Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tepezza

Active ingredient: teprotumumab

Sponsor: Amgen Australia Pty Ltd

August 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
AUC_{ss}	steady-state exposures
CAS	clinical activity score
CL	central clearance
C_{max}	maximum concentration
$C_{max,ss}$	maximum serum concentration at steady state
$C_{min,ss}$	minimum serum concentration at steady state
GO-QoL	Graves' Ophthalmopathy Quality of Life
IGF-1R	insulin-like growth factor-1 receptor
ITT	intent-to-treat
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
Q	inter-compartment clearance
RMP	Risk management plan
SD	standard deviation
SE	standard error
TEAE	Treatment emergent adverse event
TED	Thyroid eye disease
TGA	Therapeutic Goods Administration
Vc	volume of distribution in the central compartment
Vp	volume of distribution in the peripheral compartment

Tepezza (teprotumumab) submission

Type of submission:	New biological entity
Product name:	Tepezza
Active ingredient:	teprotumumab
Decision:	Approved
Date of decision:	13 March 2025
Approved therapeutic use for the current submission:	Tepezza is indicated for the treatment of moderate to severe thyroid eye disease (TED)
Date of entry onto ARTG:	27 March 2025
ARTG numbers:	Tepezza teprotumumab 500 mg injection powder vial (444610)
▼*Black Triangle Scheme:*	Yes
Sponsor's name and address:	Amgen Australia Pty Ltd Level 11, 10 Carrington St, Sydney NSW 2000
Dose form:	Powder for injection.
Strength:	Each vial contains 500 mg of teprotumumab. The reconstituted Tepezza solution contains 47.6 mg/mL (500 mg / 10.5 mL) of teprotumumab.
Container:	20 mL type I clear glass vial, with a grey stopper (flurotec coated chlorobutyl) and an aluminium seal with a polypropylene matte red flip-off cap.
Pack size:	Each carton contains one vial.
Route of administration:	intravenous infusion
Dosage:	10 mg/kg for the initial dose followed by 20 mg/kg every three weeks for 7 additional doses. For further information regarding dosage refer to the Product Information.
Pregnancy category:	Category X Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Proposed indication

This AusPAR describes the submission by Amgen Australia Pty Ltd (the Sponsor) to register Tepezza (teprotumumab) for the following proposed indication:

Tepezza is indicated for the treatment of thyroid eye disease (TED)

The condition

Thyroid Eye Disease (TED), also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy or Graves' orbitopathy, is a serious, debilitating and painful autoimmune disease associated with major comorbidities that can lead to blindness. Although it is most commonly associated with Graves' disease hyperthyroidism, TED may also occur in patients with other autoimmune thyroid diseases.

Current treatment options

Treatment typically involves correction of thyroid dysfunction, i.e., restoration of a euthyroid state. Supportive therapy includes smoking cessation, alleviation of exposure symptoms, reduction of periorbital oedema using cool compresses and head elevation, temporary management of diplopia by monocular occlusion or prisms. In moderate-to-severe TED the following are usually considered (some are off-label; treatments may be combined):

- Immunosuppressive therapy (e.g., with corticosteroids, rituximab, tocilizumab)
- External orbital radiation/radiotherapy
- Orbital decompression surgery

Clinical rationale

Teprotumumab is a fully human IgG1 monoclonal antibody produced in Chinese Hamster Ovary (CHO-DG44) cells by recombinant DNA technology that binds to the insulin-like growth factor-1 receptor (IGF-1R) and blocks its activation and signalling.

At the molecular level, the two major autoantigens implicated in TED include thyroid-stimulating hormone receptor and IGF-1R,[1,2,3] which have been shown to be physically and functionally coupled in a macromolecular signaling complex.[4,5,6] These molecular events

[1] Boschi A, Daumerie Ch, Spiritus M, Beguin C, Senou M, Yuksel D, et al. Quantification of cells expressing the thyrotropin receptor in extraocular muscles in thyroid associated orbitopathy. Br J Ophthalmol. 2005;89(6):724-9. doi:10.1136/bjo.2004.050807

[2] Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362(8):726-38. doi:10.1056/NEJMra0905750

[3] Smith TJ. Insulin-like growth factor-I regulation of immune function: a potential therapeutic target in autoimmune diseases? Pharmacol Rev. 2010;62(2):199-236. doi:10.1124/pr.109.002469.

[4] Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. J Clin Endocrinol Metab. 2004;89(10):5076-80. doi:10.1210/jc.2004-0716.

[5] Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol. 2008;181(6):4397-405. doi:10.4049/jimmunol.181.6.4397.

[6] Kumar S, Iyer S, Bauer H, Coenen M, Bahn RS. A stimulatory thyrotropin receptor antibody enhances hyaluronic acid synthesis in graves' orbital fibroblasts: inhibition by an IGF-I receptor blocking antibody. J Clin Endocrinol Metab. 2012;97(5):1681-7. doi:10.1210/jc.2011-2890.

underpin the pathophysiology of acute TED. Inhibiting IGF-1R function using an anti-IGF-1R mAb similar to teprotumumab blocks pathophysiological responses specifically elicited by autoantibodies on orbital fibroblasts from TED patients.[7,8,9]. Consistent with this, teprotumumab inhibits the activation of fibrocytes, which are the cellular progenitors for a subtype of orbital fibroblast critical to TED pathogenesis.[10,11]. As such, teprotumumab has the potential to be a disease modifying therapeutic.

Regulatory status

Australian regulatory status

This product is a new biological entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by the Medicines and Healthcare products Regulatory Agency (submitted 18 March 2024), Health Canada (submitted 25 March 2024), European Medicines Agency (submitted 25 April 2024) and Swissmedic (submitted 24 June 2024).

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the priority registration process.

Table 1. Registration timeline for Tepezza (teprotumumab)

Description	Date
Priority determination	20 March 2024
Submission dossier accepted and evaluation commenced	30 April 2024
Evaluation completed	14 October 2024
Advisory Committee meeting	6 December 2024
Registration decision (Outcome)	13 March 2025
Registration in the ARTG completed	27 March 2025
Number of working days from submission dossier acceptance to registration decision*	224 days

[7] Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. J Immunol. 2003;170(12):6348-54. doi:10.4049/jimmunol.170.12.6348.

[8] Smith and Hoa, 2004.

[9] Hoa N, Tsui S, Afifiyan NF, Hikim AS, Li B, Douglas RS, et al. Nuclear targeting of IGF-1 receptor in orbital fibroblasts from Graves' disease: apparent role of ADAM17. PLoS ONE. 2012;7(4):e34173. doi:10.1371/journal.pone.0034173.

[10] Chen H, Mester T, Raychaudhuri N, Kauh CY, Gupta S, Smith TJ, et al. Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab. 2014;99(9):E1635-40. doi:10.1210/jc.2014-1580.

[11] Chen H, Shan SJC, Mester T, Wei Y-H, Douglas RS. TSH-mediated TNFα production in human fibrocytes is inhibited by Teprotumumab, and IGF-1R antagonist. PloS ONE. 2015`;10(6)e0130322. doi:10.1371/journal.pone.0130322.

*Target timeframe for priority submissions is 150 working days from acceptance for evaluation to the decision.

Assessment overview

Quality evaluation summary

There were no significant issues identified from the quality evaluation of the submitted data that would indicate the product should not be registered on the basis of quality, or safety-related issues arising from the quality of the product. The Sponsor has satisfied all requirements with respect to:

- Good Manufacturing Practice compliance,
- stability and release specifications,
- history, control and traceability of cell lines/cell banks,
- validation of analytical procedures,
- appropriate choice/synthesis and validation of reference materials,
- appropriate in-process controls within the manufacturing process and identification of critical manufacturing steps,
- consistency of medicine manufacture verified by process validation and demonstrated through batch analysis,
- satisfactory control of impurities,
- adequate characterisation and justification of excipients,
- medicine sterility/appropriate control of infectious disease & adventitious agents,
- appropriate/compatible container closure systems and
- labelling that conformed to Therapeutic Goods Order 91.

There were no objections to registration from a quality perspective.

Nonclinical evaluation summary

The nonclinical dossier was of good overall quality and adequate in scope, consistent with ICH S6 (R1).[12] All pivotal safety-related studies were GLP-compliant except one, which was otherwise well documented and conducted in a well-established laboratory.

Teprotumumab is a monoclonal antibody (IgG1) directed against the insulin like growth factor-1 receptor (IGF1R), and represents a novel pharmacological class.

In vitro experiments established that teprotumumab possesses nanomolar affinity for human IGF1R, blocking the binding of the receptor's endogenous ligands, inhibiting receptor activation and reducing its cell surface expression (by promoting receptor internalisation). Teprotumumab was shown to inhibit IGF 1-induced stimulation of proliferation of mouse fibroblasts expressing human IGF1R. Inhibition of thyroid stimulating hormone-induced production of pro

[12] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline. 2011.

inflammatory cytokines in cultured human fibrocytes (precursor cells to orbital fibroblasts) by teprotumumab is reported in the literature. There are no relevant animal models of TED. The primary pharmacology studies offer support for the utility of teprotumumab for the proposed indication.

Teprotumumab also recognises the cynomolgus monkey form of IGF1R (displaying similar affinity cf. human), but did not bind to the mouse, rat or marmoset forms of IGF1R.

Teprotumumab was shown not to additionally bind to the human insulin receptor (which shares a high degree of sequence homology with IGF1R), and not to induce antibody-dependent cell-mediated cytotoxicity in vitro.

Immunohistochemical assays involving a panel of human and cynomolgus monkey tissues revealed a staining pattern for teprotumumab consistent with the known extensive expression of IGF 1R.

Safety pharmacology assessment — incorporated into the general repeat-dose toxicity program — revealed no effect of teprotumumab on CNS, cardiovascular or respiratory function in cynomolgus monkeys.

Teprotumumab showed a pharmacokinetic profile typical of an IgG antibody in cynomolgus monkeys and humans, characterised by a long serum half-life and limited volume of distribution.

A low order of acute toxicity by the IV route was evident for teprotumumab in cynomolgus monkeys.

Repeat-dose toxicity studies by the IV route were conducted in cynomolgus monkeys (up to 9 months duration). Thymic lymphoid depletion was identified as the key toxicity for teprotumumab, with effects on body weight and bone turnover also observed. These effects are consistent with the drug's primary pharmacological activity, inhibiting IGF 1R-mediated signalling. Clinical relevance cannot be excluded.

No genotoxicity studies were submitted, which is acceptable for a protein drug. Carcinogenicity studies were not performed and are not required, with no cause for concern for carcinogenicity seen from findings in the general repeat-dose toxicity program or from knowledge of the physiological role of IGF1R and the drug's mechanism of action.

No functional fertility studies were performed. While examination of surrogate endpoints in a 3 month repeat-dose toxicity study in monkeys revealed no treatment-related effects on reproductive organ weights or histology, potential for impairment of fertility in patients is seen from knowledge of the physiological role of IGF 1R and the drug's mechanism of action.

While Tepezza is not proposed for paediatric use, a juvenile toxicity study was included in the submission. Treatment of juvenile cynomolgus monkeys caused suppression of skeletal growth, decreased bone mineral density and content, and effects on the spleen in addition to effects seen in adult animals.

Teprotumumab was shown to be well tolerated locally by the IV route in cynomolgus monkeys.

Teprotumumab was shown to be clearly teratogenic in cynomolgus monkeys. Every fetus exposed to teprotumumab either died or displayed multiple malformations, including misshapen cranium, closely set eyes, micrognathia, and pointing and narrowing of the nose; impaired/abnormal ossification of the skull, teeth, sternebrae, carpals and tarsals was also observed. Teprotumumab caused generalised suppression of fetal growth, with final fetal weight almost halved, and decreased placental weight and size, and reduced amniotic fluid volume. These adverse effects on embryofetal development occurred in the absence of maternal toxicity, and at a clinically relevant dose (based on the extent of IGF 1R inhibition as well as relative

exposure). Concerns for embryofetal harm with teprotumumab are held at the highest level, and warrant assignment to Pregnancy Category X rather than Category D as the Sponsor proposes.

Teprotumumab is to be contraindicated in pregnancy, and women of childbearing potential directed to use effective contraception prior to initiation of treatment, during treatment and for 6 months after the last dose of Tepezza.

There are no nonclinical objections to the registration of Tepezza for the proposed indication.

Clinical evaluation summary

Summary of clinical studies

Pharmacology

Pharmacology data were derived from one dedicated pharmacokinetic (PK) study:

- Study HZNP-TEP-102: A Phase 1, Open-Label, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tepezza Subcutaneous Administration in Healthy Adult Participants.

PK and immunogenicity of teprotumumab were also evaluated as exploratory endpoints in the following Phase 2/3/4 studies in patients with TED:

- TED01RV, HZNP-TEP-301 (OPTIC), HZNP-TEP-303 (OPTIC-J), HZNP-TEP-302 (OPTIC-X), HZNP-TEP-403, and HZNP-TEP-401.

The population pharmacokinetics (PopPK) report Horizon-PopPK-003 was a PopPK analysis with data from clinical studies HZNP-TEP-102, TED01RV, HZNP-TEP-301, HZNP-TEP-302, HZNP-TEP-303, and HZNP-TEP-403.

Efficacy/Safety

Pivotal studies

- HZNP-TEP-301 (OPTIC): Phase 3, Randomised, Double-Masked, Placebo-Controlled, Parallel-Group, Multicentre Study Evaluating Teprotumumab (HZN-001) Treatment in Participants with Active TED (OPTIC).
- HZNP-TEP-303 (OPTIC-J): A Phase 3, Randomised, Double-Masked, Placebo-Controlled, Parallel-Group, Multicentre Trial Evaluating Teprotumumab (HZN-001) Treatment in Japanese Patients with Active TED.
- HZNP-TEP-403: A Phase 4, Randomised, Double-masked, Placebo-controlled, Multicentre Trial to Evaluate the Efficacy and Safety of Tepezza in Treating Patients with Chronic (Inactive) TED.

Supportive studies:

- HZNP-TEP-302 (OPTIC-X) (extension of OPTIC): Phase 3, Multicentre, Safety and Efficacy, Open-label Extension Study Evaluating Teprotumumab (HZN-001) Treatment in Participants with TED.
- Study TED01RV: A Phase 2, Multicentre, Double-masked, Placebo-controlled, Efficacy and Safety Study of Teprotumumab (HZN-001), an Insulin-Like Growth Factor-1 Receptor Antagonist Antibody (Fully Human), Administered Every 3 Weeks by IV Infusion in Patients Suffering from Active TED.

- Study HZNP-TEP-401: A Phase 3b 24-week open-label, multicentre, single-arm expanded access protocol (EAP).

Pharmacology

Pharmacokinetics

The PK information for IV teprotumumab was derived from the following studies using both non-compartmental and population PK analyses:

- 10 healthy participants in Phase 1 study HZNP-TEP-102
- 135 participants with acute TED in studies TED01RV, OPTIC, OPTIC-J and OPTIC-X, and 41 participants with chronic TED in study HZNP-TEP-403
- PopPK Report Horizon-PopPK-003

Absorption

The absorption of teprotumumab was not evaluated as it is intended for IV use only.

Distribution

The PopPK estimated means for central and peripheral volume of distribution of teprotumumab were 2.91 L and 3.67 L, respectively following the proposed teprotumumab dosing regimen. No plasma protein binding study was conducted as the proposed product is a therapeutic protein.

Metabolism

The metabolism of teprotumumab has not been fully characterised. The Sponsor has justified this with the known mechanism of proteolysis clearance for IgG antibodies are through mostly intracellular catabolism by lysosomal degradation to amino acids after uptake by either pinocytosis, an unspecific fluid phase endocytosis, or by a receptor-mediated endocytosis process.

Excretion and elimination

The population estimate of clearance was 0.255 L/day and the geometric mean elimination half-life 21.4 days (%CV: 16.9) in TED participants, consistent with other IgG1 mAbs.

Dose proportionality

At the dose range of 3 to 20 mg/kg, teprotumumab displayed linear PK, but nonlinear PK at low doses (< 3 mg/kg), suggesting a contribution of target-mediated clearance and saturation of target-mediated clearance at higher doses.

Immunogenicity

Of 111 TED participants (Studies TED01RV, HZNP-TEP-301, and HZNP-TEP-303) who received teprotumumab treatment, 4 participants were confirmed ADA-positive at post-baseline visits. Testing for neutralising antibodies was not conducted in any trial. Overall, the immunogenicity results in the trials appeared not to be clinically significant.

