25 April 2025
EMA/175329/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tepezza

International non-proprietary name: teprotumumab

Procedure No. EMEA/H/C/006396/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BAP	Bone Alkaline Phosphatase
CAS	Clinical Activity Score
CDC	Complement-Dependent Cytotoxicity
CE-SDS	Capillary Electrophoresis-Sodium Dodecyl Sulfate
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CIEX	Cation Exchange Chromatography
CL	Clearance
CMC	Chemistry, Manufacturing, and Controls
COVID-19	Coronavirus Disease 2019
CrCL	Creatinine Clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DME	Diabetic Macular Edema
DNA	Deoxyribonucleic Acid
ECLIA	Electrochemiluminescence Immunoassay

EAP	Expanded Access Program
EMA	European Medicines Agency
EOPC	End-of-Production Cells
FcRn	Neonatal Fc Receptor
FDA	Food and Drug Administration
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GMP	Good Manufacturing Practice
GO-QoL	Graves' Ophthalmopathy Quality of Life
HCP	Host Cell Proteins
HbA1c	Glycated Hemoglobin
HLT	High-Level Term
HMW	High Molecular Weight
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation
IGF-1R	Insulin-like Growth Factor-1 Receptor
IND	Investigational New Drug
IP	Investigational Product
IRR	Infusion-Related Reaction
ITT	Intent-to-Treat
KIRA	Kinase Receptor Assay
LMW	Low Molecular Weight
LS	Least Squares
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MVM	Minute Virus of Mice
NOR	Normal Operating Range
NSCLC	Non-Small Cell Lung Cancer
OL	Open-Label
PAR	Proven Acceptable Range
pcVPC	Prediction-Corrected Visual Predictive Checks

PK	Pharmacokinetics
PopPK	Population Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PRV	Pseudorabies Virus
PT	Preferred Term 1
Q3W	Every 3 Weeks
QW	Every Week
RVLP	Retrovirus-like Particles
SAE	Serious Adverse Event
SEC	Size-Exclusion Chromatography
SE-UHPLC	Size-Exclusion Ultra High-Performance Liquid Chromatography
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SV-AUC	Sedimentation Velocity Analytical Ultracentrifugation
TEAE	Treatment-Emergent Adverse Event
TED	Thyroid Eye Disease
TSE	Transmissible Spongiform Encephalopathies
UF/DF	Ultrafiltration/Diafiltration
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 25 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Tepezza, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0381/2023 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance teprotumumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	25 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 February 2025
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a <positive> <negative> opinion for granting a marketing authorisation to Tepezza on	25 April 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Thyroid eye disease (TED) is also known as Graves' orbitopathy (GO) or thyroid-associated orbitopathy (TAO). It is primarily a disease of the orbit where the orbital tissue undergoes inflammation, expansion and remodeling. Acute TED is characterized by inflammation of the orbital connective tissue, inflammation and fibrosis of the extraocular muscles and adipogenesis within the orbits. The inflammation and expansion of tissue volume behind the eye result in proptosis, one of the most prevalent and widely known signs of TED. Proptosis can lead to diplopia, strabismus, corneal ulceration and optic nerve compression, which can threaten sight. During the chronic phase, inflammation subsides and the disease plateaus, but significant remodeling of orbital tissue remains that does not return to baseline. For the large majority of patients, acute TED lasts 1 to 3 years and then the inflammation subsides to leave what was historically believed to be permanent sequelae of chronic TED. As acute TED progresses and transitions into chronic disease, the histopathology becomes increasingly fibrotic in nature. The clinical manifestations of TED, such as disturbances in visual function, physical discomfort and facial disfigurement, can result in significant psychological morbidity that can be detrimental to a patient's quality of life. Visual impairment can have a significant impact on functional status, resulting in limitations of daily activities, such as work productivity. The facial disfigurement caused by TED negatively influences facial expression, communication, self-perception and social interactions. Patients with TED are at increased risk for anxiety and depression (Kahaly et al, 2005). A study examining quality of life and occupational disability in 192 patients with TED showed an association between diplopia and occupational disability (Ponto et al, 2009). Among them, 28% were disabled, 5% retired early and 3% had lost their jobs. The clinical manifestations of TED can lead to marked reductions in health and quality of life, comparable to diabetes and other chronic diseases, and significant socioeconomic consequences (Wiersinga, 2012; Ponto et al, 2013). An analysis showed a significantly higher risk of death by suicide in TED patients compared to matched controls (Ferlov-Schwensen et al, 2017).

2.1.2. Epidemiology and risk factors

The estimated incidence in Europe is 0.54–1.9 cases/100,000/year in men and 2.67–8 cases/100,000/year in women. TED is most commonly mild and non-progressive, with moderate-to-severe forms accounting for only 5–6% of cases. Pathophysiology of TED is still incompletely understood, cigarette smoking is the strongest modifiable risk factor for TED (odds ratio among smokers vs. nonsmokers, 7.7).

2.1.3. Aetiology and pathogenesis

Although TED is most commonly associated with Graves' hyperthyroidism/disease, TED also occurs rarely in patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis and euthyroid states. Other risk factors include demographic (female sex and European ethnicity), anatomical (wider lateral wall orbital angle), and environmental (tobacco smoking, radioactive iodine therapy) considerations. The initiating trigger for TED is not well understood, but the scientific literature indicates that autoimmune activation and proliferation of orbital fibroblasts is central to the pathophysiology of TED. These express Thyroid Stimulating

Hormone Receptor (TSHR) and anti-insulin-like growth factor-1 receptor (IGF-1R) which can be activated by circulating autoantibodies; all of which are expressed at higher levels in Graves' TED patients. Cases of TED in which anti-TSHR antibodies are absent, such as in Hashimoto's thyroiditis and euthyroid TED, exhibit autoantibodies against ocular muscle and orbital soft-tissue antigens: calsequestrin, collagen XIII, flavoprotein, and protein G2s. Orbital inflammation leads to extraocular muscle oedema, which can restrict motility and cause diplopia. Increased orbital fat and immune infiltration increase the volume of orbital soft tissue, leading to venous congestion and proptosis. Worsening congestion can compress the optic nerve, leading to neuropathy and permanent vision loss. Elevated orbital pressure can lead to forward protrusion of the eye, known as exophthalmos (proptosis).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The natural history of TED involves an initial progressive worsening of signs and symptoms with visible signs of inflammation known as the active/acute phase (for the large majority of patients, active/acute TED lasts 1 to 3 years) followed by an inactive/chronic phase during which inflammation subsides and no further deterioration occurs, but some symptoms and remodeling of orbital tissue and protoptosis may remain. In the active/acute phase, patients may present with orbital pain, periorbital inflammation, proptosis, eyelid retraction, strabismus and diplopia. Sight-threatening disease affects 6% of TED patients. As active/acute TED progresses and transitions into inactive/chronic disease, the histopathology becomes increasingly fibrotic in nature. European Group on Graves' orbitopathy (EUGOGO) has published a classification of GO or TED based on severity (Bartalena et al, 2021).

Table 1. *Classification of Severity of Graves' Orbitopathy (GO) or Thyroid Eye Disease TED)*

Classification	Features
Mild GO or TED	Patients whose features of GO or TED have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: minor lid retraction (<2mm) mild soft-tissue involvement exophthalmos <3mm for race and gender no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO or TED	Patients without sight-threatening GO or TED whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active/acute) or surgical intervention (if inactive/chronic). They usually have two or more of the following: lid retraction ≥2mm moderate or severe soft-tissue involvement exophthalmos ≥3mm above normal for race and gender inconstant or constant diplopia
Sight-threatening (very severe) GO or TED	Patients with dysthyroid optic neuropathy and/or corneal breakdown

2.1.5. Management

Most patients with mild GO or TED experience spontaneous resolution of eye manifestations. Therefore, a watchful strategy and local treatments are sufficient. Conversely, sight-threatening GO or TED is an emergency that should be treated immediately.

In patients with moderate-to-severe GO or TED, the initial goal is to shorten the acute/active phase of the disease and improve subjective and objective eye manifestations. In general, the most commonly used medical therapy for treating moderate to severe GO or TED patients in the acute/active phase is corticosteroids. Combination of a moderate cumulative dose of i.v. methylprednisolone + a moderate daily dose of oral enteric-coated mycophenolate sodium is the EUGOGO recommended first-line treatment for patients with moderate-to-severe and active/acute GO or TED (with or without diplopia). An alternative first-line treatment is the administration of high single doses of i.v. methylprednisolone starting with 0.75 g per day and week for six consecutive weeks. This regimen is recommended for patients with constant/inconstant diplopia, severe proptosis, and severe inflammatory soft-tissue changes. Once GO or TED is in inactive/chronic phase, surgery can be performed to repair the sequelae of TED; however, multiple sequential surgeries (orbital decompression, strabismus and lid retraction) are often required to fully address the condition.

2.2. About the product

Teprotumumab (HZN-001) is a human monoclonal antibody (mAb) that targets and inhibits the insulin-like growth factor-1 receptor (IGF-1R)/thyroid-stimulating hormone receptor signalling complex, thereby blocking the autoimmune activation of orbital fibroblasts, potentially inhibiting the underlying pathogenesis of TED.

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) is presented as a powder for concentrate for solution for infusion containing 500 mg of teprotumumab as active substance (AS). Other ingredients are: histidine, histidine hydrochloride monohydrate, polysorbate 20 (E432) and trehalose dihydrate.

The product is available in a 20 mL type I clear glass vial, with a grey stopper (flurotec coated chlorobutyl) and an aluminium seal.

2.3.2. Active substance

2.3.2.1. General information

Teprotumumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against human insulin-like growth factor-1 receptor (IGF-1R). The antibody is composed of 2 heterodimers, each consisting of a heavy and light chain. The 4 peptide chains are linked by disulphide bonds. The antibody bears a single carbohydrate chain in the constant region of both heavy chains. Teprotumumab has a molecular mass of 148 kDa. Teprotumumab inhibits the endogenous ligands, IGF-1 and IGF-2, from binding to IGF-1R and thus, inhibits IGF-1R downstream signalling and subsequently inflammatory responses. Despite the fact that teprotumumab is an IgG1 molecule data suggest that does not induce significant antibody-dependent cell-mediated cytotoxicity (ADCC) or other Fc-mediated activities such as antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC).

2.3.2.2. Manufacture, process controls and characterisation

The site involved in manufacturing of teprotumumab AS is listed in Table 2.

Table 2: Active substance manufacturing

Facility Name and Address	Technical Responsibility
AGC Biologics A/S Vandtaarnsvej 83b Soeborg 2860 Denmark	Manufacture of drug substance

Appropriate evidence of EU GMP compliance has been provided. The AS manufacturing process is standard for monoclonal antibodies and consists of cell culture process (cell expansion, production, and recovery) and purification process (purification, viral inactivation/removal step).

Control of Materials

The raw materials used during the AS process are listed and their respective TSE certificates are provided. The incoming testing requirements for the non-compendial grade materials are provided. All compendial materials are tested in accordance with the specific pharmacopeia monographs. The incoming testing requirements for the non-compendial grade materials used during the purification process are sufficient. Qualitative composition of the cell culture media is provided, as well as confirmation that an agreement is in place with the supplier to notify the MAH in case of changes to the media.

A detailed description of the genetic elements of expression plasmid is presented. The verified coding sequence is identical to the expected sequence, and adequate data was provided on the sequencing method.

A two-tiered cell bank system is established. A protocol has been provided for the generation of future WCBs.

All cell banks are tested in accordance with the with ICH Q5A and Q5D requirements and found to be free of mycoplasma, bacterial and fungal contamination. Cells harvested from the MCB and CLVC small scale runs were tested for genetic stability and the results demonstrate comparability between the MCB and CLVC. It is stated that analytical testing (SEC, CIEX, CE-SDS and Glycan analysis) was performed on the harvest CLVC and WCB material with comparable results aside from minor differences in CIEX basic and main peaks.

Control of critical steps and intermediates

Critical process parameters (CPP) were identified during process characterisation and the CPPs were further refined post-PPQ in 'Post-PC Failure Mode Effect Analysis and Parameter Refinement. Target values and proven acceptable ranges (PAR) are defined accordingly. Notably for process validation the normal operating range (NOR) is defined as acceptance range which in general is tighter than the PAR. Microbial controls are in-process bioburden and endotoxin measurements implemented throughout the process. The proposed hold times for process intermediates are supported by a physicochemical and microbiological intermediate hold time study and are acceptable as microbial controls are in place with acceptable limits to sufficiently guarantee microbial control of the manufacturing process.

Process validation

A stepwise life-cycle approach is followed for defining designing, and validating, and continuously verifying that the process remains in a validated state of control. Three consecutive process performance qualification (PPQ) batches were required to document process consistency and reproducibility. Overall, the manufacturing process performance can be considered robust and reproducible.

During development several process improvements/major process changes and site changes were implemented. A comprehensive comparability study was conducted which included comparison of pre- and post-change AS and FP using side-by-side analysis, release data, additional characterisation data and accelerated and stress stability studies, in line with principles of ICH Q5E. The data generated indicate that teprotumumab produced at AGC Biologics is comparable to teprotumumab produced during development demonstrated by a range of physical, biochemical, and activity-based assays. The commercial manufacturing process at AGC Biologics was also scaled up. A comparability study was performed between pre-change and post-change AS batches and included comparison of release data, characterisation data and accelerated and stress stability studies, in line with principles of ICH Q5E. It can be concluded that the comparability between

the pre- and post-change AS has been successfully demonstrated. The proposed process is highly comparable to the pre-change process, and is considered suitable for future commercial use.

Characterisation

Teprotumumab is a fully human IgG1 monoclonal antibody containing a single glycosylation site in the constant region of both heavy chains. It is directed against human IGF-1R. The physicochemical and biological properties of teprotumumab active substance have been characterised, and the product-related substances have been identified. The characteristics are considered typical for an IgG monoclonal antibody. The primary structure was characterised by amino acid sequencing and N- and C-terminal peptides analysis. Both the heavy and light chain were confirmed to match the expected sequence. The secondary structure and the higher order structure of teprotumumab were assessed. Expected disulphide bonds were confirmed experimentally. Teprotumumab is detected as predominantly monomer with minor amounts of high molecular weight (HMW) species, dimer and low molecular weight (LMW) species. Teprotumumab has expected migration for an IgG1. Post-translational modifications include N-terminal pyroglutamate formation on heavy chain (89%) and C-terminal truncation of lysine (91%). Low levels of methionine oxidation, asparagine deamidation and succinimide intermediates were detected. The glycosylation site was confirmed at N298. The main isoform of glycan was determined to be fucosylated bi-antennary agalactosylated with minor isoforms of fucosylated bi-antennary with one and two galactose residues. The applicant provided a tabulated summary of the main N-linked glycans identified and a quantification thereof.

