (in kg) and transfer into the intravenous bag containing 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion. Do not shake. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

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 or up to 48 hours under refrigerated conditions 2°C to 8°C protected from light.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Prior to reconstitution, TEPEZZA is white to off-white lyophilized powder (cake). Upon reconstitution, TEPEZZA is a nearly 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 at least 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, and pre-medication is recommended for subsequent infusions.

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

- Hypersensitivity to the active substance or to any of the excipients [*see Description (11)*].
- Pregnancy [*see Pregnancy (8.1)*].

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 Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of inflammatory bowel disease (IBD). IBD has been reported in some patients without a prior diagnosis of IBD *[see Adverse Reactions (6.2)]*. Monitor patients for signs and symptoms of IBD. If IBD exacerbation is suspected, discontinue use of TEPEZZA.

5.3 Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In the placebo-controlled double-masked TED clinical trials, 13.2% of patients (80% of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia *[see Adverse Reactions (6.1)]*. Adverse events of hyperglycemic complications, including diabetic ketoacidosis and hyperosmolar hyperglycemic state have been reported [*see Adverse Reactions (6.1) and (6.2)*]. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

Blood glucose monitoring is recommended for 6 months after completion of treatment with TEPEZZA.

5.4 Hearing Impairment Including Hearing Loss

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent [*see Adverse Reactions (6.1)*]. In clinical trials, events associated with hearing impairment included hearing loss (reported as deafness, including sensorineural deafness, eustachian tube dysfunction, eustachian tube patulous, hyperacusis, hypoacusis, autophony and tinnitus and tympanic membrane disorder), have been observed.

Assess patients' hearing before starting treatment (first infusion), during treatment (around third or fourth infusion), and after completing treatment with TEPEZZA. If a patient experiences subjective hearing changes during treatment, additional audiometric assessments are recommended, as necessary. If necessary, monitor for hearing changes for 6 months after completion of treatment with TEPEZZA, or longer, for patients who develop hearing changes, at the discretion of the treating physician.

Physicians should conduct an individualised benefit-risk assessment for each patient, particularly for those with pre-existing hearing impairment, as pre-existing impairment may worsen. In patients with chronic TED, the potential risk of hearing loss must be carefully weighed against the anticipated proptosis reduction achieved with TEPEZZA [*see Clinical Trials (14)*].

Patients should be advised to stop smoking and avoid high intensity noises during treatment with TEPEZZA. Additionally, blood pressure and blood glucose should be appropriately controlled before and while receiving TEPEZZA.

Caution is needed when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity (e.g. aminoglycosides, vancomycin, platinum containing chemotherapeutic medicinal products, loop diuretics) due to the potential risk of additive effects on hearing impairment.

Patients should be informed of potential adverse effects prior to commencement of treatment. Patients should be advised to report symptoms of altered hearing promptly to their healthcare professional.

6 ADVERSE REACTIONS

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

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Inflammatory Bowel Disease *[see Warnings and Precautions (5.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.3)]*
- Hearing Impairment Including Hearing Loss *[see Warnings and Precautions (5.4)]*

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.

Adverse reactions presented in Table 1 were determined based on pooled data from four placebo-controlled, double-masked clinical trials (TED01RV, HZNP-TEP-301, HZNP-TEP-303, and HZNP-TEP-403) in 285 patients with Thyroid Eye Disease (TED). The data from these studies includes 152

patients who received TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for remaining 7 infusions) and 133 patients who received placebo given as an infusion every 3 weeks for a total of 8 infusions. The most commonly reported adverse reactions (occurring in ≥ 10% of patients) were: muscle spasms, diarrhea, nausea, hearing impairment, alopecia, fatigue, hyperglycemia, and headache.

Frequency is provided by CIOMS category (e.g., very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%).