Pharmacokinetics in the target population

Teprotumumab concentration-time profiles were simulated using the Bayesian *post hoc* estimates of individual PK parameters based on the PopPK model for 176 participants with TED in the dataset following 10 mg/kg for the first IV infusion and 20 mg/kg Q3W for the remaining 7 infusions.

Overall, the PK findings in patients with chronic/inactive TED were similar to those observed in patients with acute/active TED. A summary of actual serum concentrations is in Table 17 (Appendix).

Drug-drug interaction studies

No dedicated drug interactions studies were conducted. Drug-drug interactions between teprotumumab and thyroid medications (e.g., levothyroxine, propylthiouracil) commonly taken by TED patients are not expected, as teprotumumab and small molecule drugs do not share common or overlapping clearance pathways. Monoclonal antibodies are not expected to directly affect the hepatic, renal or biliary elimination of small molecules.

Population PK data from study Horizon-PopPK-003

Methods

The PopPK analysis was performed using the non-linear mixed effects modelling approach. This approach estimates the typical (mean) value of parameters and their variances. PopPK estimation was performed using the first order conditional estimation with interaction (FOCEI) method in NONMEM.

The PopPK model was developed based on data from the following 6 studies involving patients with TED: TED01RV, HZNP-TEP-102 (healthy subjects via both SC and IV routes), HZNP-TEP-301, HZNP-TEP-302 (open-label, long-term extension study), HZNP-TEP-303, and HZNP-TEP-403 (chronic TED). The final analysis dataset included 1168 teprotumumab serum concentration measurements from 186 participants.

Results

Model: Teprotumumab PK following IV dosing in the proposed clinical dose range can be described by a two-compartment model with first-order elimination from the central compartment and redistribution from the peripheral compartment. The final base model was chosen based on the objective function value, goodness-of-fit (GOF) plots, and reliability of model parameter estimates.

Estimated parameters: For a typical 73 kg participant, the estimated central clearance (CL) was 0.255 L/day, the volume of distribution in the central compartment (Vc) was 2.91 L, the inter-compartment clearance (Q) was 0.478 L/day, and the volume of distribution in the peripheral compartment (Vp) was 3.67 L. The inter-individual variability values for CL, Vc, and Vp were 20.4%, 24.4%, and 32.4%, respectively. The geometric mean elimination half-life of teprotumumab was 21.4 days with a CV of 16.9% in participants with TED.

Table 1. PopPK Study Horizon-PopPK-003. Summary of Population PK parameters of IV Teprotumumab in a typical 73 kg adult.

PK Parameters Description	Population Estimate (%standard error)	Inter-individual Variability (%standard error)
CL (L/day)	0.255 (1.52%)	20.4 (6.74%)
V_c (L)	2.91 (1.64%)	24.4 (14.1%)
Q (L/day)	0.478 (2.80%)	-
V_p (L)	3.67 (2.16%)	32.4 (13.7%)
Influence of body weight on CL	0.709 (4.17%)	-
Influence of body weight on V_c	0.618 (4.05%)	-
Residual error (%)	19.3 (5.28%)	-

CL=central clearance: PK=pharmacokinetic; Q=intercompartmental clearance; Vc=volume of distribution in the central compartment: Vp=volume of distribution in the peripheral compartment.

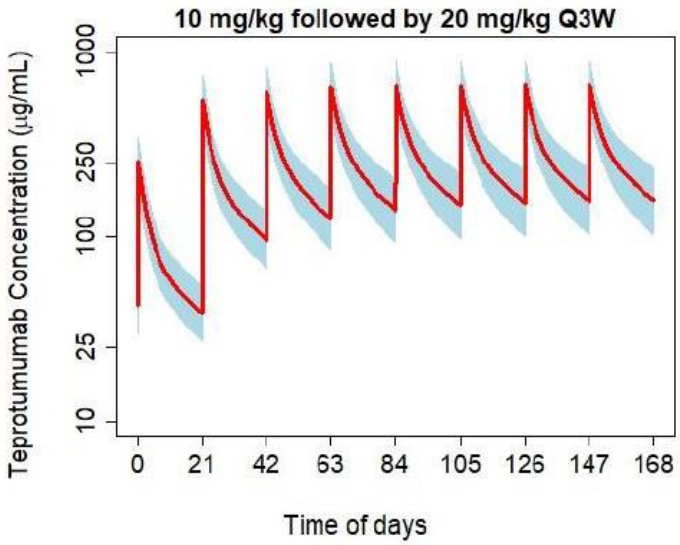
Covariate analyses suggest that no dosage adjustments based on weight, age, sex, ethnicity, race, health status, trial region, smoking status or renal or hepatic function are required. The following differences in the geometric mean steady-state exposures (AUC_{ss}) maximum serum concentration at steady state ($C_{max,ss}$), and minimum serum concentration at steady state ($C_{min,ss}$) were simulated:

- between male and female participants (≤6.23%)
- between adults aged ≥65 years and <65 years (<0.70%)
- between Japanese region and non-Japanese region (≤18.0%)
- between Hispanic and non-Hispanic (≤13.6%)
- between smoker and non-smoker (≤11.8%)
- across studies (within ±17.3%)
- across race groups (within ±16.9%)
- across body weight quartiles (within ±12.9%)
- across health status groups (within ±17.3%)
- across renal function categories (within ±4.91%)
- across hepatic categories (≤2.88%)

Simulated concentration-time profiles: The predicted trough C_{min} was 20.37 µg/mL after the first infusion and 68.71 µg/mL at steady state, i.e. consistently above 20 µg/mL for the dosing regimen used in the Phase 3 trials (that is also proposed as the recommended dosage regimen).

Following the proposed dose regimen (first infusion at 10 mg/kg followed by 7 repeated doses of 20 mg/kg Q3W), the mean (± standard deviation [SD]) estimates for AUC_{ss} was 139 (±27) mg*hr/mL, C_{max} was 675 (±147) µg/mL, and C_{min} trough concentration was 159 (±38) µg/mL.

Figure 1. PopPK Study Horizon-PopPK-003. Simulated teprotumumab concentration-time profile in participants with TED.



'Q3W=every 3 weeks; TED=thyroid eye disease. Red line is the median of model predictions and blue shaded areas represent the spread (5%ile and 95%ile) of the model predictions.

Table 3. PopPK Study Horizon-PopPK-003. Model-predicted teprotumumab exposures in participants with TED (10 mg/kg followed by of 20 mg/kg Q3W).

Variable	AUC_{ss} (µg*hr/mL)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	C_{min}[a] (µg/mL)
Mean	139133	675.0	159.3	39.31
SD	27125	147.3	38.34	8.44
Median	135653	667.6	156.4	38.49
Minimum	87968	380.5	68.71	20.37
Maximum	214485	1621.8	264.4	63.48

Pharmacodynamics

Mechanism of action

Teprotumumab appears to bind to IGF-1R and blocks its activation and signalling. However, the mechanism of action of teprotumumab in TED has not been fully characterised.

ER analysis

No clinically relevant exposure-response relationships were observed between teprotumumab exposure and the efficacy or safety endpoints in studies TED01RV, HZNPTEP- 301, HZNP-TEP-302, HZNP-TEP-303, and HZNP-TEP-403 for TED patients. Although the median AUC_{ss} and $C_{max,ss}$ of teprotumumab were slightly higher in subjects with muscle spasm (than without muscle spasm) and in those with infusion related reactions (IRRs) (than those without IRRs), this was not confirmed in logistic regression analysis.

Efficacy

Phase 2, 3, and 4 studies TED01RV, OPTIC, OPTIC-J and 403

Design

The trial design, main inclusion and exclusion criteria, and endpoints is shown in Table 4.

Table 4. Studies TED01RV, OPTIC, OPTIC-J and 403. Trial design, main inclusion and exclusion criteria, and endpoints.

Trial Identifier and Objective	Number of Trial Centers Locations	Trial Start Enrollment Status/Date Enrollment Planned/Actual	Trial Design Control Type	Trial and Control Drugs Dosage, Route, Regimen and Duration	# of Participants by Treatment: Treated/ Completed	Gender Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary/Other Endpoints
TED01RV Efficacy and Safety	15 US and Europe	24-week Treatment Period: 24Jun2013 Completed/ 23Mar2016 84 planned/ 88 randomized/ 87 treated/ 48-week Follow-up Period: Completed/ 22Feb2017	24-week Treatment Period with a subsequent 48-week Follow-up Period 24-week Treatment Period: randomized, double-masked; placebo-controlled, parallel-group 48-week Follow-up Period: no additional treatment for TED during the first 3 months unless medically indicated. Participants who received TED treatment in the Follow-up Period were treated as relapsed from the time of TED treatment forward.	**24-week Double-masked Treatment Period**				
				Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Teprotumumab 43[a]/37 Placebo 44/39	M: 23 F: 64 W: 75 B: 8 A: 3 NH/PI: 1 52.9 years (20 – 77)	18 - 75 years of age; clinical diagnosis of acute TED with CAS ≥ 4 for more severe eye; < 9 months from onset of TED; and euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	*Primary:* Overall responder rate (percentage of participants with a reduction in proptosis ≥ 2 mm AND a decrease in CAS ≥ 2 points from Baseline in the study eye, without deterioration [increase in proptosis ≥ 2 mm or increase in CAS ≥ 2 points] in the fellow eye) at Week 24 *Secondary* (tested in a hierarchical stepwise fashion comparing teprotumumab vs. placebo): 1 Mean change from Baseline to Week 24 in GO-QoL overall score 2 Mean change from Baseline to Week 24 in proptosis measurements in the study eye 3 Mean change from Baseline to Week 24 in CAS in the study eye 4 Mean change from Baseline to Week 24 in GO-QoL visual functioning subscale score 5 Mean change from Baseline to Week 24 in GO-QoL appearance subscale score
				48-week Follow-up Period				
				No IP administration	Teprotumumab Completed Trial 36 Placebo Completed Trial 38	NA	Completed 24-week Treatment Period	*Primary:* Responder rate at Week 28 (percentage of participants with a reduction in proptosis of ≥ 2 mm AND a reduction in CAS of ≥ 2 points in the study eye and no deterioration [increase in proptosis of ≥ 2 mm or an increase in CAS of ≥ 2 points] in the fellow eye) *Secondary:* Proptosis responders at Week 28 (percentage of participants with a reduction in proptosis of ≥ 2 mm from Baseline in the study eye) Proptosis responders who relapsed from Week 24 to Week 72 Mean change from Baseline in CAS in the study eye Mean change from Baseline in GO-QoL overall score, visual functioning subscale score and appearance subscale score Mean change from Baseline in Clinical Measures of Severity
HZNP-TEP-301 (OPTIC) Efficacy and Safety	13 US and Europe	24-week Treatment Period: 04Oct2017 Completed/ Data Cutoff 19Feb2019 76 planned/ 83 randomized/ 83 treated 48-week Follow-up Period: Completed/ 21Jan2020	24-week Treatment Period with a subsequent 48-week Follow-up Period 24-week Treatment Period: randomized, double-masked; placebo-controlled, parallel-group. 48-week Follow-up Period: no additional treatment for TED Proptosis non-responders at Week 24 or proptosis responders at Week 24 who relapse during the Follow-up Period were eligible for enrollment in an OL extension trial	**24-week Double-masked Treatment Period**				
				Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Teprotumumab 41/39 Placebo 42/40	M: 23 F: 60 W: 72 B: 6 A: 3 O: 2 50.2 years (20 – 79)	18 - 80 years of age; clinical diagnosis of acute TED with CAS ≥ 4 for more severe eye; < 9 months from onset of TED; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	*Primary:* Proptosis responder rate at Week 24 (percentage of participants with a ≥ 2-mm reduction from Baseline in proptosis in the study eye without deterioration of proptosis [increase ≥ 2 mm] in the fellow eye) *Secondary* (tested in a hierarchical stepwise fashion comparing teprotumumab vs. placebo): 1 Overall responder rate (percentage of participants with ≥ 2-mm reduction in proptosis AND ≥ 2-point reduction in CAS from Baseline in the study eye, provided there was no corresponding deterioration [≥ 2-mm/point increase] in proptosis or CAS in the fellow eye) at Week 24 2 Percentage of participants with a CAS value of 0 or 1 (no or minimal inflammatory symptoms) in the study eye at Week 24 3 Mean change from Baseline to Week 24 in proptosis measurement in the study eye 4 Diplopia responder rate (percentage of participants with Baseline diplopia grade > 0 in the study eye who have a reduction of ≥ 1 grade with no corresponding deterioration [≥ 1 grade worsening] in the fellow eye) at Week 24. 5 Mean change from Baseline to Week 24 in GO-QoL overall score
				48-week Follow-up Period				
				No IP administration	Teprotumumab 36/20 Placebo 4/3	NA	Completed 24-week Treatment Period	Time to relapse

Trial Identifier and Objective	Number of Trial Centers Locations	Trial Start Enrollment Status/Date Enrollment Planned/Actual	Trial Design Control Type	Trial and Control Drugs Dosage, Route, Regimen and Duration	# of Participants by Treatment: Treated/ Completed	Gender Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary/Other Endpoints
HZNP-TEP-302 (OPTIC-X) Safety and Efficacy	13 US and Europe	24-week Treatment Period: 08Jun2020 51 participants (37 placebo, 14 teprotumumab) entered from OPTIC 24-week Follow-up Period (for proptosis non-responders in OPTIC): Completed/ 08Jun2020	24-week Treatment Period with a subsequent Follow-up Period 24-week Treatment Period: OL 24-week Follow-up Period: no additional treatment for TED	**24-week Treatment Period**				
				Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Overall: 51/48 By treatment received in OPTIC: Teprotumumab 14/12 Placebo 37/36	M: 13 F: 38 W: 44 B: 2 A: 3 O: 2 50.6 years (21 - 80)	Completed 24-week Treatment Period in OPTIC; proptosis non-responder[b] at Week 24 of OPTIC OR proptosis responder at Week 24 who relapsed during the Follow-up Period of OPTIC; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits) at most recent clinic visit	*Primary:* Proptosis responder rate at Week 24 (percentage of participants with a ≥ 2-mm reduction from Baseline in proptosis in the study eye without deterioration of proptosis [increase ≥ 2 mm] in the fellow eye) *Secondary:* 1 Percentage of participants with a CAS value of 0 or 1 (no or minimal inflammatory symptoms) in the study eye at Week 24 2 Mean change from Baseline to Week 24 in proptosis measurement in the study eye 3 Diplopia responder rate (percentage of participants with Baseline diplopia grade > 0 in the study eye who have a reduction of ≥ 1 grade with no corresponding deterioration [≥ 1-grade worsening] in the fellow eye) at Week 24 4 Mean change from Baseline to Week 24 in GO-QoL overall score
				24-week Follow-up Period				
				No IP administration	Overall: 40/40 By treatment received in OPTIC: Teprotumumab 4/4 Placebo 36/36	NA	Completed 24-week Treatment Period	1 Sustained proptosis response 2 Sustained CAS categorical response 3 Sustained overall response (≥ 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 and no additional TED treatment received by the time of the visit)
HZNP-TEP-303 (OPTIC-J) Efficacy and Safety	20 Japan	24-week Treatment Period: 15Feb2023 Completed/ Data Cutoff 14Jun2023 50 planned/ 54 randomized/ 54 treated 24-week OL Treatment Period: ongoing Follow-up Period: ongoing	24-week Double-masked Treatment Period with a subsequent 24-week OL Treatment Period (proptosis non-responders) or 30-day Follow-up Period 24-week Treatment Period: randomized, double-masked; placebo-controlled, parallel-group Follow-up Period: no additional treatment for TED Proptosis non-responders at Week 24 are eligible for OL treatment with teprotumumab	**24-week Double-masked Treatment Period**				
				Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Teprotumumab 27/26 Placebo 27/25	M: 16 F: 38 A: 54 48.3 years (20 – 74)	20 - 80 years of age; clinical diagnosis of Graves' disease associated with acute TED with CAS ≥ 3 for more severe eye; proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED), as estimated by treating physician, and/or proptosis ≥ 18 mm < 9 months from onset of TED; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	*Primary:* Proptosis responder rate at Week 24 (percentage of participants with a ≥ 2-mm reduction from Baseline in proptosis in the study eye without deterioration of proptosis [increase ≥ 2 mm] in the fellow eye) *Secondary* (tested in a hierarchical stepwise fashion comparing teprotumumab vs. placebo): 1 Overall responder rate (percentage of participants with ≥ 2-mm reduction in proptosis AND ≥ 2-point reduction in CAS from Baseline in the study eye, provided there was no corresponding deterioration [≥ 2-mm/point increase] in proptosis or CAS in the fellow eye) at Week 24 2 Percentage of participants with a CAS value of 0 or 1 (no or minimal inflammatory symptoms) in the study eye at Week 24 3 Mean change from Baseline in proptosis measurement in the study eye at Week 24 4 Binocular diplopia responder rate (percentage of participants with Baseline diplopia grade > 0 in the study eye who had a reduction of ≥ 1 grade) at Week 24 5 Complete binocular diplopia responder rate (percentage of participants with Baseline binocular diplopia > 0 and a score of 0) at Week 24 6 Mean change from Baseline in GO-QoL overall score at Week 24 7 Mean change from Baseline in the GO-QoL questionnaire visual functioning and appearance subscale scores at Week 24
				24-week OL Treatment Period				
				Teprotumumab Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Teprotumumab 26 ongoing as of 14Jun2023 (3 had received teprotumumab and 23 had received placebo)	NA	Completed 24-week Double-masked Treatment Period and were proptosis non-responders at Week 24 of the Double-masked Treatment Period	Descriptive summaries of efficacy analysis results