Product-related substance

Teprotumumab was detected as predominantly monomer with minor amounts of high molecular weight species. There are two high molecular weight species present, HMW I and HMW II which are proposed to be a dimer and trimer respectively.

Product variants (including post-translational modifications and product related substances) have been adequately investigated for biological activity in connection to their observed levels.

In vitro functional activity

The proposed mechanism of action of teprotumumab is to decrease IGF-1R signalling via a reduction in phosphorylation and associated downstream signalling through these pathways. Teprotumumab binding to the receptor reduces phosphorylation. As a result, the pro-proliferative pathway resulting in cell growth and differentiation as well as protein synthesis is impeded.

A cell-based bioassay to assess inhibition of IGF-1R autophosphorylation was established. As teprotumumab is a fully human IgG mAb, Fab- and Fc-mediated biological activity have been studied. Product-related impurities have been characterised. The purification process has been designed to remove or reduce these impurities to an acceptable level. Process-related impurities derived from the cell substrate and purification process have either been demonstrated to be adequately removed during purification process or are controlled at AS release.

2.3.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications for the AS are set in accordance with ICH Q6B and include tests for appearance, osmolality, pH, identity, quantity, potency, purity and impurities, polysorbate 20, and safety related tests.

The commercial specifications take the recommendations in ICH Q6B into consideration as well as product specific knowledge for teprotumumab. The release specification confirms the overall quality of each batch of AS with respect to quantity, identity, purity and potency, as well as specific CQAs including aggregates, fragments, impurities and contaminants.

Analytical Methods

The analytical methods used for release and stability testing of the AS are described in sufficient detail. Information on method principle, equipment, reagents, procedure, evaluation and calculation and acceptance criteria are provided.

The Kinase Receptor Assay (KIRA)-ELISA is used to determine the potency of teprotumumab AS and FP for release and stability testing. The cell-based assay is designed to quantify the inhibition of the IGF-1R signalling pathway using an ELISA based assay format. Validation reports for non-compendial methods are provided. Verification data are provided for the compendial tests. Overall, the provided method validation data confirm suitability of the analytical procedures for their intended use.

Reference materials

A two-tiered (primary and working) reference standard (RS) system has been implemented for teprotumumab. The qualification testing of reference standards demonstrates suitability for intended use. Annual stability testing and shelf-life extension protocol is provided in the dossier and supported.

Batch analyses

Consistent manufacturing of AS at AGC Biologics A/S, Denmark is demonstrated with batch analyses data for commercial, validation and clinical batches. All batches comply with the AS release specification in place at the time of testing.

Container closure

The AS is dispensed into and stored in pre-sterilised 5 L and 2 L polycarbonate square bottles. The container materials are stated to meet the requirements of FDA Compliance, and USP Class VI and are classified as non-cytotoxic material. Compliance of the containers with Ph. Eur. has also been confirmed.

2.3.2.4. Stability

A shelf-life of 60 months at a storage temperature of ≤ -60°C is proposed for the AS.

The data generated at long-term conditions show no change in the quality of any of the parameters tested. The analytical procedures used in the stability program are the same as those used for batch release testing and have been fully validated in accordance with ICH requirements. The shelf-life acceptance criteria are the same as those for release testing.

The container closure used for the stability studies is the same as the commercial container closure.

Forced degradation and photodegradation studies were conducted to elucidate the degradation pathway of teprotumumab and demonstrate the stability indicating capabilities of the analytical methods.

Post-approval stability protocol and commitments are provided.

In conclusion, the AS stability data provided for the representative batches support the proposed shelf life of 60 months when stored at ≤ -60°C.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Teprotumumab finished product powder for concentrate for solution for infusion, is presented as a single vial of a preservative-free, lyophilised powder. The FP is supplied in a 20 mL, Type 1 clear glass vial, closed with an elastomeric stopper and sealed with a flip-off aluminum seal. Teprotumumab is formulated in histidine, trehalose and polysorbate 20. The finished product composition is provided in Table 3.

Table 3: Finished product composition

Material	**Function**
Active Ingredient	
Teprotumumab	Active
Excipients	
L-Histidine, Ph. Eur., USP, JP	Buffer
L-Histidine hydrochloride, monohydrate, Ph. Eur.	Buffer
α, α – Trehalose dihydrate, Ph Eur., NF, JP	Bulking agent, tonicity agent
Polysorbate 20, Ph.Eur., NF, JPE	Surfactant

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

No overages are used in the finished product formulation. The excipients used are of pharmacopoeial quality and no novel excipients are used.

At time of use, the product is reconstituted with 10 mL of water for injections (WFI), which is supplied by the hospital pharmacy. After reconstitution of the lyophilisate with 10 mL of WFI, the minimum extractable volume is 10.5 mL resulting in a minimum teprotumumab concentration of 47.6 mg/ml (500 mg/10.5 mL).

At the time of administration by infusion to the patient, for each vial used, 10.5 mL of reconstituted FP is extracted from the vial and transferred into an intravenous bag containing 0.9% sodium chloride solution.

Manufacturing process development

The finished product manufacturing process involves formulation and aseptic filling, capping and lyophilisation of the product. A comparison of the processes utilised during development is provided. Data has been provided to demonstrate sufficient comparability of the materials used in clinical trial and the proposed commercial material.

Container closure

The container closure system is composed of a type I glass vial which is closed with a flurotec coated chlorobutyl rubber stopper.

Prior to administration, the reconstituted FP solution must be transferred into an infusion bag containing 0.9% (w/v) sodium chloride solution. Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for up to 4 hours at room temperature (20°C – 25°C) or up to 48 hours at 2°C to 8°C storage condition.

Chemical and physical in-use stability of the diluted solution in the infusion bag has been demonstrated for 24 hours at 2°C to 8ºC followed by 24 hours at room temperature (20°C – 25°C) storage condition.

The microbial hold time data on three teprotumumab FP lots are provided separately for reconstituted and diluted solution, hence, no combined storage time can be supported by this data. So, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. This is in line with NfG on Maximum shelf-life for sterile products for human use after first opening or following reconstitution.

The two infusion solutions were incubated in different administration sets to assess the compatibility with the different materials. The two infusion solutions were prepared with a final volume of 80 mL. After reconstituting the lyophilized finished product, the vials were kept at room temperature for 1 hour before adding the FP solution to the infusion bags.

The chemical and physical in-use stability of the reconstituted solution in the vial and the diluted solution in the infusion bag are considered to be demonstrated through the in-use stability studies.

2.3.3.2. Manufacture of the product and process controls

Batch release in EEA is performed by Horizon Therapeutics Designated Activity Company, Ireland and Amgen NV (for Belgium only).

The finished product manufacturing process has been adequately presented. The FP batch size is dependent on the amount of AS supplied. At the FP manufacturing site up to four AS batches can be pooled to manufacture one FP batch.

The finished product manufacturing process involves thawing and pooling of AS, formulation and aseptic filling, capping and lyophilisation of the product. Tabular overviews about the critical steps in the finished product manufacturing process are provided. Overall, the control of the process seems adequate.

Process validation

Process validation was carried out using 3 validation batches which were successfully executed. The results were all within the specifications and acceptance criteria.

Auxiliary validations including aseptic process validation, filter validation, sterilisation method validation, leachable and extractables and shipment qualification were carried out.

2.3.3.3. Product specification, analytical procedures, batch analysis

Finished product specifications are set in accordance with ICH Q6B requirements and include control of identity, quantity, potency, purity/impurities, charge heterogeneity, sterility and other general tests.

The proposed specifications and acceptance limits are acceptable.

No new impurities are being introduced during the FP manufacturing process. A nitrosamine risk assessment has been completed for FP taking in account the sources of nitrosamine impurities from the manufacturing process, active substance, container closure, manufacturing equipment, excipients and WFI. The likelihood of nitrosamines being present or forming during or after FP manufacture is negligible.

An elemental impurities risk assessment has been completed for the process as per ICH 3QD taking into account the potential sources of elemental impurities from the active substance, container closure, manufacturing equipment, excipients and WFI. The applicant's conclusion that no additional control measures are required is acceptable.

Analytical procedures

Analytical methods have been adequately described. Compendial methods have been verified and non-compendial analytical methods have been appropriately validated.

Batch analysis

Batch release data for the latest 30 commercial FP batches as well as PPQ and clinical batches have been provided. All acceptance criteria were met.

Reference materials

Release and stability testing of the finished product is performed using the same reference standard described for teprotumumab active substance.

2.3.3.4. Stability of the product

A finished product shelf life of 48 months at 2-8°C was proposed by the applicant.

Stability data generated so far at the intended storage temperature of 5 ± 3°C, as well as at the accelerated and stressed conditions, show compliance with proposed specifications and little or no change in the quality of any of the parameters tested except for charge variants where slight increase in acidic species of up to 2-3% is observed post 24 months for PPQ and post 6-9 months for clinical material.

Protocols for stability testing are provided and considered adequate. The stability studies are carried out in accordance with ICH guidelines. Analytical methods for stability testing are the same as the ones used for FP. Post approval stability commitments are provided in line with guidelines. Currently 36 months real-time stability data is available for the FP batches manufactured at the proposed commercial manufacturing site. Therefore, in accordance with ICH Q5C a shelf life claim of 36 months is acceptable based on the data set provided.

Forced degradation studies (thermal, agitation, freeze-thaw, acidic, basic, oxidation) were performed and results gained with this study elucidated the degradation pathway of teprotumumab and demonstrated the stability indicating nature of the analytical methods chosen to monitor the stability. Forced degradation by

low and high pH at ambient and 37°C temperature, was also performed using PPQ batches. A summary of the results is provided.

Photodegradation studies were performed at 1X, 2X, 5X and 10X ICH conditions on one AS batch and one FP batch. Appropriate data is provided. It is concluded that the product should be protected from light and this is appropriately reflected in the SmPC.

In conclusion, the data supports a shelf life of 36 months at 2-8°C. The proposed in-use shelf life for the reconstituted and diluted infusion solution as outlined in the SmPC is acceptable.

2.3.3.5. Adventitious agents

Non-viral adventitious agents

No animal- or human-derived substances are used during the production of the teprotumumab AS and FP except the CHO-derived expression cell line. The MCB and WCBs were deposited using serum-free medium in the absence of animal derived material. Foetal calf serum (FCS) have been used only during early cell line development. A European Pharmacopoeia Certificate of Suitability (CEP) has been provided for the FCS. In summary, compliance with the TSE Guideline EMEA/410/01 - rev 03 has been demonstrated for the cell banks and manufacturing process of teprotumumab. Testing of cell banks, culture media, feed and AS process intermediates demonstrates the absence of mycoplasma. Bioburden and endotoxins are appropriately controlled during the AS/FP processing.

Adventitious viruses

A comprehensive program in accordance with ICH Q5A and ICH Q5D is employed to test, evaluate, and eliminate the potential risks of adventitious and endogenous viral agents. The program includes the use of the well-known CHO host cell line, establishment of a two-tiered cell bank system, testing for potential virus contaminants in the cell banks, testing of production cultures for potential viral contaminants, development and use of a chemically-defined cell culture medium, purification process, formulation that are devoid of human or animal components, employment of dedicated virus removal steps in the purification process, and a rational evaluation of the overall ability of the purification process to remove/inactivate viruses.

Several steps in the manufacturing process have been validated for virus reduction. The virus reduction capacity of the down-stream purification process has been investigated using suitable model viruses. The overall virus clearance is deemed sufficient.

2.3.1. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The stability results support the proposed shelf life for active substance and finished product. Acceptable information has been provided to ensure safety of the product with regards to adventitious agents.

2.3.2. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tepezza is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with

existing guidelines. In conclusion, based on the review of the data provided, the marketing authorisation application for Tepezza is considered approvable from the quality point of view.

2.4. Non-clinical aspects

2.4.1. Introduction

Teprotumumab (HZN-001, RV 001, R1507, RO4858696) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against human insulin-like growth factor-1 receptor (IGF-1R).

IGF-1R is a hetero-tetrameric transmembrane protein composed of 2 extracellular α-chains and two transmembrane β-chains which are linked by cysteine disulfide bonds. Binding of ligands, i.e. IGF-1 and IGF-2, to the α chain triggers conformational changes of the β-chains and activates the tyrosine kinase activity of the receptor leading to receptor autophosphorylation. In the end, the signal cascade results in activation of mitosis, differentiation and protection from apoptosis. Furthermore, upon ligand binding, the IGF-1R-ligand-complex is internalised and degraded, leading to loss of surface receptors, a process termed down-modulation.

Teprotumumab is being proposed for treatment of sever to moderate Thyroid Eye Disease (TED). Current pathophysiologic understanding of TED involves activation and proliferation of orbital fibroblasts by signalling through the IGF-1R and the thyroid-stimulating hormone receptor; these receptors are autoantigens thought to be constitutively activated by autoantibodies. Inhibition of IGF-1R function by teprotumumab is expected to block the pathophysiological responses elicited by auto-antibodies.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The applicant has provided a concise package of in vitro PD studies to evaluate the activity of teprotumumab, a mAb directed against the type 1 insulin-like growth factor receptor (IGF-1R).

According to literature data, the IGF-1R is widely expressed across many cell types in pre- and post-natal tissues. The IGF-1R expression profile was confirmed in an immunohistochemistry study with a rabbit mAb (G11) directed against the IGF-1R β chain. In human and cynomolgus tissue micro-array samples, membrane-associated expression of IGF-1R was observed in epithelia from prostate, stomach, esophagus, small intestine, colon, placenta, pancreas, thyroid, mammary gland, endometrium, cervix, urinary bladder, kidney, tonsil, thymus, and skin. In addition, the cytoplasm of endothelial cells stained positive for IGF-1R expression in both normal human and cynomolgus monkey tissues. In this study, a similar expression profile of the IGF-1R in human and cynomolgus tissues was observed.