Table 1. Adverse Reactions Occurring in Patients Treated with TEPEZZA and Greater Incidence than Placebo

System Organ Class	Adverse Reaction Preferred Term	Frequency	Overall Subject Incidence (TEPEZZA arm) N = 152 n (%)	Overall Subject Incidence (Placebo arm) N = 133 n (%)
Ear and labyrinth disorders	Hearing impairment[1]	Very common	21 (13.8%)	3 (2.3%)
	Ear discomfort	Common	10 (6.6%)	2 (1.5%)
Gastrointestinal disorders	Diarrhea	Very common	22 (14.5%)	12 (9.0%)
	Nausea	Very common	16 (10.5%)	9 (6.8%)
	Inflammatory bowel disease	Uncommon	1 (0.7%)	0
General disorders and administration site conditions	Fatigue[2]	Very common	19 (12.5%)	8 (6.0%)
Infections and infestations	COVID-19	Common	10 (6.6%)	5 (3.8%)
Injury, poisoning and procedural complications	Infusion-related reaction[3]	Common	6 (3.9%)	4 (3.0%)
Metabolism and nutrition disorders	Hyperglycemia[4]	Very common	20 (13.2%)	4 (3.0%)
	Diabetic ketoacidosis	Uncommon	1 (0.7%)[a]	0
Musculoskeletal and connective tissue disorders	Muscle spasms	Very common	42 (27.6%)	8 (6.0%)
Nervous system disorders	Headache	Very common	16 (10.5%)	10 (7.5%)
	Dysgeusia[5]	Common	13 (8.6%)	1 (0.8%)
Reproductive system and breast disorders	Menstrual disorders[6]	Very Common	7 (13.0%)	1 (2.2%)
Skin and subcutaneous tissue disorders	Alopecia	Very common	20 (13.2%)	7 (5.3%)
	Dry skin	Common	15 (9.9%)	0
	Nail disorder[7]	Common	9 (5.9%)	1 (0.8%)

[1] Hearing impairment includes: Autophony, Conductive deafness, Deafness, Deafness unilateral, Eustachian tube dysfunction, Eustachian tube patulous, Hyperacusis, Hypoacusis, Neurosensory hypoacusis, Tinnitus, Tympanic membrane disorder.
[2] Fatigue includes: Asthenia, Fatigue.
[3] Infusion-related reaction includes: Feeling hot, Hypertension, Infusion-related reaction, Rash, Tachycardia.
[4] Hyperglycemia includes: Blood glucose increased, Diabetes mellitus, Glucose tolerance impaired, Glycosylated hemoglobin increased, Hyperglycemia.
[5] Dysgeusia includes: Dysgeusia, Taste disorder.
[6] Menstrual disorders denominator included menstruating women only. Menstrual disorders includes: Amenorrhea, Hypomenorrhea, Dysmenorrhea, Irregular menstruation, Heavy menstrual bleeding.
[7] Nail disorder includes: Ingrowing nail, Nail bed disorder, Nail discoloration, Nail disorder, Onychoclasis.

System Organ Class	Adverse Reaction Preferred Term	Frequency	Overall Subject Incidence (TEPEZZA arm) N = 152 n (%)	Overall Subject Incidence (Placebo arm) N = 133 n (%)

[a] Event of Diabetic ketoacidosis was reported in a subject randomized to placebo arm with undiagnosed and untreated diabetes mellitus inadvertently administered TEPEZZA for the first infusion. All subsequent infusions were placebo.

In clinical trials, gastrointestinal complaints including exacerbation of inflammatory bowel disease were reported.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: bowel perforation, exacerbation of inflammatory bowel disease (IBD), including patients without a prior diagnosis of IBD.
Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).
Otologic: severe hearing impairment including hearing loss, which in some cases may be permanent.

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) signaling, 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. Cynomolgus monkeys dosed once weekly with teprotumumab during pregnancy resulted in placental changes, decreased fetal growth during pregnancy, decreased fetal size and weight, and multiple external and skeletal abnormalities in offspring. 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. Women of childbearing age should have a pregnancy test performed by their doctor before starting treatment with 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.

Data

Animal Data
In an abridged pilot embryo-fetal 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.

Teprotumumab induced developmental toxicity in animals. Thus, as a precautionary measure, teprotumumab should not be used during breastfeeding.

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

Teprotumumab should not be used in children from birth to adolescence before growth is complete because of safety concerns related to potential decrease in bone mass and decrease in body weight gains.

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, 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) 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, L-histidine (7.82 mg), L-histidine hydrochloride monohydrate (33.43 mg), polysorbate 20 (1.05 mg), and trehalose dihydrate (993 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's mechanism of action in patients with Thyroid Eye Disease has not been fully characterized. Teprotumumab binds to IGF-1R and blocks its activation and signaling.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with teprotumumab.