Trial Identifier and Objective	Number of Trial Centers Locations	Trial Start Enrollment Status/Date Enrollment Planned/Actual	Trial Design Control Type	Trial and Control Drugs Dosage, Route, Regimen and Duration	# of Participants by Treatment: Treated/ Completed	Gender Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary/Other Endpoints
				24-week Double-masked Treatment Period				
HZNP-TEP-403 Efficacy and Safety	11 US	24-week Treatment Period: 12Aug2021 Completed/ Data Cutoff 17Mar2023 57 planned/ 62 randomized/ 61 treated 24-week OL Treatment Period: ongoing Follow-up Period: ongoing	24-week Double-masked Treatment Period with a subsequent 24-week OL Treatment Period (proptosis non-responders) or 30-day Follow-up Period 24-week Treatment Period: randomized, double-masked; placebo-controlled, parallel-group Follow-up Period: no additional treatment for TED Proptosis non-responders at Week 24 are eligible for OL treatment with teprotumumab	Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion	Teprotumumab 41/39 Placebo 20/19	M: 12 F: 49 W: 34 B: 14 A: 8 O: 5 48.4 years (18 - 75)	≥ 18 years of age with an initial diagnosis of TED ≥ 2 years but < 10 years prior to Screening; clinical diagnosis of stable chronic TED with CAS ≤ 1 at Screening and Baseline; proptosis ≥ 3 mm increase from the participant's baseline (prior to diagnosis of TED), as estimated by treating physician, and/or proptosis ≥ 3 mm above normal for race and gender; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	*Primary:* Change from Baseline at Week 24 in proptosis in the study eye *Other* (tested in a hierarchical stepwise fashion comparing teprotumumab vs. placebo): 1 Proptosis responder rate (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 2 Change from Baseline at Week 24 in the GO-QoL questionnaire appearance and visual functioning subscales 3 Change from Baseline at Week 24 in diplopia as ordinal response categories 4 Binocular diplopia responder rate, defined as the percentage of participants with Baseline binocular diplopia > 0 who had a reduction of ≥ 1 grade at Week 24 5 Complete binocular diplopia responder rate, defined as the percentage of participants with Baseline binocular diplopia > 0 and a score of 0 at Week 24

Inclusion and exclusion criteria are shown in Table 18 (Appendix), and Table 19 (Appendix), respectively.

Treatments

An infusion Q3W (a total of 8 infusions) of

- IV teprotumumab (10 mg/kg for first infusion; 20 mg/kg for subsequent infusions) or
- Placebo (no active).

Randomisation

IRT randomisation was used and stratified by tobacco use status at baseline (non-user, user).

Table 5. Studies TED01RV, OPTIC, OPTIC-J and 403. Patient disposition.

Disposition, n (%) of Randomized	Trials in Acute TED								Trial in Chronic TED	
	TED01RV		OPTIC		OPTIC-J		Combined Analyses		HZNP-TEP-403	
	Placebo	Tepro	Placebo	Tepro	Placebo	Tepro	Placebo	Tepro	Placebo	Tepro
Randomized	45	43	42	41	27	27	114	111	20	42
Completed	39 (86.7)	37 (86.0)	40 (95.2)	39 (95.1)	27 (100)	27 (100)	106 (93.0)	103 (92.8)	19 (95.0)	39 (92.9)
Withdrew early	6 (13.3)	6 (14.0)	2 (4.8)	2 (4.9)	0	0	8 (7.0)	8 (7.2)	1 (5.0)	3 (7.1)
Reason for withdrawal										
Adverse event	1 (2.2)	5 (11.6)	1 (2.4)	1 (2.4)	0	0	2 (1.8)	6 (5.4)	1 (5.0)	0
Lack of efficacy	2 (4.4)	0	0	0	0	0	2 (1.8)	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	0	2 (4.8)
Withdrawal by participant	0	0	1 (2.4)	1 (2.4)	0	0	1 (0.9)	1 (0.9)	0	1 (2.4)
Other[a]	3 (6.7)	1 (2.3)	0	0	0	0	3 (2.6)	1 (0.9)	0	0

ITT = intent-to-treat: TED = thyroid eye disease: Tepro = teprotumumab

a. Scheduled for back surgery (placebo). dispensed incorrect treatment at Week 3 in error and Sponsor decided to discontinue the participant (placebo). optic disc edema left eye (placebo) and voluntary withdrawal due to difficulties with placing an intravenous line before receiving investigational product (teprotumumab).

Baseline characteristics:

- Patient demographics: The baseline demographic characteristics are shown in Table 20 (Appendix). They were generally comparable between the treatment groups in each trial with the notable exception of a larger portion of female participants in the placebo vs. active groups in TED01RV (80.0% vs. 67.4%), OPTIC-J (74.1% vs. 66.7%), and Study 403 (90.0% vs. 76.2%), also likely owing to the small sample sizes. Across trials, the age range was 18 to 79 years (mean range: 46.6 to 53.7 years) with more females overall as expected in a TED population. The majority of participants in TED01RV and OPTIC were white (all participants in OPTIC-J were Japanese).

- Disease characteristics: The baseline disease characteristics were reasonably balanced between groups (**Error! Reference source not found.**21**Error! Reference source not found.**). In the acute TED trials, the mean time since TED diagnosis was 5.74 months (range: 4.27 to 6.42 months) (combined placebo vs. combined active: 5.98 vs. 5.49 months). The mean study eye Clinical Activity Score (CAS) was 5.0 (range 4.0 to 5.3) (combined placebo vs. combined active: 5.0 vs. 4.9). The mean study eye proptosis was 22.52 mm. In the chronic TED trial 403, the mean time since TED diagnosis was 64.57 months (placebo) vs. 61.09 months (active). The mean study eye CAS was 0.5 (placebo) and 0.3 (active). The mean study eye proptosis was 24.40 mm.

- Patient disposition: shown in **Error! Reference source not found.**.

Magnitude of the treatment effect and its clinical significance

For CAS assessment, the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS was used (Table 22, Appendix).

Primary efficacy endpoint: The primary endpoint was the proptosis responder rate at Week 24 (defined differently in TED01RV as shown below):

- OPTIC and OPTIC-J: percentage of participants with a ≥ 2 mm reduction from baseline in proptosis in the study eye, without deterioration of proptosis (increase ≥ 2 mm) in the fellow eye.

- TED01RV: percentage of participants with a ≥ 2 mm reduction in proptosis AND a decrease in CAS ≥ 2 points from baseline in the study eye, without deterioration (increase in proptosis ≥ 2 mm or an increase in CAS ≥ 2 points) in the fellow eye.

In each TED trial, a greater proportion of participants treated with teprotumumab were proptosis responders at Week 24 compared to placebo:

- In the combined analysis of acute TED trials: the proportion of proptosis responders at Week 24 was 80.2% (combined teprotumumab group) vs. 14.0% (combined placebo group), i.e. a stratified treatment difference of 66.40% (95% CI: 56.44, 76.36).

- In the chronic TED trial 403, the proportion of proptosis responders at Week 24 was 61.9% in the teprotumumab group vs. 25.0% in the placebo group, i.e. a stratified treatment difference of 36.42% (95% CI: 12.34, 60.50).

Individual primary endpoint results are shown in Table 6.

Main secondary efficacy endpoints: A significant secondary efficacy endpoint was: the mean change from baseline in proptosis in the study eye at Week 24. In each TED trial, a greater LS

mean decrease from baseline in proptosis at Week 24 was observed in participants treated with teprotumumab vs. placebo:

- In the combined analysis of acute TED trials: the mean reduction was -2.96 mm (combined teprotumumab group) vs. -0.38 mm (combined placebo group) i.e. a treatment difference (95% CI) of -2.58 mm (-2.98, -2.19 mm).
- In the chronic TED trial 403, the mean reduction was -2.24 mm (teprotumumab group) vs. -0.75 mm (placebo) i.e. a treatment difference (95% CI) of -1.50 mm (-2.30, -0.70 mm).

Other selected secondary efficacy endpoints are shown in Table 7.

Table 2. Studies TED01RV, OPTIC, OPTIC-J and 403. Primary endpoint results.

	Trials in Acute TED								Trial in Chronic TED	
	TED01RV		OPTIC		OPTIC-J		Combined Analyses		HZNP-TEP-403	
	Placebo (N = 45)	Tepro (N = 43)	Placebo (N = 42)	Tepro (N = 41)	Placebo (N = 27)	Tepro (N = 27)	Placebo (N = 114)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 42)
Responder, n (%)[a]	9 (20.0)	31 (72.1)	4 (9.5)	34 (82.9)	3 (11.1)	24 (88.9)	16 (14.0)	89 (80.2)	5 (25.0)	26 (61.9)
Non-responder, n (%)	36 (80.0)	12 (27.9)	38 (90.5)	7 (17.1)	24 (88.9)	3 (11.1)	98 (86.0)	22 (19.8)	15 (75.0)	16 (38.1)
Stratified difference in response rates (tepro - placebo)[b]										
Estimate (SE)		52.45 (9.213)		73.45 (7.428)		77.78 (8.697)		66.40 (5.082)		36.42 (12.287)
95% CI		34.39, 70.51		58.89, 88.01		(60.73, 94.82)		(56.44, 76.36)		(12.34, 60.50)
p-value		< 0.0001		< 0.0001		< 0.0001		< 0.0001		0.0030

CI - confidence interval: ITT = intent-to-treat: SE = standard error: TED = thyroid eye disease: Tepro = teprotumumab
a Proptosis responders were defined as participants with a > 2-mm reduction from Baseline in proptosis in the study eye, without deterioration (> 2-nun increase) of proptosis in the fellow eye at Week 24. A participant missing the Week 24 evaluation was considered a non-responder.
b Results were estimated from Cochran-Mantel-Haenszel test adjusted for trial (combined analysis) and tobacco use status.

Table 7. Studies TED01RV, OPTIC, OPTIC-J and 403. Selected secondary endpoint results.

	Trials in Acute TED								Trial in Chronic TED	
	TED01RV		OPTIC		OPTIC-J		Combined Analyses		HZNP-TEP-403	
Endpoint	Placebo (N = 45)	Tepro (N = 43)	Placebo (N = 42)	Tepro (N = 41)	Placebo (N = 27)	Tepro (N = 27)	Placebo (N = 114)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 42)
Primary: 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)	16 (14.0)	89 (80.2)	5 (25.0)	26 (61.9)
p-value[a]		< 0.0001		< 0.0001		< 0.0001		< 0.0001		0.0030
Secondary: mean change from Baseline in proptosis (mm) at Week 24 in the study eye										
n	40	39	40	40	27	27	107	106	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)	-0.38 (0.149)	-2.96 (0.152)	-0.75 (0.363)	-2.24 (0.272)
p-value[b]		< 0.0001		< 0.0001		< 0.0001		< 0.0001		0.0004
Secondary: overall responder rate at Week 24										
n (%)	9 (20.0)	30 (69.8)	3 (7.1)	32 (78.0)	1 (3.7)	21 (77.8)	13 (11.4)	83 (74.8)	Not evaluated in the chronic TED trial	
p-value[a]		< 0.0001		< 0.0001		< 0.0001		< 0.0001		
Secondary: CAS categorical responder rate at Week 24 in the study eye										
n (%)	10 (22.2)	28 (65.1)	9 (21.4)	24 (58.5)	6 (22.2)	16 (59.3)	25 (21.9)	68 (61.3)	Not evaluated in the chronic TED trial	
p-value[a]		< 0.0001		0.0002		0.0031		< 0.0001		
Secondary: change from Baseline at Week 24 in diplopia as ordinal response categories at Week 24										
Common odds ratio (tepro vs. placebo)[c]		6.28		5.57		3.00		4.43		2.41
p-value (95% CI)[c]		< 0.0001 (2.53, 15.60)		0.0004 (2.14, 14.47)		0.0457 (1.02, 8.80)		< 0.0001 (2.57, 7.63)		0.3098 (0.44, 13.08)
Secondary: binocular diplopia responder rate at Week 24										
n[d]	31	38	28	28	20	22	79	88	4	14
n (%)	10 (32.3)	27 (71.1)	8 (28.6)	19 (67.9)	9 (45.0)	14 (63.6)	27 (34.2)	60 (68.2)	2 (50.0)	6 (42.9)
p-value[a]		0.0004		0.0012		0.2430		< 0.0001		0.8006
Secondary: complete binocular diplopia responder rate at Week 24										
n[d]	31	38	28	28	20	22	79	88	4	14
n (%)	8 (25.8)	19 (50.0)	7 (25.0)	16 (57.1)	4 (20.0)	11 (50.0)	19 (24.1)	46 (52.3)	1 (25.0)	4 (28.6)
p-value[a]		0.0261		0.0094		0.0430		< 0.0001		0.8854

CAS = Clinical Activity Score: CI = confidence interval: ITT = intent-to-treat: LS = least squares: MMRM = mixed model repeated-measures: SE = standard error. TED = thyroid eye disease: Tepro = teprotumumab
Note: A participant with a missing assessment at Week 24 was considered a non-responder.
Note: All p-values are nominal and compare teprotumumab versus placebo.

Note: In TEDOIRV. smoking status (smoker. non-smoker) was mapped to tobacco use status (user, non-user). For OPTIC and OPTIC-J. participants whose tobacco use status was current were considered users and participants whose tobacco use status was never or former were considered non-users. as collected on the substance use electronic case report form.
a. The p-value was estimated from Cochran-Mantel-Haenszel test adjusted for trial (combined analysis) and 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, trial, visit, visit-by-treatment and visit-by-Baseline value interactions. A change from Baseline value of 0 was imputed at the first post-Baseline visit for any participants without post-Baseline values.
c. Common proportional odds ratio. 95% CI and p-value were obtained from a logistic regression with treatment and tobacco use status as the model effect.
d. Number of participants who had binocular diplopia at Baseline.

Subgroups

The subgroup analyses were generally supportive of the primary analysis (Figure 4 and Figure 5, Appendix), noting the smaller samples size in the chronic TED trial.

Time course

The LS mean change from baseline is shown in Figure 2 (combined acute trials) and Figure 3 (chronic trial 403).

Figure 2. Studies TED01RV, OPTIC, and OPTIC-J. LS mean change from baseline in proptosis over time in the Acute TED Trials (ITT Analysis Set; Study Eye).