In vitro binding

The binding properties of teprotumumab were evaluated in vitro. Using immunofluorescence staining and confocal laser scanning microscopy, teprotumumab bound to murine cells expressing human IGF-1R but not to cells deficient for IGF-1R. This indicates selectivity for IGF-1R. By surface plasmon resonance the affinity of teprotumumab for human IFG-1R was approx. 2.2 nM, irrespective of teprotumumab source (SP2/0 or CHO-derived material).

In vitro function

Teprotumumab binds to the IGF-1R α-chain which is involved in ligand binding. In a competition assay, it was shown that teprotumumab interferes with binding of IGF-1 and IGF-2 to the receptor. Using the human cancer cell line HT29, teprotumumab inhibited IFG-1 binding with an IC50 of 0.44 nM and IGF-2 binding with an IC50 of 0.28 nM. Using the 3T3-IGF-1R cell line, which expressed higher levels of IGF-1R than the HT29 cell line, teprotumumab was shown to displace IFG-1 with an IC50 of 1.3 nM and IGF-2 with an IC50 of 2.8 nM.

Teprotumumab was also found to inhibit IGF-1-induced signalling and cell proliferation. Using 3T3 cells, overexpressing human IGF-1R, teprotumumab inhibited receptor autophosphorylation induced by IGF-1 (10 nM) with an IC50 of 1 nM. In addition, teprotumumab inhibited proliferation of 3T3-IGF-1R cells stimulated with IGF-1 (10 ng/ml) with a mean IC50 value of 6.93 nM.

By flow cytometry with human lung cancer cells (H332M), teprotumumab was shown to induce a rapid decrease in IGF-1R cell surface expression to approx. 50% within 1 hr. By confocal laser scanning microscopy, accumulation of intracellular teprotumumab was observed, suggesting that IGF-1R is indeed internalised and not shed from the cell surface.

In vivo function

In nude mice bearing human tumours expressing IGF-1R, single dose of teprotumumab (6 mg/kg IP) lead to down-regulation of IGF-1R on the tumour cells as demonstrated ex vivo.

Species cross reactivity

The cross-reactivity of teprotumumab with IGF-1R from different non-clinical species was evaluated in several studies. Based on immunoprecipitation of IGF-1R from lysates of tissues known to express IGF-1R, teprotumumab was cross-reactive with cynomolgus IGF-1R but not IGF-1R from marmoset, rat and mouse. Using surface plasmon resonance, teprotumumab was found to bind to cynomolgus and human IGF-1R with comparable affinity (2.54 nM vs. 2.2 nM). In a ligand-competition assay teprotumumab displaced radio-labelled IGF-1 from cynomolgus and human IGF-1R with comparable IC50 (0.63 nM vs. 0.46 nM). No difference was observed when CHO-derived vs SP2/0-derived material was used. Based on these data, cynomolgus can be considered a relevant species for toxicity testing of teprotumumab.

2.4.2.2. Secondary pharmacodynamic studies

Cross-reactivity with insulin receptor

IGF-1R is a tyrosine kinase cell surface receptor that shares approximately 50-60% overall homology with the insulin receptor (IR). Therefore, potential cross-reactivity of teprotumumab with the IR was evaluated. By immunofluorescence confocal laser microscopy, teprotumumab did not stain 3T3 cells expressing human IR. Furthermore, teprotumumab did not compete with insulin for binding to human IGF-1R and did not induce IR depletion from 3T3-IR cells. Together these data sufficiently demonstrate that teprotumumab does not cross-react with human IR.

Fc-dependent effector functions of teprotumumab

Teprotumumab is a human IgG1 mAb with non-modified Fc region directed against a cell surface receptor. Thus, it is conceivable that teprotumumab mediates Fc-dependent effectors functions. The potential to induce ADCC was evaluated in a study with the human tumour cell line DU145 and human PBMC as effector cells. In

this study, no cytotoxicity against DU145 cells was induced at teprotumumab concentration up to 10 µg/ml. However, a positive control for ADCC induction was missing in this study.

In contrast, in experiments using the same target cell and a Jurkat reporter cell line as effector cell, teprotumumab activated the Jurkat cells with an EC50 of 857 ng/ml. In addition, teprotumumab bound to the complement component C1q with an EC50 of 3.76 µg/ml.

Together, the ADCC and CDC data from the drug substance characterisation section suggest that teprotumumab can induce cytotoxicity against cells expressing IGF-1R. A risk for induction of cytotoxicity against IGF-1R-expressing cells cannot be excluded, which is a concern given the widespread expression of IGF-1R. On the other hand, in vivo data from the non-clinical repeat-dose toxicity studies (up to 39 weeks of treatment in cynomolgus monkeys) do not provide evidence for target-dependent cytotoxic activity against IGF-1R-positive cells and thus alleviate the theoretical concern.

2.4.2.3. Safety pharmacology programme

The effect of teprotumumab on safety pharmacology endpoints was evaluated as part of the general repeat-dose toxicity studies in cynomolgus monkeys. In line with ICH S6(R1), this is acceptable. Cardiovascular parameters (heart rate, ECG variables such as QT interval and corrected QT interval), along with respiratory rate and body temperature were evaluated. Throughout the repeat-dose toxicity studies, no treatment-related findings were observed on cardiovascular and respiratory endpoints at teprotumumab doses of up to 150 mg/kg/week for 7 weeks and up to 75 mg/kg/week for 39 weeks.

Clinical observations recorded during the repeat-dose toxicity studies did not suggest any CNS-related finding of concern. Additionally, there were no teprotumumab-related findings in histopathology of the brain and spinal cords from repeat-dose toxicity studies.

2.4.2.4. Pharmacodynamic drug interactions

PD drug interaction studies were not evaluated. Omission of these studies is sufficiently justified by the applicant.

2.4.3. Pharmacokinetics

Bioanalytical methods

Concentrations of teprotumumab in rat and cynomolgus serum were determined using a sandwich ELISA. Sample matrix was either rat or cynomolgus serum. The assay in rat matrix was qualified for use in the PK study, the assay in cynomolgus matrix was appropriately validated for use in PK and also TK studies. Assay sensitivity is 25 ng/ml.

Anti-teprotumumab antibodies were detected by ELISA in rat serum or by ECLIA in cynomolgus serum. The assay used in the pivotal cynomolgus TK studies was adequately validated. Sensitivity of the ECLIA is 16 ng/ml based on the positive control ADA (rabbit anti-teprotumumab Ab).

Information provided on the analytical methods is considered sufficient.

PK

The pharmacokinetics of teprotumumab were evaluated in single-dose PK studies in rats and cynomolgus monkeys after IV administration. This reflects the proposed clinical route of administration. The initial PK studies in rats and cynomolgus used SP2/0-derived material, while the 3rd study compared the PK of CHO- vs. SP2/0-derived teprotumumab in cynomolgus.

PK characteristics of teprotumumab after single IV administration were typical for a monoclonal antibody.

In rats, linear kinetics were observed following single-dose IV administration of teprotumumab ranging from 3 to 50 mg/kg. This may be due to the lack of teprotumumab binding to rat IGF-1R and absence of target-mediated drug disposition. As such, teprotumumab kinetics in rats are considered less relevant than the kinetics in cynomolgus, a species in which IGF-1R is bound by teprotumumab.
In cynomolgus monkeys, non-linear kinetics were observed. Once teprotumumab serum concentrations were below approx. 1 µg/ml, a steep decline in concentration were observed. This finding is consistent with target-mediated drug disposition. Mean Cmax was approximately dose-proportional, while mean AUC was slightly greater than dose-proportional between 3 and 15 mg/kg and approx. dose-proportional between 15 and 150 mg/kg. The mean systemic clearance of teprotumumab was low and dose dependent; terminal half-life was long and increased with increasing dose. The calculated volume of distribution at steady state ranged from 75 to 99 ml/kg.
Kinetics obtained after administration of 15 mg/kg of CHO- vs. SP2/0-derived teprotumumab can be considered comparable. The systemic exposure (Cmax and AUC10-840hrs) in monkeys treated with the different materials differed by less than 15%.

In accordance with ICH S6(R1), studies on distribution, metabolism and excretion were not conducted. Omission of these studies is acceptable.

No non-clinical PK drug interaction studies were conducted. This is acceptable, since teprotumumab, as monoclonal antibody, is not metabolized via CYP450 enzymes and does not affect expression of CYP450 enzymes.

2.4.4. Toxicology

Toxicity studies were conducted in a single species, i.e. cynomolgus monkeys, based on comparable binding affinity and functional activity of teprotumumab to human and cynomolgus IGF-1R and lack of reactivity with rodent IGF-1R. Selection of cynomolgus monkeys is considered adequately justified.

SP2/0-derived teprotumumab was used for the initial toxicity studies (2-wk DRF and 7-wk study), while CHO-derived teprotumumab was used in the 13-wk and 39-wk repeat-dose studies and the reproductive and developmental studies. In summary, material representative of the clinical material was used.

2.4.4.1. Single dose toxicity

Single dose toxicity studies have not been performed. Omission is acceptable in line with ICH M3 and the Q&A on the withdrawal of the 'Note for guidance on single dose toxicity' (EMA/CHMP/SWP/81714/2010).

2.4.4.2. Repeat dose toxicity

Teprotumumab was evaluated in a series of repeat-dose toxicity studies with up to 39 weeks duration. In general, adolescent to young adult monkeys (2-4 years of age) were treated, while mature animals (4.6 to

approx. 6 years of age) and a separate group of juvenile animals (approx. 2 year of age) were used in the 13-wk study.

Animals were treated IV, the intended clinical route of administration. Teprotumumab was administered at doses up to 75 mg/kg, with a frequency of 2x/wk in the initial 7-wk study, and 1x/wk in the longer 13-wk and 39-wk studies. All studies included recovery periods.

In the repeat-dose studies in cynomolgus monkeys, treatment with teprotumumab at doses up to 75 mg/kg/wk was generally tolerated, without teprotumumab-related mortality or morbidity. However, teprotumumab treatment was consistently associated with decreases in body weight gains, resulting in reduced body weight at the end of the treatment period (reversible). In clinical chemistry, reversible, decreased ALP levels were observed. Where evaluated, these corresponded with reversible decreases in bone ALP. The decreases in ALP (total and bone ALP) in the teprotumumab-treated animals were likely to be pharmacologically-related since IGF-1R is expressed in bone tissue and IGF-1 is implicated in growth factor-induced bone remodelling. In haematology, a teprotumumab-related reduction in circulating erythrocyte mass parameters (RBC count, haemoglobin, haematocrit), lower reticulocyte counts and lower neutrophil counts were observed. The findings were without histological correlates in the bone marrow and reversible.

The most prominent, teprotumumab-related finding was a reduction in thymus weight and size, that was associated with lymphocyte deletion (thymus atrophy). The finding was present at all teprotumumab dose levels without a dose response and was reversible upon clearance of teprotumumab. The teprotumumab-related thymus findings are considered pharmacology-related, since IGF-1R has a critical role in proliferation, maturation and survival of T lymphocytes. The finding was not considered adverse, as it was not associated with a reduction in circulating leukocyte counts or changes in peripheral lymphoid tissues and was not associated with occurrence of infections.

In the 13-wk and 39-wk toxicity studies study, the NOAEL was 75 mg/kg IV Q1W, the highest dose administered. This was associated with a Cmax of 3210 µg/ml and an AUC0-168hrs of 356,500 µg*h/ml. This exposure provides a sufficient margin to the exposure at the proposed clinical dose of teprotumumab.

2.4.4.3. Genotoxicity

Genotoxicity studies have not been conducted, in accordance with ICH S6(R1). This is accepted.

2.4.4.4. Carcinogenicity

No carcinogenicity studies were conducted. In line with ICH S6(R1), this is acceptable. Instead, a carcinogenicity risk assessment was submitted in eCTD module 4.3. Teprotumumab is a fully human mAb with high potency and specificity for IGF-1R inhibition. Therefore, it is considered unlikely to have off-target effects or carcinogenic metabolites. Non-clinical studies in cynomolgus monkeys with a duration of up to 39 weeks did not produce adverse neoplastic/pre-neoplastic lesions. In addition, IGF-1R is implicated in pro-proliferative effects in vitro and in vivo. In non-clinical cancer models, teprotumumab had anti-proliferative and anti-tumour effects in vitro and in vivo.

Although some factors to consider for a WoE assessment outlined in the ICH S1B guideline are formally missing from the discussion (hormone perturbation, genotoxicity, immune modulation), the provided justification is considered sufficient to support the MAA. Based on the mechanism of action and supporting literature, the risk of carcinogenicity can be expected to be low.

2.4.4.5. Reproductive and developmental toxicity

Fertility

A formal fertility study with teprotumumab has not been performed, since mating studies are not practical for NHPs. In line with the ICH S6(R1), the fertility assessment was based on evaluation of the reproductive organ weights and histopathology in 13-week and 39-week toxicity studies in sexually mature cynomolgus monkeys, which showed no histopathological changes in any reproductive organ. Although IGF-1R is highly expressed in a variety of tissues in both male and female reproductive system (numerous literature reports, results from TCR studies IM1163 and IM1202), more specialized assessments (e.g. menstrual cyclicity, sperm count, sperm morphology/motility, and male or female reproductive hormone levels) were not included in repeat-dose toxicity studies. Based on literature data, there is theoretical concern on the potential of teprotumumab to affect male and female fertility (see Discussion on non-clinical aspects). In the clinics, adverse effects on menstrual cycle (amenorrhea, hypomenorrhea, dysmenorrhea, irregular menstruation, heavy menstrual bleeding) are frequently reported in post-marketing setting (see section 4.8 of the SmPC).

Embryo-fetal development

In the embryo-fetal development study, pregnant cynomolgus females were administered teprotumumab at 0 or 75 mg/kg IV, from GD 20 to GD142; the time point when the fetuses were delivered by C-sectioning.

Fetal loss prior to GD32 was observed in both groups with a higher frequency in the teprotumumab-treated group (28.6% vs. 16.7%), although the higher fetal loss could not be definitively attributed to teprotumumab nor excluded.