12.3 Pharmacokinetics

The pharmacokinetics of teprotumumab 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 one clinical trial. Following this regimen, the mean (± standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (C_{max}), and trough (C_{trough}) concentrations of teprotumumab 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 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 was 0.27 (± 0.08) L/day and for the elimination half-life was 20 (± 5) days.

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

Specific Populations
No clinically significant differences in the pharmacokinetics of teprotumumab 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 is unknown.

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

12.6 Immunogenicity

The observed incidence of anti-drug antibody is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibody in the studies described below with the incidence of anti-drug antibodies in other studies, including those of TEPEZZA.

In a randomized placebo-controlled study, HZNP-TEP-301, where active TED patients were administered placebo or TEPEZZA over a 24-week period, 2.4% (1 of 42) of placebo and 0% (0 of 41) of TEPEZZA treated patients tested positive for anti-teprotumumab antibodies at post-baseline visits.

Because of the low occurrence of anti-teprotumumab antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of teprotumumab products is unknown.

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

The primary efficacy endpoint in Study 1 (TED01RV, acute TED) was the overall responder rate, defined as the percentage of participants with ≥ 2-point reduction in CAS and ≥ 2-mm reduction in proptosis measurement from baseline in the study eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2-mm increase in proptosis in the fellow eye) at week 24.

The primary efficacy endpoint in Study 2 (HZNP-TEP-301) and Study 3 (HZNP-TEP-303, acute TED) was the proptosis responder rate defined as the percentage of participants with a ≥ 2-mm reduction from baseline in proptosis in the study eye, without deterioration (≥ 2-mm increase) of proptosis in the fellow eye at week 24. The primary efficacy endpoint in Study 4 (HZNP-TEP-403, chronic TED) was the mean change from baseline in proptosis at week 24 in the study eye. The first secondary efficacy endpoint was the proptosis responder rate defined exactly the same as the primary efficacy endpoint in Studies 2 and 3.

The percentage of patients achieving the proptosis responder rate and overall responder rate was statistically significantly higher in TEPEZZA-treated patients than patients who received placebo. Likewise, the mean change from baseline in proptosis was statistically significantly higher in TEPEZZA-treated patients than patients who received placebo. These results are presented in Table 2.

Table 2. Efficacy Results in Studies 1, 2, 3 and 4

	Study 1		**Study 2**		**Study 3**		**Study 4**	
	PBO (N = 45)	**TEP (N = 43)**	**PBO (N = 42)**	**TEP (N = 41)**	**PBO (N = 27)**	**TEP (N = 27)**	**PBO (N = 20)**	**TEP (N = 42)**
Proptosis responder rate at week 24 in the study eye								
n (%)	9 (20.0)	31 (72.1)	4 (9.5)	34 (82.9)	3 (11.1)	24 (88.9)	5 (25.0)	26 (61.9)
Difference: TEP- PBO (95% CI)	52.45 (34.39, 70.51)		73.45 (58.89, 88.01)		77.78 (60.73, 94.82)		36.42 (12.34, 60.50)	
p-value[a]	< 0.0001		< 0.0001		< 0.0001		0.0030	
Overall responder rate at week 24								

	Study 1		Study 2		Study 3		Study 4	
	PBO (N = 45)	**TEP (N = 43)**	**PBO (N = 42)**	**TEP (N = 41)**	**PBO (N = 27)**	**TEP (N = 27)**	**PBO (N = 20)**	**TEP (N = 42)**
n (%)	9 (20.0)	30 (69.8)	3 (7.1)	32 (78.0)	1 (3.7)	21 (77.8)		
Difference: TEP- PBO (95% CI)	50.32 (32.11, 68.52)		70.82 (55.89, 85.75)		74.07 956.87, 91.28)		Not Applicable	
p-value[a]	< 0.0001		< 0.0001		< 0.0001			
Mean change from baseline in proptosis (mm) at week 24 in the study eye								
n	40	39	40	40	27	27	20	39
LS mean (SE)	-0.29 (0.252)	-2.95 (0.263)	-0.53 (0.235)	-3.32 (0.233)	-0.37 (0.303)	-2.36 (0.302)	-0.75 (0.363)	-2.24 (0.272)
Difference: TEP- PBO (95% CI)	-2.66 (-3.37, -1.95)		-2.79 (-3.40, -2.17)		-1.99 (-2.75, -1.22)		-1.50 (-2.30, -0.70)	
p-value[b]	< 0.0001		< 0.0001		< 0.0001		0.0004	

CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; SE = standard error; PBO = placebo; TEP = TEPEZZA

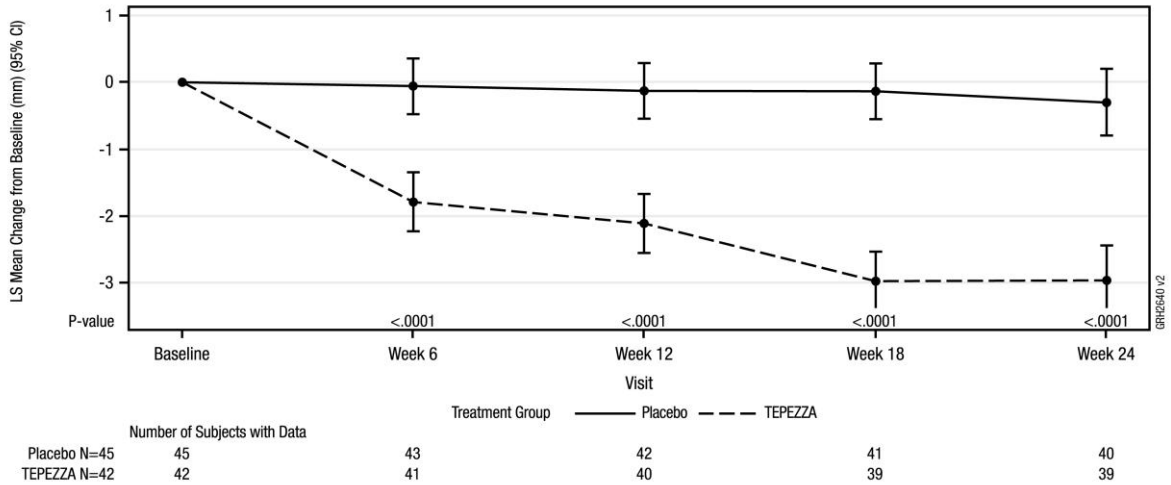
Note: A participant with a missing assessment at week 24 was considered a non-responder.

[a] The p-value was estimated from Cochran-Mantel-Haenszel test adjusted for tobacco use status.

[b] The p-value was estimated from an MMRM analysis with unstructured variance-covariance matrix, including change from baseline value as the dependent variable and the following covariates: Baseline value, treatment group, tobacco use status, visit, visit-by-treatment and visit-by-baseline value interactions.

In patients with acute and chronic TED, a greater decrease from baseline in proptosis was observed for patients treated with TEPEZZA compared with patients who received placebo at all trial visits. The decrease from baseline in proptosis was larger at the later visits (Figures 1, 2, 3 and 4).

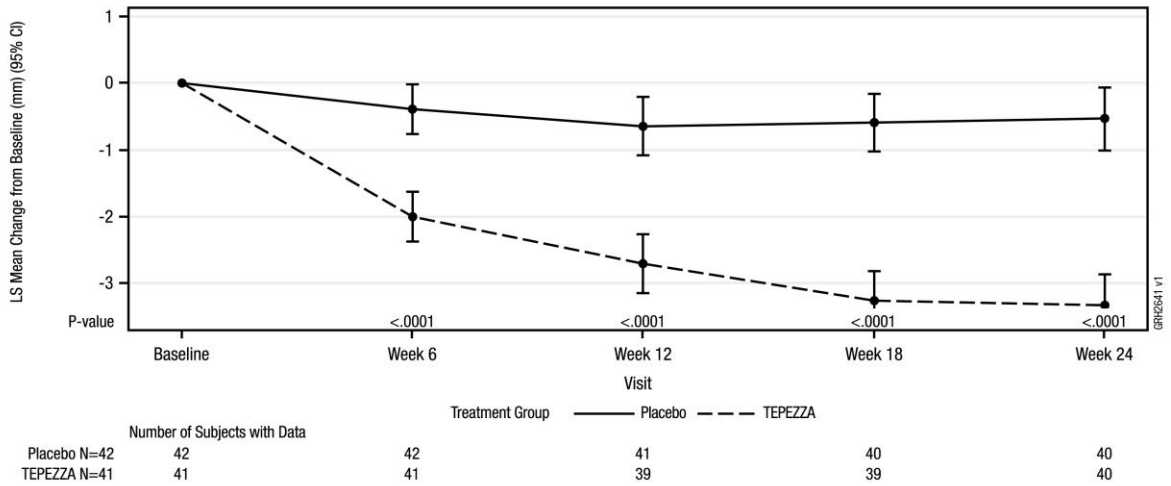
Figure 1. Change from Baseline in Proptosis Over 24 Weeks in Acute TED Study 1 (ITT Analysis Set; Study Eye)