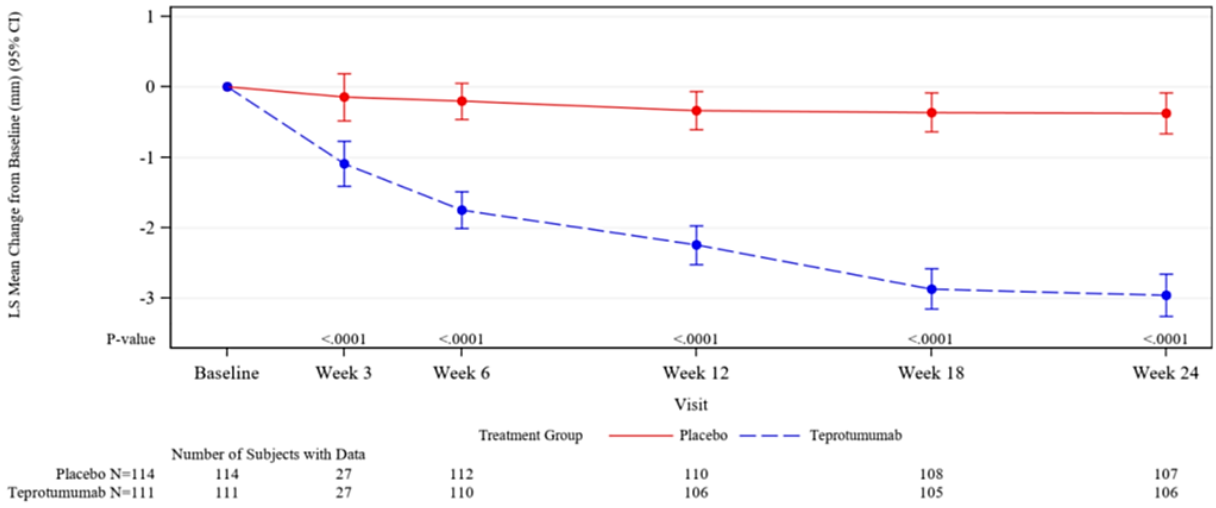
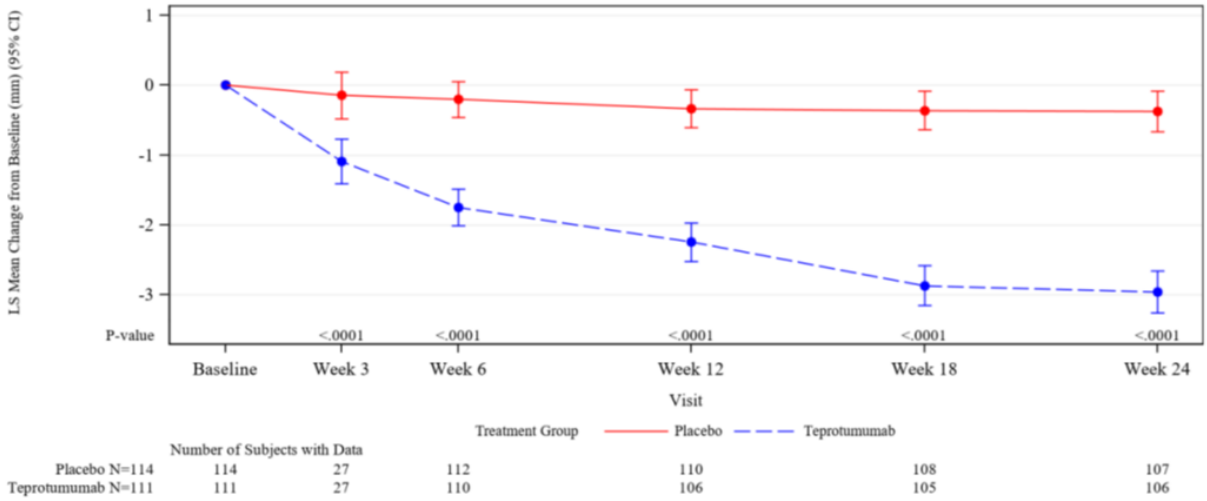


Figure 3. Study 403. LS mean change from baseline in proptosis over time in the Chronic TED Trial (ITT Analysis Set; Study Eye).



OPTIC study biomarker evaluation

At Baseline, all 83 patients in the ITT Population were positive for thyroid-stimulating antibody and the majority (37/42 [88.1%] for placebo vs. 34/41 [82.9%] for teprotumumab) were positive for thyrotropin receptor blocking immunoglobulins.

At Weeks 12 and 24, 97.6% (40/41) vs. 97.5% (39/40), and 92.3% (36/39) vs. 95.0% (38/40) respectively, were positive for thyroid-stimulating antibody.

At Weeks 12 and 24, 88.9% (32/36) vs. 88.9% (32/36), and 90.9% (30/33) and 88.2% (30/34), respectively, were positive for thyrotropin receptor blocking immunoglobulins.

All subjects were negative for thyroid blocking antibody on Day 1 and at Weeks 12 and 24.

OPTIC longer-term data (no study drug administration)

At the end of the Double-Masked Treatment Period (Week 24) of the OPTIC study, subjects who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter the open-label extension study OPTIC-X. Proptosis responders, as well as non-responders who chose not to enrol in OPTIC-X, entered an OPTIC study Follow-Up Period, during which no study drug was administered.

Week 72: 21 subjects originally randomised to teprotumumab had evaluable Week 72 data. Of those, 90.5% of patients in the teprotumumab group were proptosis responders, and 100% in the placebo group (from a sample size of 3 patients, and thus less meaningful) (observed cases as denominator; Table 8).

When considering the efficacy results in relation to Week 24 responders: 55.9% (19/34) were sustained proptosis responders (but using a conservative approach of imputing lack of data as lack of response; Table 9).

The mean decrease from baseline in proptosis remained consistent with Week 24 during the Follow-Up Period (-3.32 mm at Week 24 for 40 subjects, -3.51 mm at Week 28 for 35 subjects, and -3.62 mm at Week 72 for 21 subjects).

Table 8. OPTIC study Follow-Up Period. Efficacy results at Week 72 (ITT population, observed cases as denominator).

Efficacy Endpoints at Week 72 (ITT Population; Observed Cases) [1]	Placebo	Teprotumumab
Primary: Proptosis responder rate, n/N (%)	3/3 (100.0)	19/21 (90.5)
Secondary		
Overall responder rate, n/N (%)	2/3 (66.7)	18/21 (85.7)
CAS categorical responder rate, n/N (%)	2/3 (66.7)	14/21 (66.7)
Average change from Baseline in proptosis (mm) through Week 72, mean (SD)	(N = 3) -2.67 (0.577)	(N = 21) -3.62 (1.387)
Diplopia responder rate, n/N (%)	1/3 (33.3)	12/15 (80.0)
Average change from Baseline in GO-QoL overall score through Week 72, mean (SD)	(N = 3) 43.68 (35.666)	(N = 21) 21.19 (20.650)

CAS = clinical activity score; GO-QoL = Graves' Ophthalmology Quality of Life; ITT = intent-to-treat; SD = standard deviation. Note: Although 20 teprotumumab subjects completed the 48-week Follow-Up Period of the study, 1 additional subject had evaluable data that fell within the Week 72 Visit window and was included in analysis.

1. The denominator for each endpoint is the number of subjects with non-missing evaluations at the Week 72 Visit, except for diplopia which' only includes subjects with diplopia at Baseline and non-missing evaluations at the Week 72 Visit.

Table 9. OPTIC study Follow-Up Period. Efficacy results at Week 72 (Week 24 responders as denominator with lack of data imputed as lack of response).

Maintenance of Response at Week 72 (Week 24 Responders) [1]	Placebo	Teprotumumab
Sustained proptosis responder rate, n/N (%)	2/4 (50.0)	19/34 (55.9)
Sustained overall responder rate, n/N (%)	2/3 (66.7)	18/32 (56.3)
Sustained CAS categorical responder rate, n/N (%)	2/9 (22.2)	12/24 (50.0)
Sustained diplopia responder rate, n/N (%)	1/8 (12.5)	11/19 (57.9)
Sustained diplopia Grade 0 responder rate, n/N (%)	1/7 (14.3)	8/16 (50.0)

CAS = clinical activity score For sustained responder rates, a subject missing the Week 72 evaluation was considered a non-responder.

1. The denominator for each sustained responder rate is based on the number of subjects who were responders for that specific endpoint at Week 24.

Week 120 addendum (dated 18 May 2021)

23 subjects (3 placebo, 20 teprotumumab) completed the Week 72 Visit and had a successful contact in the Follow-Up Contact Period. One subject could not be contacted at Week 120. During the Follow-Up Contact Period, no subject underwent decompression or strabismus surgery.

Supportive study results

Study HZNP-TEP-302 (OPTIC-X)

This was a multicentre, open-label extension trial of the efficacy and safety of teprotumumab in subjects who completed the 24-week double-masked Treatment Period in HZNP-TEP-301 (OPTIC).

All subjects were to receive 8 infusions of teprotumumab every 3 weeks (q3W) (10 mg/kg for the first infusion followed by 20 mg/kg for the remaining 7 infusions). The Baseline (Day 1) Visit occurred within 14 days after the final visit of OPTIC (Week 24 for proptosis non-responders and up to Week 72 for proptosis responders who relapsed).

51 patients entered the trial. In the earlier OPTIC study, 37 had received placebo and 14 had received teprotumumab. In OPTIC-X, the 37 patients were in the “first-course” group (received placebo in OPTIC) and 14 in the “second-course” group (received teprotumumab in OPTIC, but were non-responders).

- First-course group results: the percentage of proptosis responders at week 24 from study baseline was 89.2% (similar to the teprotumumab results in OPTIC: 82.9%) despite a longer

duration of TED compared to OPTIC (mean duration since TED diagnosis: 12.3 months (range 7 to 16 months) vs. 6.2 (1 to 10 months; Table 10).

- Second-course group results: 14 non-responder patients from the OPTIC study ("second course"). 53.8% (7/13) were proptosis responders: Of the 5 patients who were proptosis non-responders at Week 24 in OPTIC, 2 were proptosis responders at Week 24 in OPTIC-X. Of the 8 patients who relapsed during the Follow-up Period of OPTIC, entered OPTIC-X and had Week 24 data, 5 (62.5%) were proptosis responders at Week 24 in OPTIC-X relative to Study Baseline (Table 10).

Table 10. Study OPTIC-X. Summary of main results (and comparison to OPTIC).

	OPTIC Data	OPTIC-X Data	
Endpoint	Teprotumumab (N = 41)	First-course (OPTIC Placebo) (N = 37)	Second-course (OPTIC Teprotumumab) (N = 14)
Primary: Proptosis responder rate at Week 24[1], n (%)	34/41 (82.9)	33/37 (89.2)	7/13 (53.8)
Secondary			
CAS categorical responder rate at Week 24[2], n (%)	24/41 (58.5)	21/32 (65.6)	4/11 (36.4)
Mean change from Study Baseline in proptosis (mm) at Week 24 (SD)	N = 40 -3.24 (1.617)	N = 36 -3.47 (1.732)	N = 11 -1.77 (1.126)
Diplopia categorical responder rate at Week 24[3], n/N (%)	19/28 (67.9)	14/23 (60.9)	3/4 (75.0)
Mean change from Study Baseline in GO-QoL transformed overall score at Week 24, mean (SD)	N = 40 18.33 (20.016)	N = 36 13.39 (17.890)	N = 11 14.73 (11.777)

CAS = clinical activity score; COVID-19 = coronavirus disease 2019; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; SD = standard deviation
Note: For responder rates, per the statistical analysis plan, subjects missing Week 24 values were considered non-responders. aside from those with missing data related to the COVID-19 pandemic. Second-course Subject US-I03-006 was excluded from all Week 24 summaries due to COVID-19 pandemic (visit delayed).
1. Proptosis responders were defined as subjects with a ≥22-mm reduction from Study Baseline in proptosis in the study eye, without deterioration (≥2-mm increase) of proptosis in the fellow eye at Week 24.
2. CAS responders were defined as subjects with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) as a categorical response variable at Week 24. The denominators in OPTIC-X are the numbers of subjects with CAS >1 at Study Baseline.
3. Diplopia responders were defined as subjects with 1 grade or greater reduction in diplopia in the study eye without worsening by at least 1 grade in the fellow eye at Week 24. Denominators are the number of subjects with diplopia at Baseline (OPTIC or OPTIC-X, as applicable).

Study HZNP-TEP-401

A Phase 3b, uncontrolled, multicentre, open-label, expanded access program (EAP) to collect data on the efficacy and safety of teprotumumab in patients in the U.S. with moderate-to-severe active TED. Enrolment was closed upon approval of Tepezza by the FDA on 21 January 2020 and commercial availability in the U.S. The EAP was conducted from 2 Dec 2019 to 14 Oct 2020 at 8 sites in the USA.

Teprotumumab was administered by intravenous (IV) infusion q3W for a total of 8 infusions during the 24-week treatment period; the first dose was 10 mg/kg and subsequent doses were 20 mg/kg.

Efficacy was only assessed using the Go-QoL.35 Patients' assessment of the effects of TED were evaluated by determining the mean change from Baseline to Week 12 and Week 21 in the GO-QoL questionnaire visual functioning, appearance and overall combined scores.

The change from baseline in GO-QoL visual functioning, appearance and overall mean transformed scores was > 20 points at both week 12 and week 21 study visits (Table 23, Appendix).

Safety

The integrated safety data was summarised in two main safety analysis populations (Table 11):

- Double-masked Population: any participant who received at least 1 dose of IP (placebo or teprotumumab) during the Double-masked Treatment Period in TED01RV, OPTIC, OPTIC-J or HZNP-TEP-403.
- All Teprotumumab Population: any participant who received teprotumumab in TED01RV, OPTIC, OPTIC-X, OPTIC-J, the EAP trial or HZNP-TEP-403.

This overview focusses on the double-masked period of the studies.

Exposure

The Double-masked Population included a total of 285 participants (152 and 133 in the teprotumumab and placebo groups, respectively; Table 11).

93.4% vs. 94% of participants in the teprotumumab and placebo groups, respectively, completed the double-masked treatment period (Table 24, Appendix); the incidence of discontinuations due to TEAEs was low but numerically higher in the teprotumumab compared to placebo group (3.9% (6/152) vs. 2.3% (3/133)). 87.5% vs. 90.2% of participants received all 8 infusions of IP (Table 12).

The 'All teprotumumab' population included a total of 246 patients who received teprotumumab across the 6 clinical studies. The mean total duration of teprotumumab treatment was similar in acute (151.9 days) and chronic TED (150.3 days).

Table 11. Safety analysis: Exposure summary by Integrated Safety Analysis Population and Treatment Group.

Analysis Population **Trial**	**Treatment Group**	
Double-masked Population	**Placebo**	**Teprotumumab**
Overall	133	152
TED01RV, Phase 2	44	43
OPTIC, Phase 3	42	41
OPTIC-J, Phase 3	27	27
HZNP-TEP-403, Phase 4	20	41
All Teprotumumab Population[a]	**Teprotumumab**	
Overall	**246**	
TED01RV, Phase 2	43	
OPTIC, Phase 3	41	
OPTIC-X, Phase 3	37	
OPTIC-J, Phase 3	50	
The EAP trial, Phase 3b	22	
HZNP-TEP-403, Phase 4	53	

a. To present unique participant counts, participants were summarized according to the trial in which teprotumumab was first received.

Table 12. Safety analysis: Extent of Exposure (Double-masked Population).

	Acute TED		Chronic TED		Overall	
	Placebo (N = 113)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 41)	Placebo (N = 133)	Tepro (N = 152)
Total number of doses administered, n						
Mean (SD)	7.7 (1.16)	7.6 (1.29)	7.6 (1.10)	7.5 (1.40)	7.7 (1.14)	7.6 (1.32)
Median	8.0	8.0	8.0	8.0	8.0	8.0
Min, max	1, 8	1, 8	4, 8	2, 8	1, 8	1, 8
Total number of doses administered, n (%)						
1 dose	1 (0.9)	1 (0.9)	0	0	1 (0.8)	1 (0.7)
2 doses	1 (0.9)	3 (2.7)	0	2 (4.9)	1 (0.8)	5 (3.3)
3 doses	2 (1.8)	1 (0.9)	0	0	2 (1.5)	1 (0.7)
4 doses	0	0	1 (5.0)	0	1 (0.8)	0
5 doses	2 (1.8)	0	1 (5.0)	1 (2.4)	3 (2.3)	1 (0.7)
6 doses	1 (0.9)	3 (2.7)	0	1 (2.4)	1 (0.8)	4 (2.6)
7 doses	3 (2.7)	4 (3.6)	1 (5.0)	3 (7.3)	4 (3.0)	7 (4.6)
8 doses	103 (91.2)	99 (89.2)	17 (85.0)	34 (82.9)	120 (90.2)	133 (87.5)
Total number of days on IP, n[a]						
Mean (SD)	142.9 (24.73)	142.2 (26.09)	141.2 (20.41)	141.1 (28.36)	142.7 (24.07)	141.9 (26.63)
Median	148.0	148.0	148.0	148.0	148.0	148.0
Min, max	1, 176	1, 162	64, 149	22, 162	1, 176	1, 162
Participants with any doses not administered completely, n (%)	1 (0.9)	2 (1.8)	0	2 (4.9)	1 (0.8)	4 (2.6)
Participants with any infusion interruptions, n (%)	4 (3.5)	5 (4.5)	0	3 (7.3)	4 (3.0)	8 (5.3)

IP = investigational product; max = maximum; min = minimum; SD = standard deviation; TED = thyroid eye disease; Tepro = teprotumumab

a. Number of days on drug = last dose date – first dose date + 1.