In maternal animals, teprotumumab was not associated with toxicity. The only teprotumumab-related finding in maternal animals was a reduction in body weight gain from GW8 to GW20, which may have been secondary to fetal effects. The maternal NOAEL is 75 mg/kg associated with a Cmax of 3510 µg/ml and an AUC0-168hrs of 385,000 µg*h/ml.

In fetuses from teprotumumab-treated maternal animals, numerous abnormalities were detected: decreased placental weight, decreased primary disk measurements, and decreased amniotic fluid volume. Fetal body weight was reduced (approx. 50%), associated with decreased organ weights and decreased fetal measurements (e.g. body and limb length). By external evaluation, abnormalities of the head were detected in all fetuses from the teprotumumab-treated group, (rounding of the cranium, closely set eyes, open fontanelles, underdevelopment of the lower portion of the face, pointing and narrowing of the nose, and thinning of the cranial bones.) Abnormalities of the head on external evaluation had corresponding findings in the skeletal radiographs (e.g. ossification abnormalities of multiple bones and teeth). No visceral abnormalities were noted. The developmental adverse effects observed are consistent with the pharmacology of teprotumumab as an inhibitor of IGF signalling pathways which are known to be involved in regulation of fetal growth and development. In summary, in the absence of maternal toxicity, teprotumumab was associated with fetal and developmental toxicity, a fetal NOAEL was not determined.

Taking into account the embryo-fetal toxicity associated with the pharmacology of teprotumumab, use of teprotumumab during pregnancy is contra-indicated (see SmPC Section 4.3). In addition, contraception prior to initiation, during treatment and for 6 months after the last administration of teprotumumab in women of childbearing potential is recommended (see SmPC Section 4.6). Overall, the findings of developmental toxicity are adequately reflected in Section 5.3 of the SmPC.

Pre-/post-natal development

A PPND study was not performed. This is justified, because teprotumumab is a mechanism-based teratogen and potential increased foetal loss could not be ruled out, therefore studies evaluating PPND in cynomolgus monkeys would not be practical or feasible.

Juvenile toxicity study

Developmental toxicity of teprotumumab was also evaluated in juvenile cynomolgus, aged 11 to 14 months at treatment initiation. Animals were administered teprotumumab for a period of 13 weeks at the same dose levels as adult monkeys in the repeat-dose toxicity studies.

Teprotumumab-related adverse findings were observed in this juvenile animal study: Reductions in body weight gain (down to 45% of the body weight gain in controls) resulting in reduced body weight (approx. 88% of control) at the end of the treatment period. The finding was partially reversible. In addition, teprotumumab treatment resulted in lower bone mass (bone mineral density and bone mineral content) in males at all dose levels and in females at the mid and high-dose level. Lower bone mass was confirmed for males at the tibia metaphysis (by pQCT) and was mainly associated with lower trabecular bone density. Evidence of similar effects was noted for females treated at the high dose level. Overall, treatment with teprotumumab resulted in narrower bones with thinner cortices attributed to reduced periosteal expansion with no effect on endosteal circumference relative to controls, most notably in males at all dose levels and in high-dose females. There was no apparent effect on bone length. No meaningful differences were noted for the animals at the end of the recovery period except for slightly lower BMC and area for global, mid and proximal femur at 15 and 75 mg/kg.

The effect of teprotumumab on bone mass is considered a pharmacology-related effect. Growth hormone regulation of the growth plate and bone size is largely mediated by IGF-1 in epiphyseal chondrocytes that in turn increases the proliferation of chondrocytes. Despite the absence of a clear effect on bone length, the bone diameter parameters were consistently lower for all teprotumumab-treated males and females suggesting an inhibition of periosteal expansion. This was consistent with the reported effects of IGF-1 on periosteal expansion and growth. In addition, IGF-1 receptor is expressed by osteoblasts and impaired signalling pathway in human osteoblasts culture has been associated with decreased proliferation and decreased bone formation. In this study, a greater magnitude of response with regard to bone mass was noted for males relative to females, suggesting gender differences. These differences may be associated with the relationship between IGF and androgen.

Based on the adverse reductions in body weight gain and decreases in bone mass and narrower bones with thinner cortices in all teprotumumab-treated group, a NOAEL was not established in this study. These non-clinical findings were taken into account for the PIP, which granted a waiver for the paediatric population from birth to adolescence before growth is complete, on the grounds that teprotumumab is likely to be unsafe. Currently, teprotumumab is proposed for treatment of adult patients only. Information of the adverse effects observed in juvenile cynomolgus monkeys are however considered valuable for prescribers and are included in section 5.3 of the SmPC.

2.4.4.6. Toxicokinetic data

Throughout the toxicity studies, in which cynomolgus monkeys were administered teprotumumab once weekly at up to 75 mg/kg, monkeys were continually exposed to teprotumumab during the dosing phase. Increases in exposure were approximately dose-proportional. Once-weekly dosing resulted in slight to moderate accumulation. No gender difference was apparent in any dose levels. In the treatment-free periods, teprotumumab levels declined but were still quantifiable in 15 and 75 mg/kg groups after 12 weeks of

recovery. After a 24-weeks treatment-free period, systemic exposure was below the limit of quantitation for all dose groups. The presence of ADAs was confirmed in some samples, which resulted in an accelerated clearance of teprotumumab.

Exposure in pregnant animals treated at 75 mg/kg IV once weekly (18 doses) and exposure in juvenile animals (treated up to 75 mg/kg IV once weekly for 13 weeks) were consistent with the exposure observed in the repeat-dose toxicity studies.

A comparison of exposure to teprotumumab in cynomolgus monkeys and humans was made. Exposure data from the toxicity studies are based on AUC0-168 hrs at the end of treatment period; for clinical exposure an AUCtau value (with tau of 21 days) is reported. The cynomolgus AUC values were normalised to account for the difference in dosing schedule and provide a sufficient margin (approx. 8x) to the human exposure.

2.4.4.7. Local tolerance

In the general repeat-dose toxicity studies, teprotumumab was administered IV, the proposed clinical route of administration. Upon IV administration, teprotumumab was locally well tolerated.

In an exploratory study, tolerability of teprotumumab to intra-vitreous administration was evaluated in cynomolgus monkeys. Intra-vitreous injection of teprotumumab at 1.25 or 2.5 mg/eye was not tolerated and was associated with frequent severe uveitis of variable onset, which resulted in unscheduled sacrifice of 2 animals. The uveitis may have been secondary to an anti-drug antibody response. The study results are not discussed further, since intra-vitreous administration is not planned as clinical route of administration of teprotumumab.

2.4.4.8. Other toxicity studies

Immunotoxicity

An effect of teprotumumab on the immune system was evaluated as part of the repeat-dose toxicity studies. Across all repeat-dose toxicity studies, administration of teprotumumab was associated with thymic atrophy, with correlating microscopic thymic lymphoid depletion. The finding was reversible upon clearance of teprotumumab. In these studies, thymic lymphoid depletion did not result in depletion of T cells and was not associated with an increase in infections. Furthermore, in a juvenile toxicity study, the observed thymic atrophy did not impair the development of a T cell-dependent Ab response to immunisation with KLH.

Excipient studies

The excipients used in teprotumumab drug product are well-known excipients routinely used in the formulation of monoclonal antibody products. Dedicated studies on excipient safety are not warranted. In accordance with the Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the presence of polysorbate 20 is indicated in SmPC and PL.

Tissue cross-reactivity

Tissue cross-reactivity of teprotumumab with human and cynomolgus tissues was evaluated by immunohistochemistry. Based on reactivity with positive and negative control tissues, the method is considered specific. Teprotumumab staining was detected in all human tissues examined, except for bone marrow. Per tissue, different cell types stained positive: e.g. epithelial cells, endothelial cells, smooth muscle cells, nerve cells (nerve endings, axons, ganglia), peripheral blood cells (erythrocytes, lymphocytes,

monocytes), tissue macrophages. In the eye, teprotumumab stained retina, ocular lens fibres, endothelium, corneal epithelium and vascular smooth muscle cells. Majority of the teprotumumab staining was cytoplasmic; cell surface or membrane staining was only observed for epithelium and endothelium in various tissues. It is recognised that intracellular targets are not accessible to mAbs in vivo.

The teprotumumab staining observed in human tissue is considered consistent with the known broad IGF-1R expression profile. Teprotumumab staining of cynomolgus tissues was found to be similar to that observed in human tissues.

2.4.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, teprotumumab is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacology

The applicant has provided a concise package of pharmacology studies to evaluate the activity of teprotumumab, an IgG1 mAb directed against the type 1 insulin-like growth factor receptor (IGF-1R).

Taken together, the submitted in vitro / ex vivo mechanistic studies sufficiently demonstrate that teprotumumab mediates functional inactivation of IGF-1R by several mechanisms: inhibition of ligand binding, inhibition of ligand-induced signalling, inhibition of ligand-induced cancer cell proliferation, induction of IGF-1R internalisation.

Since there are no well-established animal models for thyroid eye disease (TED), the proof-of-concept for using teprotumumab in TED is based on key literature data supporting the role of IGF-1R in the pathogenesis of TED. This approach is considered to be sufficient from non-clinical perspective. Literature data suggest that IGF-1R, in a macromolecular complex with the thyroid-stimulating hormone receptor (TSHR), regulates the pathological autoimmune activation of orbital fibroblasts, and clinical experience supports this. However, the exact relationship of IGF-1R with TSHR and how the disruption of intracellular signalling between the two can be achieved by targeting IGF-1R with teprotumumab is still elusive. Therefore, the text proposed by the applicant for section 5.1 of the SmPC under the "Mechanism of action" is considered to be suitable.

The effect of teprotumumab on safety pharmacology endpoints was evaluated as part of the general repeat-dose toxicity studies, which is acceptable. There were no effects on clinical observations, physical examinations (including measurements of vital signs such as heart rate, respiration rate and body temperature), respiratory rate or electrocardiogram at doses of up to 75 mg/kg (the highest dose evaluated). Specific CNS assessment (e.g. neurofunctional and neurobehavioral endpoints) was not incorporated in repeat-dose toxicity studies. IGF-1R is one of the receptors that emerged as a target for receptor-mediated transcytosis, a transport phenomenon that can be exploited to shuttle biotherapeutics across the blood-brain barrier (BBB), Peripherally circulating IGF-1 is biologically active in CNS following its transport across the BBB by IGF-1R. Following binding to receptor and internalization to cell, the fate of teprotumumab in CNS and the amount of the antibody possibly available in the CNS is not known. However, indirect evaluation through clinical observations from repeat-dose toxicity studies along with histopathological data of the brains and spinal cords did not suggest any CNS-related finding of concern.

Pharmacokinetics

The PK of teprotumumab were evaluated after single-dose IV administration in rats and cynomolgus monkeys. IV administration reflects the proposed clinical route of administration. Since teprotumumab is not pharmacologically active in rats, the PK studies in this species do not capture target-mediated drug disposition. As such, results from the rat study are considered less relevant. In cynomolgus monkeys, a pharmacologically relevant species, non-linear kinetics were observed, indicating target mediated drug disposition. By and large, PK of teprotumumab in cynomolgus monkeys was as expected for a human mAb with a limited volume of distribution, low clearance, long terminal half-life and kinetics not affected by gender. The studies sufficiently support IV administration of teprotumumab as proposed for the current MA application.

Toxicology

Toxicity of teprotumumab was evaluated in one relevant species, which is endorsed.

Overall, the toxicity programme is an extensive programme, including repeat-dose studies with a duration of 2, 7, 13 and 39 weeks. Recovery groups were included in all studies and at all dose levels. As such, the programme reflects regulatory guidance at the time the studies were performed (2004 - 2011), prior to revision of ICH S6(R1) in 2011. In addition to these general toxicity studies, the programme included also an embryo-fetal development study and a study in juvenile monkeys. In line with recommendations of ICH S6(R1) and ICH S5(R3), the EFD study nowadays would have been replaced by a weight-of evidence discussion on the developmental risk of teprotumumab.

Teprotumumab-related findings were consistent throughout the toxicity studies and were primarily related to the pharmacology, i.e. blockade of the IGF-1R. Ubiquitous and abundant IGF-1R cell and tissue expression as well as a broad tissue cross-reactivity of teprotumumab raise multiple theoretical concerns related to potential toxicity from exaggerated pharmacology. On the contrary, there were only a few prominent toxicities observed (e.g. thymus toxicity, see below) and several findings of very small magnitude, which were considered non-adverse and of unclear clinical significance (e.g. slight ALP/BAP decrease, decrease in red blood cell (RBC) parameters and neutrophils, see below). In tissues selected for showing measurable immunohistochemical staining for IGF-1R (i.e., urinary bladder transitory epithelium, pancreatic islets, thymus squamous epithelium, skin, mammary myoepithelial cells, and prostate epithelium), high exposures to teprotumumab for 39 weeks produced minimal down-regulation of IGF-1R expression. This suggests that teprotumumab may not have pronounced effects on basal levels of IGF-1R expression in endogenous tissues in vivo and argues against the potential for pharmacological effects extending beyond the time of drug exposure.

The toxicities observed upon repeated administration of teprotumumab to cynomolgus monkeys affect the thymus, bone and embryo-fetal growth and development and are discussed below. Other noteworthy teprotumumab-related findings that were consistent across the studies were a slight weight loss or a reduction in body weight gain, ALP/BAP decrease as well as the decrease in red blood cell (RBC) parameters (RBC and reticulocyte counts, haemoglobin and haematocrit) and neutrophils decrease. These subtle teprotumumab-related effects in NHPs are not expected to exacerbate or translate to adults with TED given the current clinical data.

Changes in the thymus are decreased thymus weight and size, associated with lymphoid depletion (thymus atrophy). The finding was present at all teprotumumab dose levels without a dose response and was reversible upon clearance of teprotumumab. The teprotumumab-related thymus findings are considered pharmacology-related, since IGF-1R has a critical role in proliferation, maturation and survival of T

lymphocytes. However, the finding was not considered adverse in the toxicity studies, as it was not associated with a reduction in circulating leukocyte counts or changes in peripheral lymphoid tissues and was not associated with occurrence of infections. Furthermore, in juvenile animals, thymic lymphoid depletion did not prevent the development of a T cell-dependent antibodies in response to vaccination. Of note, thymus findings from NHPs were not translated to clinics. There have been no thymus or peripheral lymphocyte depletion effects observed in TED patients.