CI = Confidence Interval; ITT = intent-to-treat; LS = Least Squares

Similar efficacy results were observed in the fellow eye.

Figure 2. Change from Baseline in Proptosis Over 24 Weeks in Acute TED Study 2 (ITT Analysis Set; Study Eye)

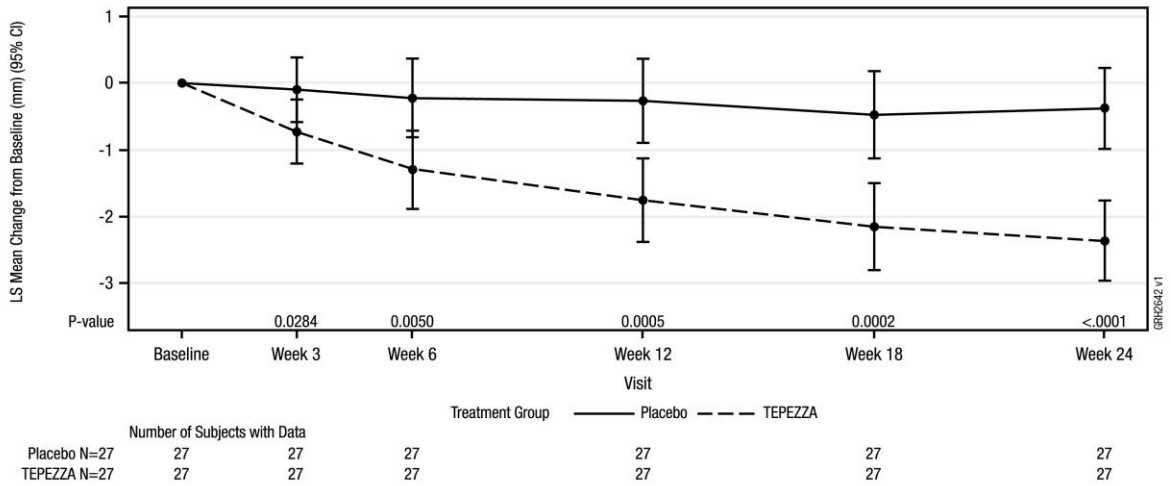


Number of Subjects with Data					
Placebo N=42	42	42	41	40	40
TEPEZZA N=41	41	41	39	39	40

CI = Confidence Interval; ITT = intent-to-treat; LS = Least Squares

Similar efficacy results were observed in the fellow eye.

Figure 3. Change from Baseline in Proptosis Over 24 Weeks in Acute TED Study 3 (ITT Analysis Set; Study Eye)