Adverse event overview

Double-masked Population: In the double-masked treatment period, 83.6% vs 72.9% experienced at least one TEAE (Table 13).

The SOCs with highest TEAE incidence (≥ 15.0% and greater in teprotumumab vs. placebo) were: Gastrointestinal disorders (36.8% vs. 18%), Infections and infestations (32.9% vs. 24.8%), Musculoskeletal and connective tissue disorders (34.9% vs. 14.3%), Skin and subcutaneous tissue disorders (30.9% vs. 18%), Nervous system disorders (25% vs. 18.8%), Ear and labyrinth disorders (19.7% vs. 5.3%), Metabolism and nutrition disorders (16.4% vs. 3.8%) and nail disorders (5.9% vs. 0.8%).

The most commonly reported TEAEs (≥ 5.0% and greater in teprotumumab vs. placebo) were: muscle spasms (27.6% vs. 6%), hearing impairment42 (14.0% vs. 2.3%), hyperglycaemia (13.2% vs. 3%), fatigue (12.5% vs. 6%), alopecia (13.2% vs. 5.3%), diarrhoea (14.5% vs. 9%), nausea (10.5% vs. 6.8%), dry skin (9.9% vs. 0%) and dysgeusia (8.6% vs. 0.8%; Table 14).

Table 13. Safety analysis: Summary of TEAEs (Double-masked Population).

	Number (%) of Participants					
	Acute TED		Chronic TED		Overall	
TEAE[a] Category	Placebo (N = 113)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 41)	Placebo (N = 133)	Tepro (N = 152)
Any	81 (71.7)	94 (84.7)	16 (80.0)	33 (80.5)	97 (72.9)	127 (83.6)
Any treatment-related	31 (27.4)	64 (57.7)	12 (60.0)	31 (75.6)	43 (32.3)	95 (62.5)
Any serious	1 (0.9)	8 (7.2)	1 (5.0)	1 (2.4)	2 (1.5)	9 (5.9)
Any treatment-related serious	0	3 (2.7)	1 (5.0)	1 (2.4)	1 (0.8)	4 (2.6)
Any with an intensity of Grade 3 or higher	1 (0.9)	6 (5.4)	1 (5.0)	1 (2.4)	2 (1.5)	7 (4.6)
Any leading to interruption of IP administration	1 (0.9)	6 (5.4)	2 (10.0)	2 (4.9)	3 (2.3)	8 (5.3)
Any leading to discontinuation of IP	3 (2.7)	6 (5.4)	1 (5.0)	1 (2.4)	4 (3.0)	7 (4.6)
Any treatment-related leading to discontinuation of IP	0	3 (2.7)	0	1 (2.4)	0	4 (2.6)
Any leading to death	0	0	0	0	0	0

IP = investigational product: TEAE = treatment-emergent adverse event: TED = thyroid eye disease; Tepro = teprotumumab

a. A TEAE was defined as an adverse event occurring after the first dose of IP (placebo or teprotumumab) on Day 1 through 3 weeks following the last dose of IP.

Table 14. Summary of TEAEs in ≥ 5.0% of teprotumumab participants with a greater incidence than Placebo by PT (Double-masked Treatment Period, Double-masked Population).

	Number (%) of Participants	
Preferred Term or Grouped Term	Placebo (N = 133)	Teprotumumab (N = 152)
Muscle spasms	8 (6.0)	42 (27.6)
Diarrhoea	12 (9.0)	22 (14.5)
Hearing impairment[a]	3 (2.3)	21 (13.8)
Alopecia	7 (5.3)	20 (13.2)
Hyperglycemia[b]	4 (3.0)	20 (13.2)
Fatigue[c]	8 (6.0)	19 (12.5)
Nausea	9 (6.8)	16 (10.5)
Headache	10 (7.5)	16 (10.5)
Dry skin	0	15 (9.9)
Dysgeusia[d]	1 (0.8)	13 (8.6)
COVID-19	5 (3.8)	10 (6.6)
Ear discomfort	2 (1.5)	10 (6.6)
Nail disorder[e]	1 (0.8)	9 (5.9)

COVID-19 = coronavirus disease 2019; TEAE = treatment-emergent adverse event
Note: Un-italicized terms indicate groupings of Preferred Terms. Italicized terms are single Preferred Terms.
a. Hearing impairment includes Autophony. Conductive deafness. Deafness. Deafness unilateral, Eustachian tube dysfunction. Eustachian tube patulous, Hyperacusis. Hypoacusis. Neurosensory hypoacusis, Tinnitus and Tympanic membrane disorder.
b. Hyperglycaemia includes Blood glucose increased. Diabetes mellitus. Diabetic ketoacidosis. Glucose tolerance impaired, Glycosylated haemoglobin increased and Hyperglycaemia.
c. Fatigue includes Fatigue and Asthenia.
d. Dysgeusia includes Dysgeusia and Taste disorder.
e. Nail disorder includes Ingrowing nail, Nail bed disorder. Nail discolouration. Nail disorder and Onychoclasis.

Treatment related adverse event (adverse drug reaction) overview

Double-masked Population: 62.5% vs. 32.3% (teprotumumab vs. placebo) experienced at least one treatment-related TEAE (adverse drug reaction) during the Double-masked Treatment Period (Table 15). Most adverse drug reactions during the Double-masked Treatment Period were considered mild or moderate in intensity. Serious adverse drug reactions are listed in the serious adverse event section below.

Table 15. Summary of treatment-related TEAEs in ≥ 2.0% of teprotumumab participants with a greater incidence than Placebo (Double-masked Treatment Period, Double-masked Population).

	Number (%) of Participants					
	Acute TED		Chronic TED		Overall	
Preferred Term	Placebo (N = 113)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 41)	Placebo (N = 133)	Tepro (N = 152)
Any TEAE	31 (27.4)	64 (57.7)	12 (60.0)	31 (75.6)	43 (32.3)	95 (62.5)
Muscle spasms	3 (2.7)	18 (16.2)	2 (10.0)	17 (41.5)	5 (3.8)	35 (23.0)
Diarrhoea	6 (5.3)	9 (8.1)	2 (10.0)	8 (19.5)	8 (6.0)	17 (11.2)
Alopecia	3 (2.7)	14 (12.6)	0	2 (4.9)	3 (2.3)	16 (10.5)
Dry skin	0	6 (5.4)	0	5 (12.2)	0	11 (7.2)
Ear discomfort	0	6 (5.4)	2 (10.0)	4 (9.8)	2 (1.5)	10 (6.6)
Nausea	5 (4.4)	8 (7.2)	0	1 (2.4)	5 (3.8)	9 (5.9)
Dysgeusia	0	5 (4.5)	1 (5.0)	4 (9.8)	1 (0.8)	9 (5.9)
Headache	2 (1.8)	6 (5.4)	2 (10.0)	3 (7.3)	4 (3.0)	9 (5.9)
Fatigue	1 (0.9)	2 (1.8)	1 (5.0)	6 (14.6)	2 (1.5)	8 (5.3)
Hypoacusis	0	3 (2.7)	0	4 (9.8)	0	7 (4.6)
Hyperglycaemia	1 (0.9)	6 (5.4)	0	1 (2.4)	1 (0.8)	7 (4.6)
Tinnitus	0	3 (2.7)	2 (10.0)	2 (4.9)	2 (1.5)	5 (3.3)
Stomatitis	1 (0.9)	4 (3.6)	0	0	1 (0.8)	4 (2.6)
Infusion related reaction	0	2 (1.8)	2 (10.0)	2 (4.9)	2 (1.5)	4 (2.6)
Blood glucose increased	1 (0.9)	3 (2.7)	0	1 (2.4)	1 (0.8)	4 (2.6)
Weight decreased	0	4 (3.6)	0	0	0	4 (2.6)
Rash	2 (1.8)	3 (2.7)	0	1 (2.4)	2 (1.5)	4 (2.6)
Abdominal pain	2 (1.8)	2 (1.8)	0	1 (2.4)	2 (1.5)	3 (2.0)
Feeling hot	2 (1.8)	2 (1.8)	0	1 (2.4)	2 (1.5)	3 (2.0)
Glycosylated haemoglobin increased	0	0	0	3 (7.3)	0	3 (2.0)
Decreased appetite	0	3 (2.7)	1 (5.0)	0	1 (0.8)	3 (2.0)
Diabetes mellitus	0	2 (1.8)	1 (5.0)	1 (2.4)	1 (0.8)	3 (2.0)
Myalgia	0	1 (0.9)	0	2 (4.9)	0	3 (2.0)
Amenorrhoea	0	3 (2.7)	0	0	0	3 (2.0)
Hair growth abnormal	0	2 (1.8)	0	1 (2.4)	0	3 (2.0)
Madarosis	0	3 (2.7)	0	0	0	3 (2.0)
Hypertension	0	2 (1.8)	0	1 (2.4)	0	3 (2.0)

IP = investigational product: TEAE = treatment-emergent adverse event: TED = thyroid eye disease; Tepro = teprotumumab

a. A TEAE was defined as an adverse event occurring after the first dose of IP (placebo or teprotumumab) on Day 1 through 3 weeks following the last dose of IP.

Deaths

No deaths occurred in the teprotumumab clinical studies for TED.

Serious adverse events

Double-masked Population: serious TEAEs in teprotumumab-treated patients included Conductive deafness, Diarrhoea, Inflammatory bowel disease, COVID-19, Escherichia sepsis, IRRs, Hashimoto's encephalopathy, Urinary retention and Pneumothorax. All of these event terms were of single occurrence. 5 were considered severe (Conductive deafness, Diarrhoea, Inflammatory bowel disease, COVID-19 and Escherichia sepsis) and 1 was considered life-threatening (Pneumothorax).

Serious TEAEs considered related to IP and all leading to IP discontinuation were: Hashimoto's encephalopathy, Diarrhoea (exacerbation of inflammatory bowel disease [IBD]), IRRs, and Conductive deafness.

Adverse event of special interest: hearing impairment

TEAEs associated with hearing impairment were reported as Autophony, Conductive deafness, Deafness, Deafness unilateral, Eustachian tube dysfunction, Eustachian tube patulous, Hyperacusis, Hypoacusis, Neurosensory hypoacusis, Tinnitus or Tympanic membrane disorder.

Across the TED clinical program, a total of 40 (40/246, 16.3%) participants experienced 52 events of hearing impairment while receiving teprotumumab or during the Follow-up Period after receipt of teprotumumab. The Sponsor stated that the majority of hearing impairment events were non-serious and mild in intensity did not lead to premature discontinuation of IP.

In the Double-masked Population, they were observed in 21 (13.8%) teprotumumab-treated participants (28 events) vs. 3 (2.3%) for placebo. One of the 21 patients also experienced hearing impairment (Deafness unilateral) during the Follow-up Period. An additional patient experienced hearing impairment (Hypoacusis) during the Follow-up Period of OPTIC (ongoing and resolved during OPTIC-X).

In the Double-masked Population, 7 teprotumumab-treated participants and 2 placebo-treated participants had hearing impairment events that were noted as not recovered/not resolved as of the data lock point for the trial or the primary Week 24 analysis (for OPTIC-J and TEP-403) and had been ongoing for ≥ 6 months after the participant's last double-masked infusion of IP.

In Study 403, a patient in the teprotumumab group (with history of hearing impairment) experienced a serious TEAE of Conductive deafness (severe) leading to premature withdrawal of IP during the Open-label Treatment Period. This event was assessed as possibly related to IP.

In OPTIC-J, a patient in the teprotumumab group experienced a TEAE of Neurosensory hypoacusis (moderate) that led to premature IP withdrawal during the Double-masked Treatment Period. This event was assessed as related to IP (despite the patient's history of Eustachian tube stenosis and neurosensory hypoacusis in both ears).

The Sponsor has been asked to provide a summary of pre- and post-market data on hearing loss and tinnitus, in particular permanent hearing loss (full or partial), including a line listing of patients with permanent hearing loss, and a causality assessment. This is briefly summarised below:

- Pre-market clinical trials: the Sponsor concluded that a review of clinical trial cases of unresolved hearing impairment found 7 cases of deafness (6 non-serious and 1 serious). 7 cases of tinnitus were also reported. Investigators assessed causality as 'related' to investigational product in 3 nonserious cases and one serious case; and as 'not-related' in the other three non-serious cases.

- Post-market experience (cumulative search of the safety database through 20 July 2024): Teprotumumab was first approved in the United States on 21 January 2020 (International Birth Date) for the treatment of thyroid eye disease and is also approved in Brazil and Saudi Arabia.

Other adverse events of special interest

Adverse events of special interest (AESI) for the teprotumumab clinical trials are IRRs, hyperglycaemia, hearing impairment, new onset IBD and exacerbation of IBD.

Hyperglycaemia: A higher incidence of TEAEs was observed in teprotumumab-treated participants compared with placebo-treated participants (13.2% [20/152] teprotumumab vs. 3.0% [4/133] placebo). Participants with diabetes (69.2% [9/13] teprotumumab vs. 9.1% [1/11] placebo) or pre-diabetes (18.4% [7/38] teprotumumab vs. 0% [0/30] placebo) at baseline were at greatest risk. The majority of hyperglycaemia events were non-serious, Grade 1 or 2 in severity and managed as needed with medications used for glycaemic control. No participants in the Double-masked Population discontinued IP due to a hyperglycaemic event.

Higher mean glucose levels were seen in teprotumumab-treated participants at every visit compared with placebo-treated participants and more teprotumumab-treated participants shifted from normal to Grade 1 or 2 high glucose levels compared with placebo; 1 teprotumumab participant shifted from normal to Grade 3.

New onset IBD: No events were observed.

Exacerbation of IBD: Exacerbation of IBD was reported for 1 of 152 (1.2%) participants who received teprotumumab and no participants who received placebo. The severe, serious event of occurred in a patient with a surgical history of partial bowel resection and IBD.

Post-market experience

The Sponsor considers the post marketing safety profile to be consistent with the clinical trial experience.

However, a signal of increased severity of hearing impairment was confirmed, with a subsequent update of the US prescribing information. No clear risk factors for hearing impairment were identified.

Risk management plan evaluation summary

Amgen Australia Pty Ltd has submitted a draft EU-RMP (no version number; 17 Jan 2024; DLP 14 Jun 2023) and Australia-specific annex (ASA) version 1.0 (25 Mar 2024) in support of this application. On 17 September 2024, the Sponsor has provided EU-RMP version 0.1 (03 April 2024; DLP 20 January 2024) and ASA version 2.0 (05 September 2024).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies documented in the EU-RMP are summarised below.

Table 16. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
	Hyperglycaemia	✓	✓*	✓	–

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Exacerbation of inflammatory bowel disease (IBD)	✓	✓*	✓	–
	Infusion related reaction	✓	✓*	✓	–
	Hearing impairment	✓	✓*†	✓	–
Important potential risks	New onset IBD	✓	✓*	–	–
Missing information					

*PASS HZNP-TEP-402
†Sub-study HZNP-TEP-402

The Sponsor has proposed routine and additional pharmacovigilance activities. The following additional pharmacovigilance activities have been summarised from ASA version 2.0 and the results will be applicable to the Australian population:

Study Details	Rationale and Study Objectives	Study Population	Milestones
Study HZNP-TEP-402 A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicentre Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab Category 3	Rationale: An FDA post marketing requirement for a descriptive trial to evaluate the safety, efficacy and need for re-treatment of 3 different teprotumumab treatment durations for TED. In addition, serum samples from patients with a Baseline CAS ≥ 3 will be evaluated for biomarkers of disease. Objectives: • To evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for retreatment. Safety concerns addressed: • Hyperglycaemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment • New onset inflammatory bowel disease	Male or non-pregnant female adult (≥ 18 years) patients with TED.	Final Clinical Study Report (CSR): May 2026
Study HZNP-TEP-402 hearing	Rationale: This substudy is an independent, trial to investigate hearing impairment. Objectives:	Male or non-pregnant female adult	Final CSR: May 2026

evaluation sub-study Category 3	• To assess the incidence of hearing impairment among TED patients treated with teprotumumab. • To assess the reversibility of hearing impairment at 3 or 6 months post teprotumumab treatment. • To explore potential risk factors associated with ototoxicity among TED patients treated with teprotumumab Safety concerns addressed: • Hearing impairment	(≥ 18 years) patients with TED.	