Changes in bone were observed in juvenile monkeys (aged 11 - 14 months at the start of treatment). While no effect on bone length was observed, teprotumumab treatment results in lower bone mass, primarily characterised by reduced bone density and bone mineral content) which was considered adverse. Overall, treatment with teprotumumab resulted in narrower bones with thinner cortices. The effect was more pronounced in males than in females suggesting gender differences. These may be associated with the relationship between IGF and androgen. The bone findings were reversible with the exception of slightly lower bone mineral content. IGF-1 receptor is expressed by osteoblasts, and impairing the signalling pathway in human osteoblasts cultures has been associated with decreased proliferation and decreased bone formation. These non-clinical findings were taken into account for the PIP, which granted a waiver for the paediatric population from birth to adolescence before growth is complete (P/0345/2016), on the grounds that teprotumumab is likely to be ineffective or unsafe in part or all of the paediatric population and that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. Thus, in SmPC section 4.2 under the Paediatric population it is stated that teprotumumab should not be used in children from birth to adolescence before growth is complete. The findings from the juvenile toxicity study are integrated in section 5.3 of the SmPC.

In the embryo-fetal development study in cynomolgus, teprotumumab affected the development of foetuses of teprotumumab-treated females, in the absence of maternal toxicity. The foetuses were small for their gestational age (approx. 50% of control foetuses) and had multiple external and skeletal abnormalities of the head, including misshapen cranium, micrognathia, and ossification abnormalities of multiple bones and teeth. The effects observed were consistent with the pharmacology of teprotumumab as an inhibitor of IGF signalling pathways, which are known to be involved in regulation of foetal growth and development. Findings from the EFD study are adequately described in section 5.3 of the SmPC.

Based on this developmental toxicity, teprotumumab is contraindicated during pregnancy and the use of contraception prior to initiation, during treatment and for 6 months after the last administration of teprotumumab in women of childbearing potential is recommended. Appropriate warnings are included section 4.6 of the SmPC.

Excretion of teprotumumab in milk was not investigated in non-clinical species. Although IgGs generally decrease to low levels in breast milk after the first few days (highest concentrations in colostrum), due to the lack of specific lactation excretion data and based on profound effects on bone development during embryo-foetal period as well as in juvenile animals, teprotumumab should not be used during breastfeeding as a precautionary measure (see section 4.6 of the SmPC).

The fertility assessment was based on evaluation of the reproductive organ weights and histopathology in 13-week and 39-week toxicity studies in sexually mature cynomolgus monkeys, which showed no histopathological changes in any reproductive organ. Although IGF-1R is highly expressed in a variety of tissues in both male and female reproductive system, specialized fertility parameters (e.g. menstrual cyclicity, sperm count, sperm morphology/motility, and male or female reproductive hormone levels) were not assessed in the repeat-dose toxicity studies for teprotumumab since there were no reproductive effects

or signals of concern from previous repeat-dose study histopathology. In addition, there was no evidence in the literature at the time of the chronic studies to suggest a direct effect on male/female fertility.

A formal waiver for fertility studies was submitted for the purpose of teprotumumab BLA, since the mechanism of action and literature information suggested that an effect of teprotumumab on fertility could not be excluded. The rationale for requesting a waiver for conducting a fertility study was based on the pharmacological properties of teprotumumab, lack of identified potential risks from non-clinical studies, duration of clinical exposure (24 weeks), and an assessment of available literature on IGF-1R-inhibition effect on fertility. A review of the relevant literature found no reports linking 24-week period of IGF-1R inhibition to long-term effects on fertility. It is concluded that the scientific literature suggests that there is potential for teprotumumab to reduce fertility during drug exposure. However, as this suggestion is mainly based on in vitro and rodent data, the predictive validity was assessed to be uncertain. Additionally, literature data suggests IGF/IGF-1R signalling as not critical in reproductive biology (one as many endocrine and paracrine factors that regulate and determine fertility) in contrast to e.g. gonadotrophins.

Since teprotumumab shows developmental toxicity and women of childbearing potential should anyway use effective contraception prior initiation, during the treatment and for 6 months after the last administration of teprotumumab, no significant risks with the potentially reduced fertility during the teprotumumab treatment may be anticipated. Non-clinical data on fertility in sections 4.6 and 5.3 of the SmPC are considered to be adequately reflected. The chronicity and clinical significance of menstrual abnormalities reported in clinical trials, especially in post-marketing setting, may be addressed through further clinical trials.

Genotoxicity and carcinogenicity studies with teprotumumab were not conducted, which is acceptable. The carcinogenic potential of teprotumumab was evaluated to be low based on a weight of evidence approach taking into account the mechanism of action, data from repeat-dose toxicity studies and supporting literature, and provides sufficient support to the recommended clinical dosing regimen of 8 infusions during the 6 month-course.

ERA

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, teprotumumab is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Overall, the applicant provided a comprehensive evaluation of pharmacological, pharmacokinetic and toxicological properties of teprotumumab which supports the intended clinical use and there are no issues identified.

The non-clinical in vitro, in vivo and literature data provide adequate pharmacological basis for the option to treat TED with teprotumumab.

Pharmacokinetic properties of teprotumumab are sufficiently described and do not differ from those of other monoclonal antibodies.

The toxicity programme for teprotumumab was comprehensive and by large in alignment with the applicable ICH S6(R1) guideline.

The MAA of teprotumumab is approvable from non-clinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 4. Clinical trials

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

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-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)

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-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
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	**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 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

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 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 24/7 As of 17Mar2023	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

A = Asian; B = black or African American; CAS = Clinical Activity Score; CSR = clinical study report; F = female; FT3 = free triiodothyronine; FT4 = free thyroxine; GO-QoL = Graves' Ophthalmopathy Quality of Life; IP = investigational product; IV = intravenous; M = male; NA = not applicable; NH/PI = Native Hawaiian or other Pacific Islander; O = other (participants with more than 1 race indicated appear in the "other" category); OL = open-label; Q3W = every 3 weeks; TED = thyroid eye disease; US = United States; W = white

a. Participant 029-0002 was randomized to placebo but received teprotumumab.

b. < 2-mm reduction from Baseline in proptosis in the study eye

Source: TED01RV CSR for 24-week Treatment Period and CSR Addendum for 48-week Follow-up Period, OPTIC CSR for 24-week Treatment Period, OPTIC Week 72 CSR Addendum, OPTIC CSR for 24-week Treatment Period, OPTIC-J CSR for 24-week Treatment Period, OPTIC-X CSR and HZNP-TEP-403 CSR for 24-week Treatment Period

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The pharmacokinetics (PK) of teprotumumab was evaluated using population pharmacokinetic (PopPK) analysis and is used primarily for descriptive purposes. Rich PK data is available from one Phase 1-study with 10 healthy volunteers, and sparse PK data from five other studies with a total of 176 patients. Only one dose (scaled by body weight) was tested.

Analytical methods

Determination of Teprotumumab in Human Serum

Three bioanalysis methods were used to analyse teprotumumab concentrations in study TED01RV, HZNP-TEP-102, HZNP-TEP 301, HZNP-TEP-302, HZNP-TEP-303 and HZNP-TEP-403.

Method 2165-006 (used for study TED01RV)

ELISA plates coated with the capture reagent were utilized. Prior to sample plating, the plate was blocked with Superblock, incubated and washed. Standards, quality controls, blanks, and diluted samples were added to duplicate wells of the coated plate, and the plate was incubated and washed. The detection antibody was added to the wells, and the plate was incubated and washed. SA-HRP was then added to the wells, and the plate was incubated and washed. 1-Step™ Ultra TMB-ELISA Substrate was added to the wells and the plate was incubated. Finally, stop solution (~2N sulfuric acid) was added to the wells.

Method AR138-C1133-17-0124 (used for study HZNP-TEP-301, HZNP-TEP-302)

Standards, controls, and test samples are incubated with monoclonal mouse anti-HZN-001 (anti-teprotumumab) antibody, which has been immobilized on an MSD MULTI-ARRAY Standard 96-well plate. Bound teprotumumab is then incubated with a different monoclonal mouse anti-HZN-001 (anti-teprotumumab) antibody that has been conjugated with SULFO-TAG, visualized with MSD Read Buffer T (2X), and read on the MSD QuickPlex™ SQ 120.

Method BIO.VR.0029-2772 (used for study HZNP-TEP-102, HZNP-TEP-303, HZNP-TEP-403)

Standards, controls, and test samples are incubated with monoclonal mouse anti-teprotumumab antibody which has been immobilized on a Standard Bind MSD plate. Bound teprotumumab is then incubated with a different monoclonal mouse anti-teprotumumab antibody that has been conjugated with SULFO-TAG, visualized with MSD Gold Read buffer, and read on the MSD QuickPlex™ SQ 120.

Determination of anti-drug antibodies (ADAs) in human serum

A three-tiered immunogenicity assay strategy was used for the detection of ADA responses. Three methods were used to evaluate presence of ADA in study TED01RV, HZNP-TEP-102, HZNP-TEP 301, HZNP-TEP-302, HZNP-TEP-303 and HZNP-TEP-403.

Method 2165-002 (used for study TED01RV)

MSD streptavidin-coated plates were utilized. Prior to sample plating, the plate was blocked with blocking buffer (3% BSA in 1× PBS). Required samples were added to the appropriate wells of a storage plate. Teprotumumab Master mix [teprotumumab-biotin + teprotumumab-SULFO-TAG + assay buffer (0.5% BSA,

0.05% Tween® 20 in 1× PBS)] was added to required wells of the storage plate, and the storage plate was incubated. The incubated samples were added to duplicate wells of the preblocked and washed streptavidin-coated plate. The plate was incubated and washed. The 2× Read Buffer T was added to the wells.

Method AR138-C1133-17-0128 (used for study HZNP-TEP-301, HZNP-TEP-302)

Samples were treated with acid to dissociate any antibody drug complexes and then incubated with master mix (4 µg/mL biotinylated-teprotumumab +4 µg/mL SULFO-TAGteprotumumab). Samples were transferred to blocked MSD streptavidin-coated 96-well plate, incubated, visualized with MSD Read Buffer T (2×), and read on the MSD QuickPlex™ SQ 120.

Method BIO.VR.0029-2773 (used for study HZNP-TEP-102, HZNP-TEP-303, HZNP-TEP-403)

Samples, PCs, and NCs were incubated with assay buffer (for Screening or Titer tier) or assay buffer +100 µg/mL teprotumumab (for Confirmatory tier) and master mix (4 µg/mL biotinylated-teprotumumab +4 µg/mL SULFO-TAG-teprotumumab). Samples were transferred to blocked MSD Streptavidin GOLD 96-well SECTOR plate, incubated, visualized with MSD Gold Read buffer, and read on the MSD QuickPlex™ SQ 120.

Population pharmacokinetic analysis

The PopPK analysis dataset included data from six clinical studies. The final analysis dataset included 1168 teprotumumab serum concentration measurements from 186 subjects.

An overview of the baseline population covariates is provided in Table 5. Creatinine clearance was calculated using the Cockcroft-Gault formula. Regarding the Health status variable, there is a possibility for a study effect since this characteristic never varied within a study.

Table 5. Baseline population characteristics in the teprotumumab PopPK analysis dataset.

Characteristics		TED01RV (n=43)	HZNP-TEP-102 (n=10)	HZNP-TEP-301 (n=40)	HZNP-TEP-302 (n=25)	HZNP-TEP-303 (n=27)	HZNP-TEP-403 (n=41)	Total (n=186)
Continuous Covariates (Median [min-max])								
Age (years)		50.5 (22.3, 72.6)	43.5 (19.0, 53.0)	53.0 (31.0, 79.0)	51.0 (26.0, 80.0)	46.0 (20.0, 73.0)	49.0 (18.0, 73.0)	50.0 (18.0, 80.0)
Baseline body weight (kg)		75.0 (47.6, 169)	71.9 (55.6, 90.9)	72.0 (49.4, 110)	69.9 (44.5, 120)	59.0 (43.4, 100)	79.9 (48.6, 131)	72.7 (43.4, 169)
Aspartate aminotransferase (U/L)		21.0 (14.0, 66.0)	20.5 (13.0, 38.0)	19.0 (11.0, 73.0)	20.0 (13.0, 44.0)	18.0 (11.0, 56.0)	19.0 (8.00, 49.0)	20.0 (8.00, 73.0)
Alanine aminotransferase (U/L)		20.0 (10.0, 106)	18.0 (7.00, 46.0)	16.5 (7.00, 174)	16.0 (9.00, 59.0)	14.0 (8.00, 95.0)	16.0 (8.00, 57.0)	17.0 (7.00, 174)
Total bilirubin (µmol/L)		8.00 (3.40, 24.3)	7.80 (4.10, 23.3)	7.00 (4.00, 20.0)	6.00 (3.00, 14.0)	7.70 (3.20, 16.2)	7.50 (2.60, 24.5)	7.00 (2.60, 24.5)
Creatinine (mg/dL)		0.723 (0.441, 1.25)	0.969 (0.599, 1.10)	0.808 (0.463, 1.20)	0.791 (0.463, 1.10)	0.599 (0.305, 0.904)	0.701 (0.497, 1.20)	0.718 (0.305, 1.25)
Creatinine clearance (mL/min)		116 (52.2, 278)	111 (77.5, 148)	95.2 (41.6, 205)	102 (32.6, 191)	114 (81.9, 201)	121 (72.3, 237)	114 (32.6, 278)
Categorical Covariates [N (%)]								
Sex	Male	15 (34.88%)	6 (60.00%)	11 (27.50%)	5 (20.00%)	9 (33.33%)	10 (24.39%)	56 (30.11%)
	Female	28 (65.12%)	4 (40.00%)	29 (72.50%)	20 (80.00%)	18 (66.67%)	31 (75.61%)	130 (69.89%)
Race	White	37 (86.05%)	6 (60.00%)	34 (85.00%)	21 (84.00%)	—	22 (53.66%)	120 (64.52%)
	Asian	1 (2.33%)	1 (10.00%)	2 (5.00%)	2 (8.00%)	27 (100.00%)	7 (17.07%)	40 (21.51%)
	Black	4 (9.30%)	3 (30.00%)	4 (10.00%)	1 (4.00%)	—	9 (21.95%)	21 (11.29%)
	Other	1 (2.33%)	—	—	1 (4.00%)	—	3 (7.32%)	5 (2.69%)
Study region	Non-Japanese	—	—	—	—	27 (%)	—	27 (14.5%)
	Japanese	43 (100%)	10 (100%)	40 (100%)	25 (100%)	—	41 (100%)	159 (85.5%)
Ethnicity	Not Hispanic or Latino	41 (95.35%)	5 (50.00%)	38 (95.00%)	25 (100.00%)	27 (100.00%)	35 (85.37%)	171 (91.94%)
	Hispanic or Latino	2 (4.65%)	5 (50.00%)	2 (5.00%)	—	—	6 (14.63%)	15 (8.07%)
Heath status	Active TED patient	43 (100.00%)	—	40 (100.00%)	25 (100.00%)	27 (100.00%)	—	135 (72.58%)
	Chronic TED patient	—	—	—	—	—	41 (100.00%)	41 (22.04%)
	Healthy subject	—	10 (100.00%)	—	—	—	—	10 (5.38%)
Smoking status	Non-user	32 (74.42%)	—	31 (77.50%)	19 (76.00%)	23 (85.19%)	35 (85.37%)	140 (75.27%)
	User	11 (25.58%)	—	9 (22.50%)	6 (24.00%)	4 (14.82%)	6 (14.63%)	36 (19.36%)
	Missing	—	10 (100.00%)	—	—	—	—	10 (5.38%)

Based on the known PK properties of teprotumumab, the structural model is a two-compartment model with first-order elimination from the central compartment and redistribution from the peripheral compartment. Parameter estimates for the final teprotumumab PK model are shown in Table 6.