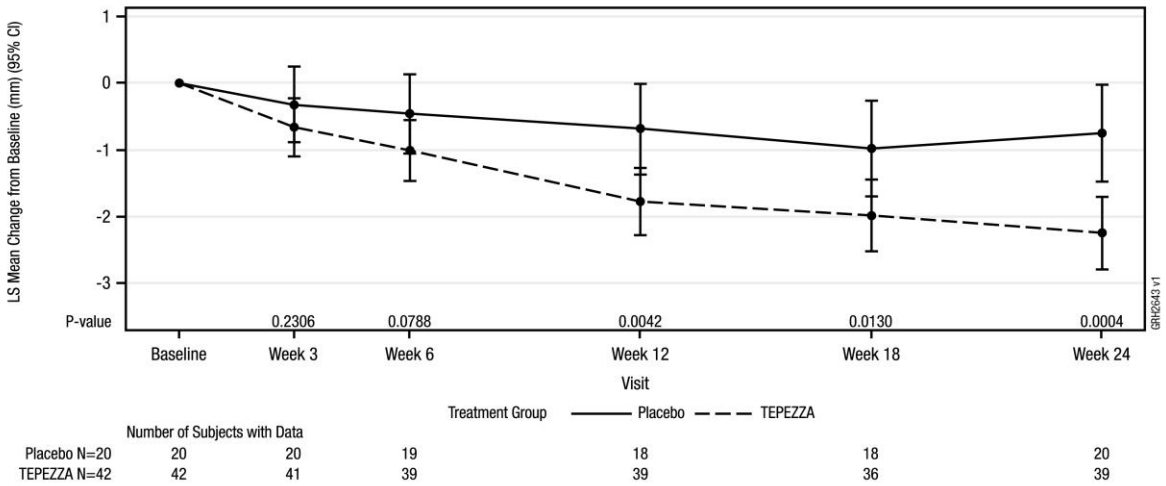


Number of Subjects with Data						
Placebo N=27	27	27	27	27	27	27
TEPEZZA N=27	27	27	27	27	27	27

CI = Confidence Interval; ITT = intent-to-treat; LS = Least Squares

Similar efficacy results were observed in the fellow eye.

Figure 4. Change from Baseline in Proptosis Over 24 Weeks in Chronic TED Study 4 (ITT Analysis Set; Study Eye)



CI = Confidence Interval; ITT = intent-to-treat; LS = Least Squares

Similar efficacy results were observed in the fellow eye.

Complete diplopia responder rate

Among patients with binocular diplopia at baseline, a greater proportion of patients treated with TEPEZZA were complete binocular diplopia responders at week 24 compared with patients who received placebo (see Table 3).

Table 3. Complete Binocular Diplopia Responder Rate at Week 24

	Study 1		**Study 2**		**Study 3**	
	Placebo (N = 45)	**TEP (N = 43)**	**Placebo (N = 42)**	**TEP (N = 41)**	**Placebo (N = 27)**	**TEP (N = 27)**
Baseline (n)	31	38	28	28	20	22
Responder rate (n)	25.8% (8)	50% (19)	25% (7)	57.1% (16)	20% (4)	50% (11)
Difference: TEP- Placebo (95% CI)	24.92% (2.97%, 46.88%)		32.14% (7.88%, 56.41%)		29.09% (0.92%, 57.26%)	
p-value[a]	0.0261		0.0094		0.043[b]	

CI = confidence interval; TEP = TEPEZZA;
Complete binocular diplopia responder rate was defined as the percentage of participants with baseline binocular diplopia > 0 and a score of 0 at week 24. A score of 0 = no diplopia.
[a] p-value was estimated from Cochran-Mantel-Haenszel test adjusted tobacco use status.
[b] Statistical significance could not be claimed in the hierarchy analysis.

Quality of life

TEPEZZA demonstrated a clinically meaningful improvement in functional vision and appearance at week 24 in all studies using the disease-specific quality of life scale (Graves' Ophthalmopathy Quality of Life [GO-QoL] questionnaire).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

TEPEZZA is supplied in 20 mL glass vial, with a stopper and a flip-off aluminium seal.

Carton containing one 500 mg single-dose vial.

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

The expiry date can be found on the packaging.

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.

Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD), including patients with or without a prior diagnosis of IBD. Advise patients to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, fecal urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control measures including medications as appropriate. Encourage compliance with glycemic control. Inform patients blood glucose monitoring is recommended for 6 months after completion of treatment with TEPEZZA.

Hearing Impairment Including Hearing Loss

- Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Inform patients that their treating physicians will decide if any additional hearing tests are needed and if patients' hearing should be monitored for 6 months after completing treatment. Treating physicians may stop treatment with TEPEZZA if patients experience hearing loss which requires medical treatment or affects their ability to perform everyday tasks or is getting worse. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing. Inform patients they are advised to stop smoking and avoid high intensity noises during treatment with TEPEZZA.

18 NAME AND ADDRESS OF THE PRODUCT OWNER

Amgen Inc.
One Amgen Center Drive

Thousand Oaks, CA 91320.

19 DATE OF REVISION OF THE TEXT

April 2026

SGTEPPI01