CAS = Clinical Activity Score; TED = Thyroid eye disease

Risk-benefit analysis

Teprotumumab, a monoclonal insulin-like growth factor-1 receptor (IGF-1R) antagonist, appears to bind to IGF-1R and blocks its activation and signalling. However, the mechanism of action of teprotumumab in TED has not been fully characterised.

Clinical trial program

The main efficacy, safety, and pharmacology results are shown in sections 2.4.2, 2.4.3, and 2.4.1, respectively. Specific issues or concerns are discussed below.

The main clinical data for TED are derived from Studies TED01RV, OPTIC, OPTIC-J and 403 with supportive data from OPTIC-X and Study 401.

Endpoints

The main endpoint used the main trial involved the measurement of proptosis, and this is considered a reasonable choice of endpoint. The Clinical Activity Score (CAS) assessment used the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) and covered other clinical features of TED. Additionally, the Graves' Orbitopathy Quality of Life (GO-QOL) survey is a common and validated TED QoL outcome measure.

A visual acuity endpoint (e.g. Best-corrected visual acuity [BVCA]) or measurements of intraocular pressure appear not to have been utilised and should have been considered. The clinical trials excluded patients with a decrease BCVA due to optic neuropathy.

Study contributions to efficacy

Studies TED01RV, OPTIC, OPTIC-J demonstrated efficacy in acute (active) TED patients, and Study 403 demonstrated some efficacy in chronic (inactive) TED patients (clinically stable chronic TED). Overall, the sample size was rather small, and particularly so for patients with chronic TED. The studies in active TED only evaluated patients with moderate to severe active TED, and this should be reflected in the indication.

In the combined analysis of acute TED trials: the proportion of proptosis responders at Week 24 was 80.2% (combined teprotumumab group) vs. 14.0% (combined placebo group), i.e. a stratified treatment difference of 66.40% (95% CI: 56.44, 76.36). The beneficial effect appeared to be consistent in all three studies.

In the chronic TED trial 403, the proportion of proptosis responders at Week 24 was 61.9% in the teprotumumab group vs. 25.0% in the placebo group, i.e. a stratified treatment difference of 36.42% (95% CI: 12.34, 60.50).

The OPTIC study Follow-Up Period provided evidence for the persistence of a treatment effect after IP cessation. Of 21 patients with evaluable Week 72 data, 90.5% in the teprotumumab group were proptosis responders, and 100% in the placebo group (from a sample size of 3 patients, and thus less meaningful) (observed cases as denominator) (Table 8).

When considering the efficacy results in relation to Week 24 responders: 55.9% (19/34) were sustained proptosis responders (but using a conservative approach of imputing lack of data as lack of response) (Table 9).

OPTIC-X included 14 patients in a "second-course" group (i.e. those who received teprotumumab in OPTIC, but were previous non-responders or relapsed in the OPTIC Follow-up Period). This indicates a role for the treatment of patients that had been unresponsive previously, even though the sample size had been rather small.

Overall, efficacy has been demonstrated mainly in the acute TED trials.

Safety

Safety data are outlined in section 2.4.3. The incidence of adverse events was consistently higher in the teprotumumab group compared to placebo. In the Double-Masked Population, the incidence of treatment-related adverse events was almost twice as high in the teprotumumab vs placebo group (62.5% vs 32.3%). The size of the safety database is discussed below.

The AESIs of hyperglycaemia, new onset IBD, and exacerbation of IBD are not uncommonly associated with certain monoclonal antibodies, with accompanying prescriber awareness. The may be no such specific awareness of hearing impairment associated with teprotumumab use (discussed below).

Main issues

The main issues are:

- Safety: The size of the safety database
- Safety: Managing the risk of hearing impairment, including permanent impairment
- Safety: Managing the risk of teratogenicity
- The overall benefit-risk balance
- Regulatory considerations: indication wording

Safety: The size of the safety database

The safety database is rather small. The Double-masked Population included a total of 285 participants (152 and 133 in the teprotumumab and placebo groups, respectively) (Table 11). The 'All teprotumumab' population included a total of 246 patients who received teprotumumab across the 6 clinical studies. The mean total duration of teprotumumab treatment was similar in acute (151.9 days) and chronic TED (150.3 days).

The Sponsor has justified the size of the safety database mainly with the prevalence data and quoted a prevalence of approx. 9 per 10,000 for TED, and less than 5 per 10,000 for moderate to severe TED. These quoted figures are at the lower end of common European estimates (9 to 15

per 10,000 for TED). However, the Sponsor proposes an indication that does not restrict itself to moderate to severe TED.

A post-marketing trial (Study 402 referenced in the RMP) examining the safety and tolerability of teprotumumab in the treatment of Thyroid Eye Disease (TED) in adult participants is currently conducted in the US and five European countries. This trial started in September 2021 and the expected completion date is mid-2026. Enrolment in this trial has completed, with 310 patients receiving teprotumumab were enrolled with a substudy that enrolled 99 patients to further assess the safety of teprotumumab in hearing impairment.

If registered, submission of the Study 402 data would be required as a condition of registration.

Safety: Managing the risk of hearing impairment, including permanent impairment

Insulin-like growth factor-1, which binds the IGF-1 receptor, is involved in cochlear development, and its mutations are associated with hearing loss. The mechanism of teprotumumab-associated hearing impairment is uncertain, but likely related. Specific risk factors could not be identified, but it appears that both a de novo hearing impairment and worsening of an existing hearing impairment may occur.

Hearing impairment has been described as an important AESI, and acknowledged by the Sponsor as a signal.

In the post-market space, for hearing loss and tinnitus, 3806 post-marketing cases (3078 solicited, 710 spontaneous, and 18 were from post-marketing noninterventional studies) were identified. For cases suggestive of permanent hearing loss, 176 cases (containing 370 events) were identified (120 spontaneous, 56 solicited). 92 cases were medically confirmed. 194 events were considered nonserious and 176 were serious. Given the likely non-systematic collection of hearing impairment events, the actual number of cases may be greater.

At the stage, the Sponsor is proposing the following wording in the PI (only relevant wording shown), and no additional risk minimisation activities:

Section 4.2

> *Hearing impairment*
>
> *Assess patients' hearing before, during and after treatment with Tepezza (see section 4.4 Special warnings and precautions for use, Hearing impairment).*

Section 4.4.

> *Hearing impairment*
>
> *Tepezza may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during and after treatment with Tepezza and consider the benefit-risk of treatment with patients.*

Section 4.8

> *Hearing impairment*
>
> *The majority of hearing impairment events were nonserious, mild in intensity and did not lead to premature discontinuation of study drug. For clinical management of hearing impairment see section 4.4 Special warnings and precautions for use, Hearing impairment.*

The risk of hearing impairment (in particular permanent impairment) represents a serious and significant risk that require appropriate risk mitigation. A boxed warning (in the PI and/or label) may be needed to draw the attention to this serious issue. Furthermore, a strengthening of the

language in the PI, including the need for regular monitoring, is needed. Information on the number of cases of non-permanent and permanent hearing loss from post-market reports may need to be included to draw attention to this matter, to fully inform prescribers (and consequently the patients) for the purposes of an individual benefit-risk assessment, and for a decision whether to continue or cease treatment with teprotumumab. Additional risk minimisation activities may also be necessary.

Advice from the Advisory Committee on Medicines (ACM) is kindly requested.

Question (to the ACM): Can the ACM comment on managing the risk of hearing impairment associated with teprotumumab use?

Safety: Managing the risk of teratogenicity

The nonclinical evaluation revealed that teprotumumab was shown to be clearly teratogenic in cynomolgus monkeys. Every fetus exposed to teprotumumab either died or displayed multiple malformations, including misshapen cranium, closely set eyes, micrognathia, and pointing and narrowing of the nose; impaired/abnormal ossification of the skull, teeth, sternebrae, carpals and tarsals was also observed.

Teprotumumab caused generalised suppression of fetal growth, with final fetal weight almost halved, and decreased placental weight and size, and reduced amniotic fluid volume. These adverse effects on embryofetal development occurred in the absence of maternal toxicity, and at a clinically relevant dose (based on the extent of IGF 1R inhibition as well as relative exposure). Concerns for embryofetal harm with teprotumumab are held at the highest level, and warrant assignment to Pregnancy Category X rather than Category D as the Sponsor proposes.

Teprotumumab is to be contraindicated in pregnancy, and women of childbearing potential directed to use effective contraception prior to initiation of treatment, during treatment and for 6 months after the last dose of Tepezza.

For RMP purposes, the Sponsor has not included 'Embryofoetal toxicity' as an important potential risk, as requested by the RMP evaluator. The Sponsor noted the median age at onset of TED of 50 years. The Sponsor states that only ~0.5% of women becoming pregnant have Graves' Disease, and that the risk of exposure to Tepezza during pregnancy is considered negligible, and that the embryofetal toxicity concern is adequately addressed in the relevant sections of the draft Product Information.

The Sponsor's proposed approach is not considered adequate. Most monoclonal antibody medicines are currently classified in Australian Pregnancy Categories C or D, and it is very important to communicate a Category X status.

The PI needs to be updated to change the Pregnancy Category from D to X, as requested in the NCER. Furthermore, a boxed warning in the PI and/or the label are required. Further additional risk minimisation activities may be needed.

Advice from the ACM is kindly requested.

Question (to the ACM): Can the ACM comment on managing the risk of teratogenicity associated with teprotumumab use?

Overall benefit-risk balance

The question remains whether the rather significant potential safety issues with regard to hearing loss can be sufficiently mitigated and despite their presence contribute to an overall favourable benefit-risk balance. These potential safety issues may prevent use in less severe disease and a restriction of the indication should be performed.

Overall, there appears to be a role for teprotumumab in the physician's or ophthalmologist's armamentarium.

This would be dependent on managing the above described risks appropriately, including, but not limited to boxed warnings for the risk of hearing impairment and Pregnancy Category X, as well as appropriate risk minimisation activities.

Regulatory considerations: indication wording

The currently Sponsor-proposed indication wording is not considered acceptable, as too broad:

> *Tepezza is indicated for the treatment of Thyroid Eye Disease (TED).*

If registered, the indication should reflect the population studied in the clinical trial program, and may reference to section 5.1. in the PI with regard to use in chronic TED, retreatment, and the maintenance effect, for example:

> *Tepezza is indicated for the treatment of moderate to severe Thyroid Eye Disease (TED) (see section 5.1 Pharmacodynamic properties – Clinical trials).*

Question (to the ACM): Can the ACM comment on the indication wording?

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

1. ***Can the ACM comment on managing the risk of hearing impairment associated with teprotumumab use?***

The ACM considered the provided trial data, which indicated that the incidence of hearing impairment was approximately 15% of participants receiving treatment experiencing some level of hearing impairment (16.3% (40/246) in the overall clinical trial population, and in the double-masked population: 13.8% (21/152) for teprotumumab vs. 2.3% (3/152) for placebo). Most cases of hearing impairment associated with use of Tepezza were mild, with 75% of cases resolved within 6 months. Approximately 4.6% of cases (7/152) of hearing loss were considered to be permanent or unresolved in the double-masked population vs. 1.3% (2/152) in the placebo group.

The ACM agreed that patients should be screened for hearing impairment prior to treatment, due to a noted higher level of hearing impairment for patients with pre-existing hearing loss. The ACM also suggested ongoing monitoring with serial audiograms in addition to a boxed warning explaining the risk of possible permanent hearing impairment.

The ACM advised that the Consumer Medicine Information (CMI) and Product Information (PI) should be more strongly worded to reinforce the possibility of permanent hearing impairment emerging from treatment. as well as the provision of additional post market data being a requirement of registration.

2. ***Can the ACM comment on managing the risk of teratogenicity associated with teprotumumab use?***

The ACM advised that the designation of Pregnancy Category X was appropriate, and that the PI includes strong wording on the risks involved if used in pregnancy. The ACM highlighted the strict requirement in the teprotumumab clinical trials for women of childbearing potential to use 2 reliable forms of contraception. The ACM recommended that a boxed warning for the risk of major foetal malformation would be appropriate for this product, as the teratogenicity is a

risk that would be unexpected among monoclonal antibody therapies, as prescribers may not expect them in Category X.

3. Can the ACM comment on the indication wording?

The ACM agreed that it would be appropriate to limit the indication to moderate to severe Thyroid Eye Disease (TED). Additionally, the ACM supported limiting the indication to an adult population due to the mechanism of action and effects on growth and development.

4. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM advised that further information on the follow-up treatment regimen be provided in the PI, in line with the protocol used when transitioning initial non-responsive trial participants to the extension studies.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

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

Implementation of risk minimisation measures

Hearing impairment – final risk management approach

A boxed warning was not implemented. This risk is managed through routine and additional risk minimisation measures. In the Product Information (PI), Section 4.4 (Special warnings and precautions for use) contains prominently formatted warning text regarding the risk of hearing impairment, including potential permanence, and outlines specific clinical measures (e.g. assessment of hearing before, during and after treatment, and management advice if impairment occurs). The Consumer Medicines Information (CMI) also alerts patients to this risk in suitable language.

In addition, the sponsor will implement an education program for healthcare professionals as an additional risk minimisation activity.

Embryofoetal toxicity – final risk management approach

A boxed warning was not implemented. This risk is managed through routine and additional risk minimisation measures to clearly alert prescribers to the risk of major foetal harm. In the PI, Section 4.3 (Contraindications) and Section 4.6 (Fertility, pregnancy and lactation) include Pregnancy Category X, a contraindication in pregnancy, requirements for effective contraception during treatment and for the specified post-treatment period, and prominent warning statements describing the embryofoetal risk. The CMI communicates these precautions to consumers.

In addition, the sponsor will implement an education program for healthcare professionals as an additional risk minimisation activity.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Tepezza (teprotumumab) for the following indication:

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

Specific conditions of registration

Tepezza (teprotumumab) is to be included in the Black Triangle Scheme. The PI and CMI for Tepezza must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The teprotumumab EU-Risk Management Plan (RMP) (version 0.1, dated 03 April 2024, data lock point 20 January 2024), with Australian Specific Annex (version 2.0, dated 05 September 2024), included with submission PM-2024-01236-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the Sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

All batches of Tepezza teprotumumab supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

The Sponsor must finalise the additional risk minimisation activity education program materials submitted to the TGA on 7 March 2025 to the satisfaction of the post-market evaluation area of the TGA. The education program must be implemented prior to supply of Tepezza in Australia.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Appendix – Additional tables and figures

Table 17. TED studies. Summary of actual serum concentrations (µg/ml) of teprotumumab.

Median (Q1, Q3)	TED01RV	HZNP-TEP-301 (OPTIC)	HZNP-TEP-302 (OPTIC-X)	HZNP-TEP-303	HZNP-TEP-403
Postdose (Day 1)	-	230 (185, 284) N=40	254 (249, 299) N=7	196 (167, 228) N=27	281 (233, 312) N=41
Postdose (Week 3)	-	470 (397, 605) N=40	628 (565, 742) N=8	447 (409, 514) N=27	652 (553, 816) N=41
Postdose (Week 9)	-	543 (459, 665) N=40	763 (693, 869) N=11	-	-
Postdose (Week 12)	-	-	-	551 (474, 642) N=27	713 (629, 792) N=38
Predose (Day 1)	-	0 (0,0) N=40	254 (249, 299) N=7	0.005 (0.005, 0.005) N=27	0.005 (0.005, 0.005) N=41
Predose (Week 3)	38.2 (35.1% CV)[a] N=40	36.4 (32.5, 46.7) N=40	43.0 (33.7, 47.6) N=8	30.6 (26.4, 32.4) N=27	45.3 (39.4, 50.0) N=41
Predose (Week 9)	121 (24.3% CV)[a] N=39	128 (109,161) N=38	140 (117, 160) N=10	-	-
Predose (Week 12)	-	-	-	121 (106, 137) N=26	165 (131, 217) N=39
Predose (Week 24)	-	172 (124, 207) N=40	152 (117, 184) N=23	155 (142, 204) N=3	164 (135, 222) N=24

N=number of participants, CV=coefficient of variation. Q1=1st quartile; Q3=3rd quartile.
Serum concentrations of teprotumumab were summarized as median (Q1. Q3).
a Values from Study TED01RV are mean (CV%).