Table 6. Summary of estimated parameters and uncertainty from the final PopPK model.

Parameter	Parameter Description	Final PopPK Model		Bootstrap Estimates Median (2.5, 97.5%tiles)
		Estimate (% RSE)	Shrinkage	
$exp(\theta_1)*24$	Clearance, CL (L/day)	0.255 (1.52%)	12.1%	0.255 (0.245, 0.263)
θ_5	Influence of body weight on CL	0.709 (4.17%)	-	0.705 (0.556, 0.854)
$exp(\theta_2)$	Central volume, V_c (L)	2.91 (1.64%)	14.6%	2.91 (2.78, 3.02)
θ_6	Influence of body weight on V_c	0.618 (4.05%)	-	0.619 (0.475, 0.762)
$exp(\theta_3)*24$	Inter-compartmental clearance, Q (L/day)	0.478 (2.80%)	-	0.478 (0.426, 0.535)
$exp(\theta_4)$	Peripheral volume, V_p (L)	3.67 (2.16%)	43.8%	3.68 (3.38, 4.03)
ω_{CL}	IIV for CL (%)	20.4 (6.74%)	-	20.2 (17.3, 22.8)
ω_{Vc}	IIV for V_c (%)	24.4 (14.1%)	-	24.0 (17.8, 30.8)
ω_{Vp}	IIV for V_p (%)	32.4 (13.7%)	-	32.2 (22.0, 41.7)
$\Omega_{CL\sim Vc}$	Covariance (CL~V_c)	0.0214 (22.3%)	-	0.0211 (0.0125, 0.0307)
σ	Residual error (%)	19.3 (5.28%)	15.1%	19.2 (16.8, 21.6)

The ability of the final PopPK model to reproduce the central tendency and variability of the teprotumumab concentration data over time was evaluated using prediction-corrected visual predictive checks (pcVPC) based on 1000 simulated replicates of the PopPK dataset. A prediction-corrected visual predictive check (pcVPC) of teprotumumab serum concentration-time profile is shown in Figure 1. These results suggest that the final PopPK model adequately described the central tendency and variability of the observed serum teprotumumab concentration-time profiles across studies.

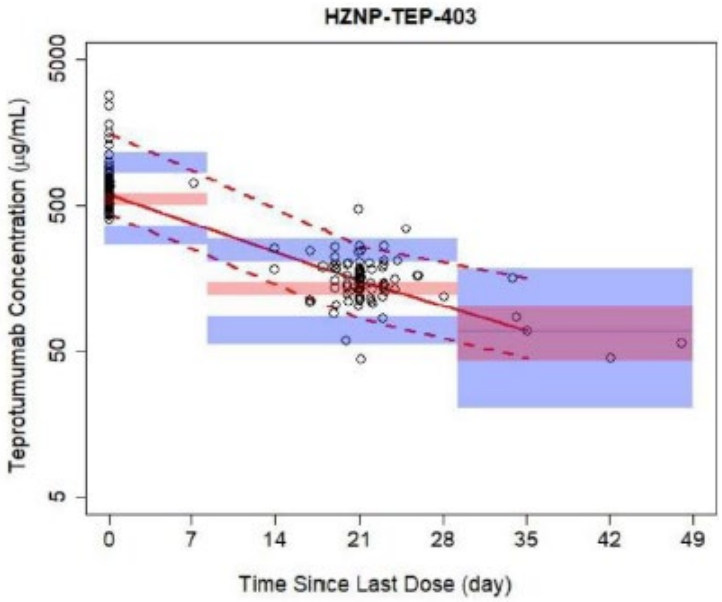


Figure 1. Prediction-corrected visual predictive checks of teprotumumab concentration-time profile. Black open circles are individual observed concentrations, solid red line represent the median observed concentrations, and dashed red lines represent 2.5th percentile and 97.5th percentiles of the observed concentrations over time. Red shaded areas represent the 95% CI of the predicted median concentrations, and blue shaded areas represent the 95% CI of the predicted 2.5th and 97.5th percentiles of the concentrations over time.

Absorption

Absorption is not relevant as the intended route of administration is intravenous.

Distribution

Population PK estimated mean (± standard deviation) for central and peripheral volume of distribution of teprotumumab were 3.01 (± 0.77) L and 3.76 (± 0.60) L, respectively.

Elimination

No specific studies have been performed to characterize the elimination of teprotumumab. Proteolytic degradation is expected and the lack of studies characterizing the elimination is acceptable. The PopPK estimated mean (± standard deviation) for the clearance of teprotumumab was 0.27 (± 0.07) L/day and for the elimination half-life was 22 (± 4) days.

Dose proportionality and time dependencies

A dose-proportional increase in exposure was observed in a Phase 1-study where 750 and 1500 mg were administered subcutaneously (see

Table 7 below). These s.c. doses correspond to somewhat lower i.v. doses but suggests linear pharmacokinetics in i.v. dose range 10–20 mg/kg.

Table 7. Geometric Mean (CV%) serum pharmacokinetic parameters of teprotumumab in study HZNP-TEP-102 after s.c. and i.v. administration

	TEPEZZA 750 mg SubQ (N=6)	TEPEZZA 1500 mg SubQ (N=10)	TEPEZZA 1500 mg IV (N=10)
C_{max} (ug/mL)	63.7 (38.3)	130 (42.1)	598 (20.7)
T_{max} (day)[a]	4.54 (3.04, 7.04)	5.04 (3.04, 7.04)	0.08 (0.08, 1.06)
AUC_{inf} (ug•day/mL)	1580 (28.2)	3670 (34.3)	6720 (25.8)
AUC_{last} (ug•day/mL)	1500 (27.1)	3250 (31.0)	6200 (24.2)
$t_{1/2}$ (day)	14.2 (10.1, 17.3)	19.6 (12.4, 29.8)	17.9 (12.8, 25.1)
CL/F (mL/day)	486 (28.2)	434 (34.3)	NA
CL (mL/day)	NA	NA	244 (25.8)

Time dependency has not been discussed by the applicant.

Intra- and inter-individual variability

Based on the post hoc individual parameter estimates of the 176 participants with TED using the final PopPK model, the geometric mean (%CV) and mean ± SD of post hoc individual CL, V_c, V_p, and $t_{½}$ are shown in Table 8.

Table 8. Summary of post hoc individual parameter estimates in participants with TED (n=176)

Parameter	Geometric Mean (%CV)	Arithmetic Mean ± SD
Clearance, CL (L/day)	0.257 (27.3%)	0.266 ± 0.0725
Central volume, V_c (L)	2.91 (25.6%)	3.01 ± 0.771
Peripheral volume, V_p (L)	3.71 (16.1%)	3.76 ± 0.603
Half-life, $t_{1/2}$ (day)	21.4 (16.9%)	21.7 ± 3.67

Pharmacokinetics in the target population

Health status was tested during PopPK covariate model development and was not identified as a significant covariate for teprotumumab PK. The geometric mean simulated exposures (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) in the healthy subjects, active TED patients, and chronic TED patients were up to 3.59% lower, 4.47% lower, and 17.3% higher, respectively, compared with those of the overall study population.

Special populations

No dedicated renal or hepatic impairment study was performed. Neither of sex, age, ethnic factors, renal function (CrCL) or hepatic function (ALT, AST, and BIL) were found to be significant covariates in the PopPK analysis. Weight was found to be a significant covariate on both clearance and central volume of distribution. When using weight-based dosing, higher body weight tends to result in higher central exposure metrics. Observed body weight ranged from 43.4 kg to 169 kg, median 72.7 kg. Variations in teprotumumab exposures over the entire observed body weight range are not expected to result in clinically meaningful changes in the efficacy or safety of teprotumumab.

Pharmacokinetic interaction studies

No PK interaction studies are performed. Conventional drug-drug interactions through metabolism and transporters are not expected for a monoclonal antibody like teprotumumab. Teprotumumab treatment did not cause obvious changes in pro-inflammatory cytokines such as IL-6 and IL-16 in the clinical studies, in

particular data from the Phase 2 study TED01RV showed similar cytokine levels at baseline, week 12 and week 24.

2.5.2.2. Pharmacodynamics

Mechanism of action

Teprotumumab (HZN-001) is a human monoclonal antibody (mAb) that targets and inhibits the insulin-like growth factor-1 receptor (IGF-1R)/thyroid-stimulating hormone receptor signalling complex, thereby blocking the autoimmune activation of orbital fibroblasts, potentially inhibiting the underlying pathogenesis of TED.

Primary and secondary pharmacology

No formal pharmacodynamic studies have been conducted with teprotumumab. In study 102, one exploratory objective was to evaluate the change in serum IGF-1 following a single SubQ or IV infusion of TEPEZZA in healthy adult subjects. Following single dose SubQ or IV administration of TEPEZZA, IGF-1 serum concentrations increased, and the increase was maintained for 70 days postdose.

With respect to CV safety, as a mAb, teprotumumab is not expected to interact directly with the hERG channel or other cardiac ion channels because of its large size and high specificity. Because of the low risk for QT liability for teprotumumab, a thorough QT study (based on ICH E14) was not considered necessary and was not conducted.

Other aspects of secondary pharmacology have not been discussed by the applicant.

Immunogenicity

Immunogenicity of teprotumumab was assessed in serum samples using a stepwise ADA analysis approach. Only the result from HZNP-TEP-301 is presented as the results from other studies are considered unreliable (e.g. problem with drug tolerance). Among 41 acute TED participants who received teprotumumab treatment, there were 2 participants confirmed ADA-positive at post-Baseline visits. Two participants were confirmed positive at Week 72 for anti-teprotumumab antibodies. However, both samples did not have sufficient antibodies (titer <1) for quantitative assessment following titer analysis.

Table 9. Summary of Immunogenicity (Anti-Drug Antibody) Results in study TEP-HZNP-301

Table 14.3.4.4.3
Incidence of Anti-Drug Antibody
(Safety Population)

	Placebo N=42	HZN-001 N=41
Incidence of Positive ADA by Visit, n/m (%) [1]		
Day 1	1/42 (2.4)	0/41
Week 3	1/41 (2.4)	0/40
Week 9	1/40 (2.5)	0/37
Week 24	1/37 (2.7)	0/38
Week 36	0/ 3	0/32
Week 72	0/ 4	2/32 (6.3)
Overall Positive, n/m (%) [2]	1/42 (2.4)	2/41 (4.9)
Cumulative Negative, n/m (%) [2]	41/42 (97.6)	39/41 (95.1)
Negative on Day 1 and Positive at any Post-Dose Visit, n/m (%) [3]	0/41	2/40 (5.0)

None of the clinical studies of teprotumumab required further evaluation of the presence of nAbs due to very low incidence of clinically relevant immunogenicity.

2.5.2.3. Pharmacokinetics-pharmacodynamics (PK/PD)

Exposure-response (E-R) analyses were performed for both safety and efficacy. However, only one dose (scaled by body weight) was tested.

2.5.2.4. Dose justification

Dose justification based on clinical pharmacology evidence rests on the assumption that saturation of elimination corresponds to saturation of target occupancy. The 90% saturation of target-mediated clearance was used as target exposure during Phase 2 dose selection.

2.5.3. Discussion on clinical pharmacology

2.5.3.1. Pharmacokinetics

The pharmacokinetics (PK) of teprotumumab is sufficiently described and used primarily for descriptive purposes.

The PK methods can overall be considered adequately validated for the intended purpose. Long-term stability covering the entire storage time period for samples in study TED01RV has not been presented. However, this issue is not further pursued as the PK is considered sufficiently characterised as there were other studies included in the submission with PK sampling that was used for the PK characterisation. Further, as stability has been shown up to 1111 days, there is no major concern for the samples not being stable at 1474 days.

Only a few patients developed ADA in study HZNP-TEP-301. The ADA incidence in other clinical studies is considered unreliable (e.g. problem with drug tolerance). Even though ADA characterisation with more than 41 participants would have been preferrable, it is considered sufficient for this application. The effect of anti-drug antibodies (ADAs) on PK appears negligible.

Teprotumumab shows classical IgG pharmacokinetics with a limited volume of distribution and a half-life of approximately three weeks, supporting drug administration every three weeks (Q3W). The observed accumulation ratio of approximately 2 aligns with the half-life of three weeks, given Q3W dosing. Proteolytic degradation is expected and the lack of studies characterizing the elimination is considered acceptable.

The population PK (PopPK) analysis was conducted using a dataset of 186 subjects (176 patients) and 1168 PK samples, which is considered adequate for describing the PK. Due to the low frequency, the exclusion of 4.42% of PK samples from the complete dataset is acceptable. The PopPK model adequately describes PK in TED patients and supports the information in section 5.2 of the SmPC.

The two-compartment model with linear elimination used for teprotumumab is well-established for monoclonal antibodies. Model parameters were estimated with adequate precision. The developed PopPK model for teprotumumab provides an adequate description of PK in TED patients and can be used to assess the impact of covariates on teprotumumab PK.

The reported clearance (CL) and half-life from Phase 1-study HZNP-TEP-102 are comparable with values from the PopPK analysis in the SmPC.

Regarding the covariate modelling, the covariates chosen for initial consideration appear reasonable concerning the criteria stated by the applicant (physiological plausibility, clinical relevance, prior knowledge of

similar compounds, and availability of data). Distributions of covariates in the analysis dataset across studies are considered adequate for performing a relevant covariate analysis. Weight was identified as a significant covariate on clearance (CL), which is expected for a monoclonal antibody and may be the reason for choosing a weight-based dosing throughout the development program. There is a tendency for a positive correlation between body weight and central exposure metrics using the proposed weight-based dosing regimen. However, this trend is negligible relative to the overall variability of exposures. Sex, age, or ethnic factors were not significant covariates in the PopPK model.

Previous data from the oncology development program suggested dose-dependent pharmacokinetics of teprotumumab at low doses (1 mg/kg), but not at the doses used in the current TED indication (10–20 mg/kg). No major time-dependency in PK is expected due to high concentrations (residing in the linear PK domain) and low immunogenicity.

Inter-individual variability in PK parameters is relatively low and not a source of concern. The same posology is recommended across all patients, and no dose adjustments are proposed for any special population. PK in healthy volunteers and patients with active TED are comparable, with slightly higher exposure observed in patients with chronic TED. This difference is not expected to have any relevant clinical impact.

The absence of dedicated PK studies in patients with severe renal or hepatic impairment is acceptable. No significant effects on PK are expected due to the nature of monoclonal antibodies.

No common CYP- or transporter mediated interactions is expected for a monoclonal antibody. In addition, it is agreed that indirect modulation of drug-metabolizing enzymes via cytokines by teprotumumab appears unlikely, given that no obvious changes in the levels of cytokines such as IL-6 were observed in the clinical studies.

Primary and secondary pharmacology were not discussed in detail by the applicant. However, potential safety issues such as hyperglycaemia and hearing impairment were identified. A thorough QT study was not performed, which is acceptable considering teprotumumab's large size and high specificity, making it unlikely to interact directly with cardiac ion channels like the hERG channel.

Pharmacokinetics-Pharmacodynamics (PK/PD)

The current application does not include any dose-ranging data, making it difficult to distinguish the effects of differences in patient characteristics on drug exposure and response from a true dose-response relationship. As a result, the exposure-response (E-R) analysis is inconclusive. This is not further pursued this analysis does not affect the assessment of the benefit-risk ratio (B/R).

Dose justification

Dose justification is mainly based on efficacy and safety data. Dose justification based on clinical pharmacology evidence rests on the assumption that saturation of elimination corresponds to saturation of target occupancy. Although the 90% saturation of target-mediated clearance was the target exposure used during Phase 2 dose selection, it is worth noting that there is no established correlation between the extent of IGF-1R saturation and TED efficacy. The proposed dose regimen is thus justified by the totality of the observed clinical efficacy and safety results.

Furthermore, as previously stated, only one dose (scaled by body weight) was tested. However, similar exposures across special populations and indications provide some clinical pharmacology justification for the proposed dose.

2.5.4. Conclusions on clinical pharmacology

In general, the pharmacokinetics of teprotumumab is adequately described. The application is approvable from a clinical pharmacology point of view.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

No dose response studies have been performed. The proposed posology is based on findings in literature that a teprotumumab serum concentration of 20 µg/mL would result in greater than 90% saturation of target-mediated clearance (implying greater than 90% saturation of IGF-1R).

A 20 mg/kg Q3W regimen for 7 doses following an initial dose of 10 mg/kg was chosen, as it was expected to maintain trough concentrations above 20 µg/mL in the majority of TED patients based on Bayesian post hoc estimates in 176 TED patients. The predicted minimum trough concentration of teprotumumab was 20.37 µg/mL after the first IV infusion and 68.71 µg/mL at steady state confirming that trough concentrations were consistently above 20 µg/mL during the whole treatment duration.

The exposure-response analysis indicated no meaningful correlation between teprotumumab exposures and minimum serum concentration at steady state and outcomes of the key efficacy and safety endpoints.

2.5.5.2. Main study(ies)

Two studies have been performed in EU/US (TED01RV and HZNP-TEP-301 (OPTIC)) and one in Japan (HZNP-TEP-303 (OPTIC-J) to support efficacy in patients with acute TED. These studies had a similar design. In addition, one follow-up study has been performed (HZNP-TEP-302/OPTIC X).

Further, the results of one study in patients with chronic TED have been submitted (HZNP-TEP-403).

Table 10. Clinical trials

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
TED01RV	24 week treatment completed March 2016 48-week Follow-up Period: Completed/ 22Feb2017	Phase II, randomized, double-masked, placebo controlled multicenter; US and Europe	Teprotumumab or placebo Q3W for a total of 8 infusions 10 mg/kg for first infusion; 20 mg/kg for subsequent infusions	Acute TED N=Teprotumumab 43, Placebo 44
HZNP-TEP-301 (OPTIC)	24 week treatment period completed 19Feb2019	Phase III, randomized, double-masked,	As above	Acute TED N=Teprotumumab 41, Placebo 42

	48-week Follow-up Period: Completed 21Jan2020	placebo controlled multicenter; US and Europe		
HZNP-TEP-303 (OPTIC-J)	24 week treatment period Completed/ Data Cutoff 14Jun2023 24-week OL Treatment Period: ongoing	Randomized, double-masked; placebo controlled, parallel-group multicenter; Japan	As above	Acute TED N=Teprotumumab 27, Placebo 27
HZNP-TEP-302 (OPTIC-X)	Completed/ 08Jun2020	24-week Follow-up Period (for proptosis non-responders in OPTIC) Multicenter; US and Europe	24-week Treatment Period with a subsequent Follow-up Period 24-week Treatment Period: OL 24-week Follow-up Period: no additional treatment	Acute TED N=51
HZNP-TEP-403	Completed 17 Mar2023 24-week OL Treatment Period: ongoing	Phase IV, randomized, double-masked, placebo controlled multicenter; US	As above	Chronic TED N=Teprotumumab 41, Placebo 20

Placebo controlled 24-week studies in patients with acute and chronic TED (TED01RV, HZNP-TEP-301, HZNP-TEP-303, HZNP-TEP-403)

Methods

TED01RV

Phase 2, multicenter, randomized,double-masked, placebo-controlled, efficacy and safety study of teprotumumab, administered every 3 Weeks by intravenous infusion in patients suffering from active thyroid eye disease (TED). Double masked section 24 weeks + follow-up phase of 48 weeks with no additional treatment during at least the first 12 weeks.

HZNP-TEP-301 (OPTIC)

Phase 3, randomized, double-masked, placebo-controlled, parallel-group, multicenter study of teprotumumab, administered every 3 Weeks by intravenous infusion in patients suffering from active thyroid eye disease (TED). Double masked section 24 weeks + open label follow-up study (HZNP-TEP-302).

HZNP-TEP-303 (OPTIC-J)

Phase 3, randomized, double-masked, placebo-controlled, parallel-group, multicenter trial evaluating teprotumumab treatment in Japanese Patients with active thyroid eye disease. Double masked section 24 weeks + open label follow-up study.

HZNP-TEP-403
Phase 4, Randomized, Double-masked, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of TEPEZZA® in Treating Patients with Chronic (Inactive) Thyroid Eye Disease. 24-week Double-masked Treatment Period.

- **Study Participants**

TED01RV, HZNP-TEP-301, HZNP-TEP-303

Main inclusion criteria

1. Aged 18-75 years (TED). 18 -80 years (OPTIC), 20-80 years (OPTIC J)

2. Clinical diagnosis of Graves' disease associated with active TED with a clinical activity score (CAS) ≥4 (≥3 OPTIC J) for the most severely affected eye (Study Eye).

3. Fewer than 9 months from onset of TED as determined by patient records.

4. Moderate-to-severe Active 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 (OPTIC and OPTIC J)

5. Proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED), as estimated by treating physician, and/or proptosis ≥ 18 mm. (OPTIC J)

6. No previous medical or surgical therapy for TED, excluding local supportive measures and oral steroids if the maximum cumulative dose was 10% for the previous 60 days.

7. Subjects were euthyroid or with mild hypo- or hyperthyroidism

8. Did not require immediate surgical ophthalmological intervention.

9. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤3 × the upper limit of normal (ULN) for the reference laboratory; serum creatinine 10% for the previous 60 days.

10. Subjects with diabetes were well controlled, demonstrated by no change in diabetes medication (oral or insulin) >10% for the previous 60 days

11. Women of childbearing potential, including those with an onset of menopause within the previous 2 years, required a negative pregnancy test at screening and all treatment visits up to follow-up Visit 2 (Week 36) postrandomization. They were also willing and able to use two different methods of

contraceptive, one of which had to be oral. Male subjects 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 study drug.

Main exclusion criteria

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision within the last 6 months of 2 lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement.
2. Corneal decompensation unresponsive to medical management.
3. Improvement in CAS of ≥2 points between screening and baseline.
4. Decrease in proptosis of ≥2 mm in the study eye between Screening and Baseline. (OPTIC)
5. Treatment with oral or IV steroids within the previous 3 months, except oral steroids for the treatment of TED with a cumulative dose of
6. 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 study.
7. Any previous treatment with rituximab (Rituxan® or MabThera®).
8. Previous orbital irradiation.
9. Identified pre-existing ophthalmic disease that in the judgment of the investigator would preclude study participation or complicate interpretation of study results

HZNP-TEP-403

Main inclusion criteria

1. Male or female at least 18 years old at Screening
2. Initial diagnosis of TED ≥ 2 years but < 10 years prior to Screening. Clinical diagnosis of
    a. stable cTED, as determined by participant medical records indicating a CAS ≤ 1 in both
    b. eyes for at least 1 year prior to Screening or all of the following:
    c. no progression in proptosis for at least 1 year prior to Screening
    d. if participant had history of diplopia due to TED, no progression in diplopia for at
    e. least 1 year prior to Screening
    f. no new inflammatory TED symptoms for at least 1 year prior to Screening
3. CAS ≤ 1 at the Screening and Baseline Visits
4. Proptosis ≥ 3-mm increase from the participant's baseline (prior to diagnosis of TED), as
    a. estimated by treating physician, and/or proptosis ≥ 3 mm above normal for race and
    b. gender
5. Participants must have been euthyroid with the baseline disease under control or had mild
    a. hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3]
    b. levels < 50% above or below the normal limits) at Screening. Every effort was made to
    c. correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state
    d. for the full duration of the trial.
6. Did not require immediate surgical ophthalmological intervention and was not planning
    a. corrective surgery/irradiation during the course of the trial

7. Diabetic participants must have had HbA1c ≤ 8.0% at Screening.
8. Participants with a history of IBD, ulcerative colitis or Crohn's disease must have been in
    a. clinical remission for at least 3 months, with no history of bowel surgery within 6 months
    b. prior to Screening and no planned surgery during the trial. Concomitant stable therapies
    c. for IBD without modifications in the 3 months prior to Screening were allowed.

Main exclusion criteria

9. Decreased BCVA due to optic neuropathy, defined by a decrease in vision of 2 lines on
10. the Snellen chart, new visual field defect or color defect secondary to optic nerve
11. involvement within the last 6 months
12. Corneal decompensation unresponsive to medical management in the study eye
13. Decrease in proptosis of ⩾ 2 mm in the study eye between Screening and Baseline
14. Prior orbital irradiation or orbital decompression in the study eye
15. Prior strabismus surgery
16. Alanine aminotransferase or aspartate aminotransferase > 3 × the upper limit of normal
17. (ULN) or estimated glomerular filtration rate ⩽ 30 mL/min/1.73 m2 at Screening
18. 7. Use of any steroid (IV, oral, steroid eye drops) for the treatment of TED or other
19. conditions within 3 weeks prior to Screening. Steroids were not to be initiated during the
20. trial. Exceptions included topical and inhaled steroids and steroids used to treat infusion
21. reactions.
22. Any treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the
23. first infusion of IP or tocilizumab (Actemra® or Roactemra®) within 6 months prior to the
24. first infusion of IP. Use of any other non-steroid immunosuppressive agent within 3 months prior to the first infusion of IP.

- **Treatments**

On Day 1 of the Double-Masked Treatment Period, subjects who met study eligibility criteria were randomly assigned in a 1:1 ratio (stratified by tobacco use status) to receive IV infusions q3W of either: Teprotumumab (10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions) or placebo (8 infusions)

- **Outcomes/endpoints**

Primary Outcomes

TED01RV

Responder rate at Week 24. A responder was defined as a subject with the following:

• A decrease in overall CAS ≥2 points AND

• A reduction in proptosis ≥2 mm, AND

• No deterioration of CAS in the Non-Study Eye (ie, increase of CAS ≥2 points OR increase in proptosis ≥2 mm) at the 24-week evaluation.

OPTIC and OPTIC J

The proptosis responder rate (percentage of subjects with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration [≥2 mm increase] of proptosis in the fellow eye) at Week 24.

HZNP-TEP-403

Change from Baseline at Week 24 in proptosis in the study eye.

Secondary Outcomes

TED01RV
GO-QoL(overall); proptosis, CAS (continuous variables); GO-QoL Visual Function; and GO-QoL Appearance.

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

HZNP-TEP-403
1. The 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. The change from Baseline at Week 24 in the GO-QoL questionnaire appearance and visual functioning subscales
3. The change from Baseline at Week 24 in diplopia as ordinal response categories
4. The 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. The complete binocular diplopia responder rate, defined as the percentage of participants with Baseline binocular diplopia > 0 and a score of 0 at Week 24

- **Sample size**

TED01RV

It was planned that 84 evaluable patients (42 per treatment arm) would be recruited over the planned recruitment period of 12 months. The study was powered at 80% if 42 evaluable patients per treatment group are included for a success rate of 30% in the placebo patients and an expected success rate of 60% in the active treatment patients. Up to 93 evaluable patients were to be enrolled to account for up to a 10% dropout rate.