Table 18. Studies TED01RV, OPTIC, OPTIC-J and 403. Inclusion criteria.

TED01RV	Trial HZNP-TEP-301 (OPTIC)	Trial HZNP-TEP-303 (OPTIC-J)	Trial HZNP-TEP-403
	Written informed consent	Written informed consent	Written informed consent
Aged 18-75 years (inclusive)	Male or female participant between the ages of 18 and 80 years, inclusive, at Screening	Male or female Japanese participant between the ages of 20 and 80 years, inclusive, at Screening	Male or female at least 18 years old at Screening
Clinical diagnosis of Graves' disease associated with acute TED with a CAS ≥ 4 (on the 7-point version of the scale) for the most severely affected eye (study eye)	Clinical diagnosis of Graves' disease associated with acute TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline	Clinical diagnosis of Graves' disease associated with acute TED with a CAS ≥ 3 (on the 7-item scale) for the most severely affected eye at Screening and Baseline	CAS ≤ 1 at the Screening and Baseline Visits
	Moderate-to-severe acute TED (not sight-threatening but had an appreciable impact on daily life), usually associated with 1 or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia	Moderate-to-severe acute TED (not sight-threatening but had an appreciable impact on daily life), usually associated with 1 or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement and/or inconstant or constant diplopia	
Fewer than 9 months from onset of TED as determined by patient records	Onset of acute TED symptoms (as determined by participant records) within 9 months prior to Baseline	Onset of acute TED symptoms (as determined by participant records) within 9 months prior to Baseline	Initial diagnosis of TED ≥ 2 years but < 10 years prior to Screening. Clinical diagnosis of stable chronic TED, as determined by participant medical records indicating a CAS ≤ 1 in both eyes for at least 1 year prior to Screening or all of the following: a. no progression in proptosis for at least 1 year prior to Screening b. no progression in diplopia for at least 1 year prior to Screening c. no new inflammatory TED symptoms for at least 1 year prior to Screening
		Proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED), as estimated by treating physician, and/or proptosis ≥ 18 mm	Proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED), as estimated by treating physician, and/or proptosis ≥ 3 mm above normal for race and gender
Participants were euthyroid or with mild hypo- or hyperthyroidism defined as FT_4 and FT_3 levels < 50% above or below the normal limits. Every effort was made to correct the mild hypo- or hyperthyroidism promptly.	Participants must have been euthyroid with the Baseline disease under control or have mild hypo- or hyperthyroidism (defined as FT_4 and FT_3 levels < 50% above or below the normal limits) at Screening. Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.	Participants must have been euthyroid with the baseline disease under control or had mild hypo- or hyperthyroidism (defined as FT_4 and FT_3 levels < 50% above or below the normal limits) at Screening. Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial	Participants must have been euthyroid with the baseline disease under control or had mild hypo- or hyperthyroidism (defined as FT_4 and FT_3 levels < 50% above or below the normal limits) at Screening. Every effort was made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the trial.
TED01RV	**Trial HZNP-TEP-301 (OPTIC)**	**Trial HZNP-TEP-303 (OPTIC-J)**	**Trial HZNP-TEP-403**
Did not require immediate surgical ophthalmological intervention	Did not require immediate surgical ophthalmological intervention and was not planning corrective surgery/irradiation during the course of the trial	Did not require immediate surgical ophthalmological intervention	Did not require immediate surgical ophthalmological intervention and was not planning corrective surgery/irradiation during the course of the trial
ALT/AST ≤ 3 × ULN for the reference laboratory; serum creatinine < 1.5 × ULN according to age	ALT or AST ≤ 3 × ULN or serum creatinine < 1.5 × ULN according to age at Screening		
Participants with diabetes were well controlled, demonstrated by no change in diabetes medication (oral or insulin) > 10% for the previous 60 days.	Diabetic participants must have had well-controlled stable disease (defined as HbA1c < 9.0% with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening).	Diabetic participants must have had HbA1c ≤ 8.0% at Screening	Diabetic participants must have had HbA1c ≤ 8.0% at Screening

		Participants with a history of IBD (ulcerative colitis or Crohn's disease) must have been in clinical remission for at least 3 months, with no history of bowel surgery within 6 months prior to Screening and no planned surgery during the trial. Concomitant stable therapies for IBD without modifications in the 3 months prior to Screening were allowed	Participants with a history of IBD, ulcerative colitis or Crohn's disease must have been in clinical remission for at least 3 months, with no history of bowel surgery within 6 months prior to Screening and no planned surgery during the trial. Concomitant stable therapies for IBD without modifications in the 3 months prior to Screening were allowed
Women of childbearing potential, including those with an onset of menopause within the previous 2 years (women without at least 12 months of nontherapy-induced amenorrhea or not surgically sterile [absence of ovaries and/or uterus]), required a negative pregnancy test at screening and all treatment visits up to follow-up Visit 2 (Week 36) post-randomization. They were also willing and able to use 2 different methods of contraceptive, one of which had to be oral.	Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]) must have had a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (ie, prior to each dose and through Week 48 of the Follow-up Period); participants who were sexually active with a non-vasectomized male partner must have agreed to use 2 reliable forms of contraception during the trial, one of which was recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must have started at least 1 full cycle prior to Baseline and continued for 180 days after the last dose of IP. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, included implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner.	Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) must have had a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified time points); participants who were sexually active with a non-vasectomized male partner must have agreed to use 2 reliable forms of contraception during the trial, one of which was recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must have been started at least 1 full cycle prior to baseline and continued for 180 days after the last dose of IP. Highly effective contraceptive methods (failure rate < 1% per year), when used consistently and correctly, include implants, injectables, combination oral contraceptives, some intrauterine devices, tubal ligation, sexual abstinence and vasectomized partner	Women of childbearing potential (including those with an onset of menopause < 2 years prior to Screening, non-therapy-induced amenorrhea for < 12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) must have had a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified time points (ie, prior to each dose and throughout participant's participation); participants who were sexually active with a non-vasectomized male partner must have agreed to use 2 reliable forms of contraception during the trial, one of which was recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must have been started at least 1 full cycle prior to Baseline and continued for 180 days after the last dose of IP. Highly effective contraceptive methods (failure rate < 1% per year), when used consistently and correctly, include implants, injectables, combination oral contraceptives, some intrauterine devices, sexual abstinence and vasectomized partner.
Male participants had to be surgically sterile or agreed to use a barrier contraceptive method. Contraception had to be continued for 3 months after the last dose of IP.	Male participants must have been surgically sterile or, if sexually active with a female partner of childbearing potential, must have agreed to use a barrier contraceptive method from Screening through 180 days after the last dose of IP.		
	Participant was willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.	Participant was willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial	Participant was willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.
No previous medical or surgical therapy for TED, excluding local supportive measures and oral steroids if the maximum cumulative dose was < 1000 mg methylprednisolone or equivalent. There were at least 6 weeks between last administration of steroids and trial randomization.			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAS = Clinical Activity Score; FT3 = free triiodothyronine; FT4 = free thyroxine; HbA1c = glycated hemoglobin; IBD = inflammatory bowel disease; IP = investigational product; TED = thyroid eye disease; ULN = upper limit of normal

Table 19. Studies TED01RV, OPTIC, OPTIC-J and 403. Exclusion criteria.

TED01RV	Trial HZNP-TEP-301 (OPTIC)	Trial HZNP-TEP-303 (OPTIC-J)	Trial HZNP-TEP-403
Decreased BCVA due to optic neuropathy as defined by a decrease in vision within the last 6 months of 2 lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement	Decreased BCVA due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months	Decreased BCVA due to optic neuropathy, as defined by a decrease in vision of 2 lines on the Snellen chart (or equivalent), new visual field defect or color defect secondary to optic nerve involvement within the last 6 months	Decreased BCVA due to optic neuropathy, defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect secondary to optic nerve involvement within the last 6 months
Corneal decompensation unresponsive to medical management	Corneal decompensation unresponsive to medical management	Corneal decompensation unresponsive to medical management	Corneal decompensation unresponsive to medical management in the study eye
Improvement in CAS of ≥ 2 points between Screening and Baseline	Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline	Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline	
	Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline	Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline	Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline
Previous orbital irradiation	Previous orbital irradiation or surgery for TED	Previous orbital irradiation or surgery for TED	Prior orbital irradiation or orbital decompression in the study eye
			Prior strabismus surgery
			Alanine aminotransferase or aspartate aminotransferase > 3 × the upper limit of normal or estimated glomerular filtration rate ≤ 30 mL/min/1.73 m^2 at Screening
Treatment with oral or IV steroids within the previous 3 months, except oral steroids for the treatment of TED with a cumulative dose of < 1000 mg methylprednisolone or equivalent, provided there was a 6-week washout prior to trial randomization. Administration of any other immunosuppressive agent for any indication in the previous 3 months. Topical steroids for dermatological conditions were not excluded.	Any steroid use (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of < 1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops was allowed if discontinued at least 4 weeks prior to Screening.	Any steroid use (IV, injection or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV, injection or oral) with a cumulative dose of < 1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops were allowed if discontinued at least 4 weeks prior to Screening	Use of any steroid (IV, oral, steroid eye drops) for the treatment of TED or other conditions within 3 weeks prior to Screening. Steroids were not to be initiated during the trial. Exceptions included topical and inhaled steroids and steroids used to treat infusion reactions.
	Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids were allowed).	Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids were allowed)	
	Selenium and biotin must have been discontinued 3 weeks prior to Screening and must not have been restarted during the clinical trial; however, taking a multivitamin that included selenium and/or biotin was allowed.	Selenium must have been discontinued 3 weeks prior to Screening and must not have been restarted during the trial; however, taking a multivitamin that included selenium (< 100 mcg daily) was allowed	
Any previous treatment with rituximab (Rituxan® or MabThera®)	Any previous treatment with rituximab (Rituxan® or MabThera®) or tocilizumab (Actemra® or Roactemra®) Use of any other non-steroid immunosuppressive agent within 3 months prior to Screening	Any previous treatment with rituximab (Rituxan®) within the last 12 months or tocilizumab (Actemra®) within the last 6 months prior to Screening or use of any other non-steroid immunosuppressive agent within 3 months prior to Screening	Any treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the first infusion of IP or tocilizumab (Actemra® or Roactemra®) within 6 months prior to the first infusion of IP. Use of any other non-steroid immunosuppressive agent within 3 months prior to the first infusion of IP
			Treatment with any monoclonal antibody within 3 months prior to Screening
Any treatment with any investigational agent for any condition in the past 60 days or treatment with an investigational agent for any condition during the trial	Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial	Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial	Use of an investigational agent for any condition within 60 days or 5 half-lives, whichever was longer, prior to Screening or anticipated use during the course of the trial
Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude trial participation or complicate interpretation of trial results	Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would have precluded trial participation or complicated interpretation of trial results	Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would have precluded trial participation or complicated interpretation of trial results	Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would have precluded trial participation or complicate interpretation of trial results
Bleeding diathesis	Bleeding diathesis that, in the judgment of the Investigator, would have precluded inclusion in the clinical trial		
Malignant condition in the past 12 months (with the exception of successfully treated basal cell carcinoma of the skin)	Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin)	Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin)	Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ)
Pregnant or lactating women	Pregnant or lactating women	Pregnant or lactating women	Pregnant or lactating women
Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the investigator or as reported by the participant	Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the participant	Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the participant	Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator, or as reported by the participant

TED01RV	Trial HZNP-TEP-301 (OPTIC)	Trial HZNP-TEP-303 (OPTIC-J)	Trial HZNP-TEP-403

	Biopsy-proven or clinically suspected IBD (eg, diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis)		
Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies	Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies	Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies	Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies
Any other condition that in the opinion of the Investigator would preclude inclusion in the trial	Any other condition that, in the opinion of the Investigator, would have precluded inclusion in the trial	Any other condition that, in the opinion of the Investigator, would have precluded inclusion in the trial	Any other condition that, in the opinion of the Investigator, would have precluded inclusion in the trial
Participants who had already been randomized and received treatment under this protocol. Under no circumstances were participants who were enrolled in this trial permitted to be re-randomized and enrolled for a second course of treatment.	Previous enrollment in this trial or participation in a prior teprotumumab clinical trial	Previous enrollment in this trial or participation in a prior teprotumumab clinical trial	Any previous treatment with teprotumumab, including previous enrollment in this trial or participation in a prior teprotumumab trial
	Human immunodeficiency virus, hepatitis C or hepatitis B infections	Human immunodeficiency virus, hepatitis C or hepatitis B infections	Poorly controlled human immunodeficiency virus infection or untreated or positive viral load for hepatitis C or hepatitis B infections
Poorly controlled diabetes			
Platelet count < 100×10^9/L at screening or Baseline. Participants with platelet count < 35×10^9/L following dosing were to be withdrawn.			
Hemoglobin concentration > 2 g/dL below the lower limit of the local laboratory reference range			

BCVA = best corrected visual acuity; CAS = Clinical Activity Score; IBD = inflammatory bowel disease; IP = investigational product; IV = intravenous; TED = thyroid eye disease

Table 20. Studies TED01RV, OPTIC, OPTIC-J and 403. Baseline demographic characteristics.

	Trials in Acute TED								Trial in Chronic TED	
	TED01RV		OPTIC		OPTIC-J		Combined Analyses		HZNP-TEP-403	
Parameter Statistic	Placebo (N = 45)	Tepro (N = 43)	Placebo (N = 42)	Tepro (N = 41)	Placebo (N = 27)	Tepro (N = 27)	Placebo (N = 114)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 42)
Sex, n (%)										
Female	36 (80.0)	29 (67.4)	31 (73.8)	29 (70.7)	20 (74.1)	18 (66.7)	87 (76.3)	76 (68.5)	18 (90.0)	32 (76.2)
Male	9 (20.0)	14 (32.6)	11 (26.2)	12 (29.3)	7 (25.9)	9 (33.3)	27 (23.7)	35 (31.5)	2 (10.0)	10 (23.8)
Age (years)										
Mean (SD)	53.7 (12.93)	51.3 (10.67)	48.9 (12.96)	51.6 (12.63)	50.0 (13.35)	46.6 (14.18)	51.1 (13.10)	50.3 (12.39)	49.0 (16.45)	48.6 (14.37)
Median	55.0	51.0	51.5	53.0	51.0	46.0	52.0	50.0	49.0	49.0
Min, max	20, 77	22. 72	20, 73	31, 79	22, 74	20, 73	20, 77	20, 79	23, 75	18, 73
Age category, n (%)										
< 65 years	36 (80.0)	39 (90.7)	38 (90.5)	32 (78.0)	23 (85.2)	25 (92.6)	97 (85.1)	96 (86.5)	16 (80.0)	37 (88.1)
≥ 65 years	9 (20.0)	4 (9.3)	4 (9.5)	9 (22.0)	4 (14.8)	2 (7.4)	17 (14.9)	15 (13.5)	4 (20.0)	5 (11.9)
Race, n (%)										
Asian	2 (4.4)	1 (2.3)	1 (2.4)	2 (4.9)	27 (100)	27 (100)	30 (26.3)	30 (27.0)	1 (5.0)	7 (16.7)
Black/AA	4 (8.9)	5 (11.6)	2 (4.8)	4 (9.8)	0	0	6 (5.3)	9 (8.1)	5 (25.0)	10 (23.8)
NH/PI	0	1 (2.3)	0	0	0	0	0	1 (0.9)	0	0
White	39 (86.7)	36 (83.7)	37 (88.1)	35 (85.4)	0	0	76 (66.7)	71 (64.0)	12 (60.0)	22 (52.4)
Other[a]	0	0	2 (4.8)	0	0	0	2 (1.8)	0	2 (10.0)	3 (7.1)
Race category, n (%)										
White	39 (86.7)	36 (83.7)	37 (88.1)	35 (85.4)	0	0	76 (66.7)	71 (64.0)	12 (60.0)	22 (52.4)
Asian	2 (4.4)	1 (2.3)	1 (2.4)	2 (4.9)	27 (100)	27 (100)	30 (26.3)	30 (27.0)	1 (5.0)	7 (16.7)
Other	4 (8.9)	6 (14.0)	4 (9.5)	4 (9.8)	0	0	8 (7.0)	10 (9.0)	7 (35.0)	13 (31.0)
Ethnicity, n (%)										
Hispanic/ Latino	4 (8.9)	2 (4.7)	1 (2.4)	2 (4.9)	0	0	5 (4.4)	4 (3.6)	5 (25.0)	6 (14.3)
Not Hispanic/ Latino	41 (91.1)	41 (95.3)	41 (97.6)	39 (95.1)	27 (100)	27 (100)	109 (95.6)	107 (96.4)	15 (75.0)	36 (85.7)

Table 21. Studies TED01RV, OPTIC, OPTIC-J and 403. Baseline disease characteristics

	Trials in Acute TED								Trial in Chronic TED	
	TED01RV		OPTIC		OPTIC-J		Combined Analyses		HZNP-TEP-403	
Parameter Statistic	Placebo (N = 45)	Tepro (N = 43)	Placebo (N = 42)	Tepro (N = 41)	Placebo (N = 27)	Tepro (N = 27)	Placebo (N = 114)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 42)
Study eye, n (%)										
Right	21 (46.7)	26 (60.5)	20 (47.6)	22 (53.7)	15 (55.6)	13 (48.1)	56 (49.1)	61 (55.0)	13 (65.0)	27 (64.3)
Left	24 (53.3)	17 (39.5)	22 (52.4)	19 (46.3)	12 (44.4)	14 (51.9)	58 (50.9)	50 (45.0)	7 (35.0)	15 (35.7)
Tobacco use status - actual, n (%)										
User	18 (40.0)	11 (25.6)	8 (19.0)	9 (22.0)	4 (14.8)	4 (14.8)	30 (26.3)	24 (21.6)	2 (10.0)	6 (14.3)
Non-user	27 (60.0)	32 (74.4)	34 (81.0)	32 (78.0)	23 (85.2)	23 (85.2)	84 (73.7)	87 (78.4)	18 (90.0)	36 (85.7)
Tobacco use status as randomized, n (%)										
User	16 (35.6)	10 (23.3)	9 (21.4)	9 (22.0)	4 (14.8)	4 (14.8)	29 (25.4)	23 (20.7)	NA	NA
Non-user	29 (64.4)	33 (76.7)	33 (78.6)	32 (78.0)	23 (85.2)	23 (85.2)	85 (74.6)	88 (79.3)	NA	NA
Time since diagnosis of TED (months)[a]										
Mean (SD)	6.06 (2.490)	5.57 (1.953)	6.42 (2.377)	6.20 (2.328)	5.18 (2.159)	4.27 (2.422)	5.98 (2.400)	5.49 (2.321)	64.57 (19.315)	61.09 (22.602)
Median	6.55	5.35	6.83	6.32	5.22	4.24	6.19	5.28	69.19	59.12
Min, max	1.2, 11.0	2.3, 10.1	1.1, 10.3	0.9, 9.7	1.7, 8.9	0.5, 8.7	1.1, 11.0	0.5, 10.1	32.0, 94.1	26.9, 104.9
Proptosis for study eye (mm)										
Mean (SD)	23.10 (2.934)	23.40 (3.124)	23.20 (3.208)	22.62 (3.322)	20.39 (2.423)	21.07 (2.456)	22.50 (3.135)	22.55 (3.159)	24.00 (2.824)	24.60 (3.007)
Median	22.50	23.00	22.75	23.00	20.00	20.00	22.00	22.00	23.00	25.00
Min, max	16.0, 31.5	17.0, 33.0	18.5, 30.0	16.0, 31.0	14.5, 26.0	17.5, 27.0	14.5, 31.5	16.0, 33.0	20.0, 28.0	18.5, 31.0
CAS for study eye										
Mean (SD)	5.2 (0.74)	5.0 (0.97)	5.3 (0.98)	5.1 (0.88)	4.0 (0.76)	4.5 (1.25)	5.0 (1.00)	4.9 (1.04)	0.5 (0.51)	0.3 (0.47)
Median	5.0	5.0	5.0	5.0	4.0	4.0	5.0	5.0	0.5	0.0
Min, max	4, 7	2, 7	4, 7	4, 7	3, 5	3, 7	3, 7	2, 7	0, 1	0, 1
CAS for study eye, n (%)										
0	0	0	0	0	0	0	0	0	10 (50.0)	29 (69.0)
1	0	0	0	0	0	0	0	0	10 (50.0)	13 (31.0)
2	0	1 (2.3)	0	0	0	0	0	1 (0.9)	0	0
3	0	0	0	0	8 (29.6)	8 (29.6)	8 (7.0)	8 (7.2)	0	0
4	6 (13.3)	11 (25.6)	10 (23.8)	10 (24.4)	12 (44.4)	6 (22.2)	28 (24.6)	27 (24.3)	0	0
5	24 (53.3)	17 (39.5)	14 (33.3)	18 (43.9)	7 (25.9)	6 (22.2)	45 (39.5)	41 (36.9)	0	0
6	13 (28.9)	12 (27.9)	13 (31.0)	10 (24.4)	0	6 (22.2)	26 (22.8)	28 (25.2)	0	0
7	2 (4.4)	2 (4.7)	5 (11.9)	3 (7.3)	0	1 (3.7)	7 (6.1)	6 (5.4)	0	0
Binocular diplopia score, n (%)										
0 – no diplopia	14 (31.1)	5 (11.6)	14 (33.3)	13 (31.7)	7 (25.9)	5 (18.5)	35 (30.7)	23 (20.7)	16 (80.0)	28 (66.7)
1 – intermittent	19 (42.2)	16 (37.2)	9 (21.4)	7 (17.1)	1 (3.7)	5 (18.5)	29 (25.4)	28 (25.2)	2 (10.0)	6 (14.3)
2 – inconstant	8 (17.8)	7 (16.3)	12 (28.6)	12 (29.3)	9 (33.3)	11 (40.7)	29 (25.4)	30 (27.0)	1 (5.0)	2 (4.8)
3 - constant	4 (8.9)	15 (34.9)	7 (16.7)	9 (22.0)	10 (37.0)	6 (22.2)	21 (18.4)	30 (27.0)	1 (5.0)	6 (14.3)

CAS = Clinical Activity Score; ITT = intent-to-treat; max = maximum; min = minimum; NA = not applicable; SD = standard deviation; TED = thyroid eye disease; Tepro = teprotumumab

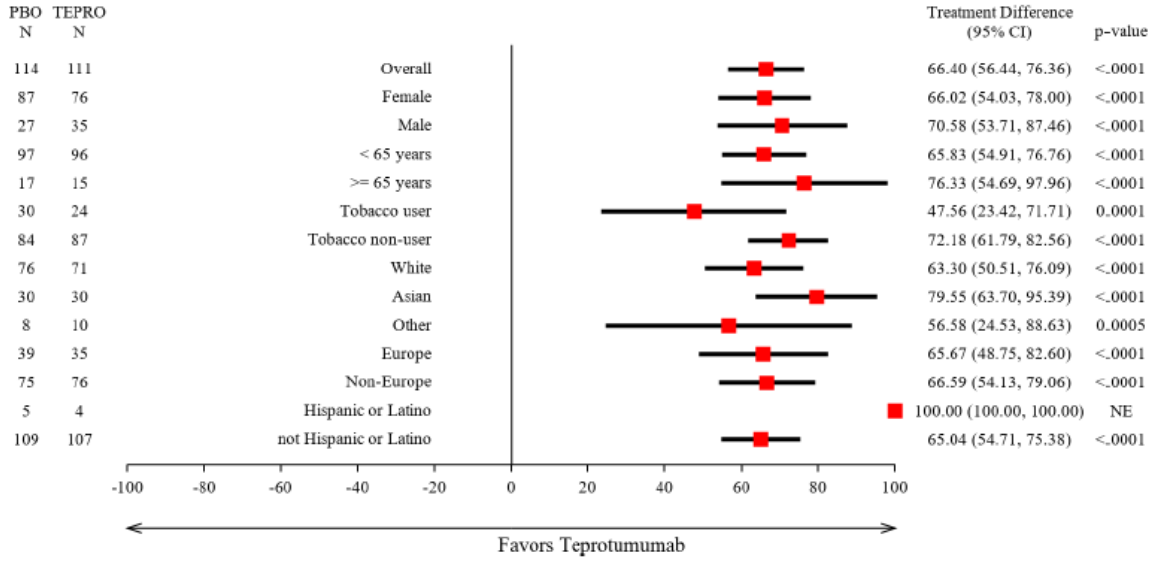
a. Time since diagnosis of TED was missing for 1 participant in the teprotumumab group in TED01RV.

Table 22. Clinical Activity Score (CAS) Assessment.

Item [1]	Description
1.	Spontaneous orbital pain.
2.	Gaze evoked orbital pain.
3.	Eyelid swelling that is considered to be due to active (inflammatory phase) TED/GO.
4.	Eyelid erythema.
5.	Conjunctival redness that is considered to be due to active (inflammatory phase) TED/GO (ignore "equivocal" redness).
6.	Chemosis.
7.	Inflammation of caruncle or plica.

[1] Each item is scored (1=present; 0=absent) and scores for each item are summed for total score.

Figure 4. Studies TED01RV, OPTIC, and OPTIC-J. Difference in Proptosis Responder Rate at Week 24 by Subgroup in the Acute TED Trials (ITT Analysis Set; Study Eye; Combined Analysis).



CI = confidence interval; ITT = intent-to-treat; NE = not estimable; PBO = placebo; TED = thyroid eye disease; TEPRO = teprotumumab
Note: p-values were estimated from Cochran-Mantel-Haenszel test adjusted for trial and tobacco use status.

Figure 5. Study 403. Difference in Proptosis Responder Rate at Week 24 by Subgroup in the Chronic TED Trial (ITT Analysis Set; Study Eye).

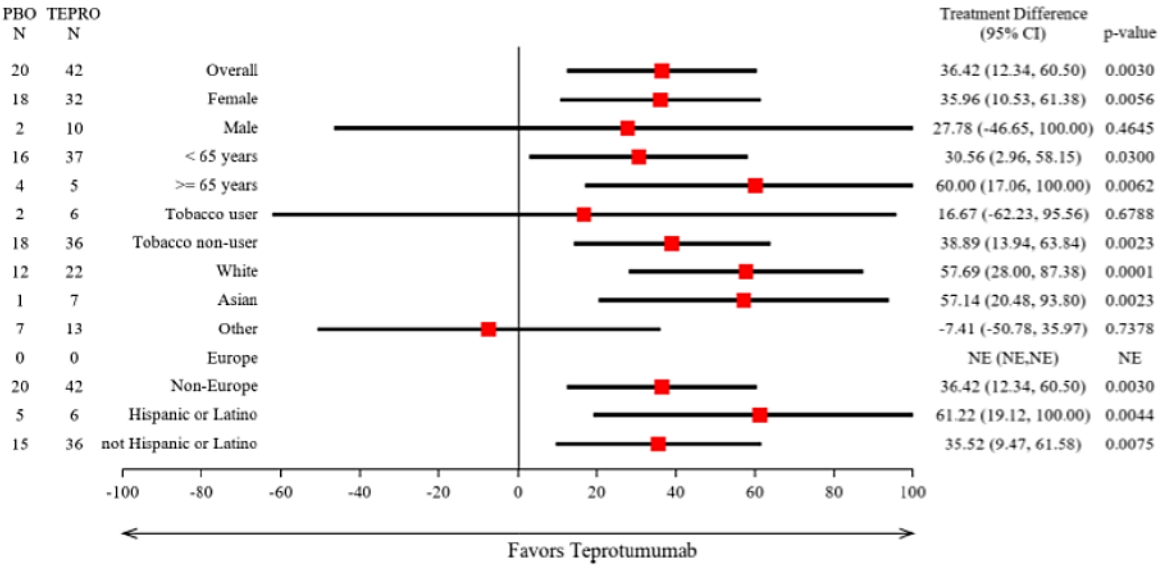


Table 23. Study HZNP-TEP-401. Mean change from baseline in GO-QoL Visual Function, Appearance and Overall Scores at Week 12 and Week 21 (Treated Population).

	Treated Population (N=22)
Visual Function - Baseline mean (SD)	52.85 (24.602)
Week 12	(n=21)
Mean change (SD)	25.37 (28.094)
Median change	25.00
Min change, max change	-10.7, 78.6
95% CI	12.58, 38.16
Week 21	(n=20)
Mean change (SD)	25.70 (25.774)
Median change	25.00
Min change, max change	-12.5, 66.1
95% CI	13.64, 37.76
Appearance - Baseline mean (SD)	42.90 (26.677)
Week 12	(n=21)
Mean change (SD)	25.60 (28.703)
Median change	18.75
Min change, max change	-12.5, 87.5
95% CI	12.53, 38.66
Week 21	(n=20)
Mean change (SD)	23.75 (26.173)
Median change	25.00
Min change, max change	-18.8, 75.0
95% CI	11.50, 36.00
Overall - Baseline mean (SD)	47.76 (21.423)
Week 12	(n=21)
Mean change (SD)	25.65 (25.860)
Median change	18.75
Min change, max change	-4.6, 83.3
95% CI	13.87, 37.42
Week 21	(n=20)
Mean change (SD)	24.89 (20.980)
Median change	20.31
Min change, max change	-12.5, 70.8
95% CI	15.07, 34.71

Table 24. Safety analysis: Patient disposition (Double-masked Population).

	Acute TED			Chronic TED			Overall		
Disposition, n (%)	**Placebo (N = 113)**	**Tepro (N = 111)**	**Overall (N = 224)**	**Placebo (N = 20)**	**Tepro (N = 41)**	**Overall (N = 61)**	**Placebo (N = 133)**	**Tepro (N = 152)**	**Overall (N = 285)**
Completed Double-masked Treatment Period	106 (93.8)	103 (92.8)	209 (93.3)	19 (95.0)	39 (95.1)	58 (95.1)	125 (94.0)	142 (93.4)	267 (93.7)
Discontinued early from Double-masked Treatment Period	7 (6.2)	8 (7.2)	15 (6.7)	1 (5.0)	2 (4.9)	3 (4.9)	8 (6.0)	10 (6.6)	18 (6.3)
Reason for early discontinuation from Double-masked Treatment Period									
Adverse event	2 (1.8)	6 (5.4)	8 (3.6)	1 (5.0)	0	1 (1.6)	3 (2.3)	6 (3.9)	9 (3.2)
Lack of efficacy	2 (1.8)	0	2 (0.9)	0	0	0	2 (1.5)	0	2 (0.7)
Withdrawal by participant	1 (0.9)	1 (0.9)	2 (0.9)	0	0	0	1 (0.8)	1 (0.7)	2 (0.7)
Lost to follow-up	0	0	0	0	2 (4.9)	2 (3.3)	0	2 (1.3)	2 (0.7)
Other	2 (1.8)	1 (0.9)	3 (1.3)	0	0	0	2 (1.5)	1 (0.7)	3 (1.1)
Completed the trial	104 (92.0)	86 (77.5)	190 (84.8)	18 (90.0)	31 (75.6)	49 (80.3)	122 (91.7)	117 (77.0)	239 (83.9)
Discontinued early from the trial	9 (8.0)	25 (22.5)	34 (15.2)	1 (5.0)	3 (7.3)	4 (6.6)	10 (7.5)	28 (18.4)	38 (13.3)
Reason for early discontinuation from the trial									
Adverse event	3 (2.7)	6 (5.4)	9 (4.0)	0	0	0	3 (2.3)	6 (3.9)	9 (3.2)
Lack of efficacy	2 (1.8)	0	2 (0.9)	0	0	0	2 (1.5)	0	2 (0.7)
Physician decision	0	2 (1.8)	2 (0.9)	0	0	0	0	2 (1.3)	2 (0.7)
Protocol deviation	0	1 (0.9)	1 (0.4)	0	0	0	0	1 (0.7)	1 (0.4)
Withdrawal by participant	1 (0.9)	2 (1.8)	3 (1.3)	1 (5.0)	0	1 (1.6)	2 (1.5)	2 (1.3)	4 (1.4)
Disease relapse	0	10 (9.0)	10 (4.5)	0	0	0	0	10 (6.6)	10 (3.5)
Lost to follow-up	0	0	0	0	3 (7.3)	3 (4.9)	0	3 (2.0)	3 (1.1)
Other	3 (2.7)	4 (3.6)	7 (3.1)	0	0	0	3 (2.3)	4 (2.6)	7 (2.5)
Have data collected in the Follow-up Period	47 (41.6)	98 (88.3)	145 (64.7)	8 (40.0)	26 (63.4)	34 (55.7)	55 (41.4)	124 (81.6)	179 (62.8)

TED = thyroid eye disease; Tepro = teprotumumab

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