OPTIC

In the prior study, TED01RV, a 51% difference (71% vs 20%) between teprotumumab and placebo was observed at Week 24 in favour of teprotumumab in proptosis reduction of 2 mm or more. A sample size of 38

subjects per group provides 90% power at the 2-sided alpha 0.05 level to detect a difference of 39% between teprotumumab and placebo; the sample size has been adjusted to allow for a 16% discontinuation rate.

OPTIC J

A total of 50 patients (25 per treatment group) was planned to be enrolled in the study. Assuming that a difference in the proptosis response rate between HZN-001 and placebo groups is 40%, this sample size provides 83% power to detect this difference using the 2-sided level of significance of 0.05. The 40% treatment difference was derived from the assumptions that the proptosis response rate in the HZN-001 group is 65% and the response in the placebo group is 25%.

HZNP-TEP-403

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

- **Randomisation and Blinding (masking)**

TED01RV, OPTIC, OPTIC J

Eligible subjects who met study entry criteria were randomly assigned (stratified by smoking status) to the double-masked treatment phase in a 1:1 ratio. On Day 1 of the Double-Masked Treatment Period, once all baseline procedures other than administration of drug had been completed, the masked site personnel accessed the interactive web response system (IWRS) to randomize the subject (OPTIC). The pharmacists responsible for preparing the HZN-001 solution or placebo solution for IV use were not masked. The investigator and all other study site personnel were masked to the treatment being administered. The study mask was to be broken only if the safety of a subject was at risk and the treatment plan depended on which medication he or she received.

HZNP-TEP-403

Eligible participants were randomized in a 2:1 ratio to teprotumumab or placebo. The pharmacists or designees responsible for preparing the teprotumumab or placebo solutions for IV administration were not masked to the identity of IP. The participant, Investigator and all other site personnel were masked to the IP being administered. The trial mask was to be broken only if the safety of a participant was at risk and the treatment plan depended on which IP he or she received.

- **Statistical methods**

Analysis populations

Safety population and Per Protocol population were defined in the same way across the 3 studies. Different definitions were used for ITT and mITT.

TED01RV

ITT population	all subjects randomized to treatment and received at least one dose of study medication
Modified Intent-to-Treat (mITT) population	all ITT subjects who had at least 1 post-baseline measurement of primary efficacy endpoint
OPTIC, OPTIC J and HZNP-TEP-403	
ITT population	all subjects randomized to treatment
Modified Intent-to-Treat (mITT) population	all ITT subjects who received at least 1 dose of study drug and had at least 1 post-baseline proptosis measurement
ALL STUDIES	
Safety population	all subjects who received at least 1 dose of study drug
Per Protocol (PP) population	all mITT subjects who completed the double-masked treatment period and did not incur any major protocol violations that would have challenged the validity of their data

ITT was the primary analysis set for efficacy analysis. The mITT and the PP analysis set were used to perform supplementary analyses of the primary efficacy analysis.

Primary analysis

Efficacy assessments were performed for both eyes at each assessment time point; however, only the study eye was to be used for the primary endpoint and the analyses for secondary endpoints as applicable. The same method used for the primary analysis was used for the fellow eye for descriptive purpose. The primary analysis in each of the studies was performed based on the ITT population.

TED01RV

The primary analysis was a logistic regression model with treatment group as the model effect and smoking status as a covariate. Patients missing the 24-week evaluation were considered to be treatment failures. The odds ratio comparing the experimental group to the control group was provided along with the corresponding 95% confidence intervals and p-value.

OPTIC

The primary analysis assessed the stratified difference in the proportions of proptosis responders between the treatment groups. Stratification for the analysis used the same factor as was used to stratify randomization, tobacco use (non-user, user). Estimates from the 2 strata were combined using Cochran-Mantel-Haenszel (CMH) weights. The test statistic was calculated by dividing the stratified difference by the standard error. A two-sided p-value was calculated assuming that the test statistic was distributed as a standard normal random variable under the null hypothesis.

Subjects missing the Week 24 evaluation were considered treatment failures (non-responders).

Further, subjects who prematurely discontinued study drug dosing prior to Week 21 during the double-masked treatment period were analysed as treatment failures (non-responders), unless an assessment at Week 24 was available.

The difference in response rates, comparing teprotumumab to placebo, was estimated along with the corresponding 95% CIs and p-values.

OPTIC J

The primary endpoint was analysed using Cochran-Mantel-Haenszel (CMH) test, adjusted for the randomization stratification factor (tobacco use status) to test the hypothesis that the proportion of proptosis responders at Week 24 differs between the HZN-001 and placebo groups. The stratified difference which is a weighted average of the difference within each stratum, standard error (SE), its 95% confidence interval (CI) and p-value were provided.

HZNP-TEP-403

A Mixed-Model for Repeated-Measures (MMRM) analysis of covariance model fitting to the individual change from baseline values for the study eye was used for the analysis of change from baseline in proptosis. The model includes baseline value, treatment group, visit, visit-by-treatment and visit-by-baseline value as fixed effects, and patient as a random effect. If there are any patients in the ITT analysis set without post-baseline values, a change from baseline value of 0 was imputed at the first post-baseline visit (in order to avoid exclusion of these patients from the MMRM analysis). The primary analysis was to test the treatment difference at Week 24. Analysis results at Week 24 include the estimated LS means, SEs and their difference with the SE, 95% CI for the difference and p-value. Further, the analysis was repeated using assessments obtained from the fellow eye based on the ITT analysis set.

Sensitivity analyses

The primary efficacy analysis was repeated for the mITT and PP populations as sensitivity analyses. In the OPTIC-J study, such analyses were named supplementary analyses.

TED01RV

In order to assess the impact of missing information, the following sensitivity analyses were performed:
- Patients missing the 24 week evaluation were analysed using their last observed value of responder status (LOCF) for the logistic regression model for the ITT population.
- All dropouts were analysed as treatment failures, notwithstanding their return for the 24 week assessment.
- An analysis was performed in which only patients with a non-missing 24 week evaluation, regardless of whether they completed all scheduled treatments, were included.

A chi-square test was performed to evaluate the difference in proportion of responders between treatment groups at Week 24 for the ITT population. The number and percentage of responders was presented by treatment, along with the treatment difference, the corresponding 95% confidence interval (CI) and p-value.

OPTIC

In order to evaluate the impact of missing data, the following additional sensitivity analyses were conducted using the primary analysis method:
- Subjects missing the Week 24 evaluation were analysed using their last available assessment for classification of responder or non-responder for the ITT Population. Data collected from premature withdrawal visits were considered for this analysis.

- An analysis was performed in which only subjects with a non-missing Week 24 evaluation were included, regardless of whether they completed all scheduled treatments.

Additionally, the primary analysis was repeated for the ITT Population using logistic regression, with treatment group as the fixed effect and tobacco use as a covariate in the model. Odds ratio, its 95% CI and p-value were provided. A chi-square test was performed to evaluate the difference in percentage of responders between treatment groups at Week 24 for the ITT population, considering subjects missing the Week 24 evaluation as treatment failures (non-responders). The number and percentage of responders was presented by treatment, along with the treatment difference, the corresponding asymptotic 95% CI and p-value.

OPTIC J

Logistic regression as described for the OPTIC study was performed. Also, a tipping point analysis was to be conducted if there are subjects who do not have data at Week 24 and therefore are considered non-responders in the primary analysis.

HZNP-TEP-403

A tipping point analysis was planned to be conducted to evaluate the robustness of the efficacy analysis result. In this analysis, multiple imputation (MI) was used to handle missing data based on the observed data in the placebo group. The full conditional specification (FCS) method was assumed as the missing data pattern and the predictive mean matching method was used to perform multiple imputation for missing data at each scheduled visit. The placebo-based MI procedure using FCS predicted mean matching method to impute missing values for proptosis measurement at each visit (Week 3, 6, 12, 18, and 24) was thoroughly described in the SAP.

Additional analyses on the primary endpoint

TED01RV

A stratified CMH test, with smoking status as the stratification factor, was conducted. The odds ratio comparing the experimental group to the control group was provided along with the corresponding 95% confidence intervals and p-value.

OPTIC

Time to proptosis response was characterized by Kaplan-Meier estimates and the treatment group difference was assessed by the log-rank test stratified by tobacco use status (non-user, user). Subjects not achieving a proptosis response within the double-masked treatment period was censored at their last visit date with a proptosis assessment within the double-masked treatment period. Any ITT subject who was randomized but not dosed was censored at Day 0.

OPTIC J

The analysis described for the primary endpoint was repeated for each of the other scheduled visits for the study eye, considering subjects missing the evaluations as treatment failures (non-responders). The same analysis was repeated for each scheduled visit using observed data.

Secondary analyses

TED01RV

Two subscales of the 16 question GO-QOL have been defined: "visual functioning" (VF) and "appearance" (A) – eight questions comprise each subscale. The sum the scores from each set of eight questions was calculated and transformed to a scale from 0 to 100 – one for VF and one for A. The scores were used as continuous measures and analysed separately for VF and A. For the overall score and the two subscale scores, a repeated measures mixed model (MMRM) was fit to the individual change from baseline in QOL scores, incorporating the baseline health score, smoking status, treatment group, time, time by treatment, and time by baseline health score interaction. If there are any patients in the ITT population without post-baseline values, a change from baseline value of 0 was imputed at the first post-baseline visit (in order to avoid exclusion of these patients from the MMRM analysis).

The analyses of the changes from baseline in proptosis values of the target eye were conducted using the same MMRM analysis as the QOL analyses, substituting the appropriate baseline assessments.

The analyses of the changes from baseline in CAS values of the target eye were conducted using the same MMRM analysis as the QOL analyses, substituting the appropriate baseline assessments.

OPTIC and OPTIC J

Secondary efficacy endpoints of overall responder rate, CAS categorical responder rate, and diplopia response rate were analysed with the same primary analysis and logistic regression analysis specified for proptosis responder rate.

Risk differences between teprotumumab and placebo was estimated along with the corresponding 95% CIs and p-values.

Secondary efficacy endpoints of change in proptosis and change in GO-QoL transformed overall score were analysed with a mixed model repeated measures (MMRM) analysis of covariance model fit to the individual change from baseline scores for the study eye, with terms in the model being the baseline score, tobacco use status (non-user, user), treatment group, visit and the visit-by treatment and visit-by-baseline-score interactions. The main results focused on the overall estimated least squares (LS) means with the associated standard errors (SE), and their difference with the SE, 95% CI and p-value. The p-value for the overall treatment difference between teprotumumab and placebo was used in the hierarchical testing of secondary endpoints.

In the OPTIC study, if there were any subjects in the ITT population without post-baseline values, a change from baseline value of 0 was imputed at the first post-baseline visit (in order to avoid exclusion of these subjects from the MMRM analysis). In the OPTIC-J, no imputation was performed.

The PK and safety data were analysed using descriptive statistics.

HZNP-TEP-403

Difference in proptosis responder rates at Week 24 for study eye between the two treatment groups (TEPEZZA minus placebo) on the ITT analysis set was compared using a two-sided Fisher Exact test. Patients whose Week 24 evaluation was missing were considered treatment failures (non-responders). A 95% exact CI around the proportion difference between the two treatment groups was provided. The same analysis was repeated using observed results. In this analysis, only patients with a non-missing evaluation at Week 24 were included.

Further, the definition of responder was applied for each scheduled visit in double-masked treatment period and the analysis of risk difference was performed, considering patients missing the evaluations as treatment failures (non-responders) and separately considering the observed results only. The analysis for fellow eye

was also conducted. A tipping point analysis was planned to be conducted to address missing data in the analysis proptosis responder rates.

The change from baseline at Week 24 in the GO-QoL questionnaire total scores and subscale scores was analysed using the same primary efficacy analysis method of MMRM model as specified for the primary efficacy endpoint.

The change from baseline at Week 24 in diplopia was categorized into the following 5 ordered categories: significant worsening (if change is 2 or 3), worsening (if change is 1), no change (if change is 0), improvement (if change is -1), significant improvement (if change is -2 or -3). The categorized variable was analysed using proportional odds model. If the Week 24 assessment was not done, the latest assessment score available for that patient was carried forward (LOCF) to define the Week 24 diplopia score for the ordinal response categorization. The estimate of the common odds ratio comparing TEPEZZA to placebo and its 95% CI was provided.

The binocular diplopia responder rate and Complete binocular diplopia responder rate was analysed by same methods as proptosis responder rates described above.

Multiplicity

To control the overall type I error, each of the individual trials analysed the primary and secondary efficacy endpoints in a hierarchical manner to control for multiplicity. If a statistically significant result in favour of teprotumumab was achieved for the primary efficacy endpoint at the 0.05 significance level, the secondary efficacy endpoints were tested at the same level in the following order:

TED01RV

1. Quality of Life - Overall Score
2. Proptosis
3. CAS
4. Quality of Life – Visual Function Score
5. Quality of Life – Appearance Score

OPTIC

1. Overall responder rate at Week 24
2. Percentage of subjects with a CAS value of 0 or 1 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 in the fellow eye at Week 24
5. Mean change from baseline to Week 24 in the GO-QoL questionnaire overall score

OPTIC J

1. Overall responder rate at Week 24
2. Percentage of subjects with a CAS value of 0 or 1 in the study eye at Week 24
3. Mean change from baseline to Week 24 in proptosis measurement in the study eye
4. Binocular diplopia responder rate at Week 24
5. Complete binocular diplopia responder rate
6. Mean change from baseline to Week 24 in the GO-QoL questionnaire overall score
7. Mean change from baseline to Week 24 in the GO-QoL questionnaire VF and A subscale scores

HZNP-TEP-403

1. Proptosis responder rate at Week 24
2. Change from Baseline at Week 24 in the GO-QoL appearance and visual functioning subscales
3. Change from Baseline at Week 24 in diplopia as ordinal response categories
4. Binocular diplopia responder rate at Week 24
5. Complete binocular diplopia responder rate.

Planned subgroup analyses

Subgroups of interest were largely similar in the OPTIC and OPTIC-J study and included following categories:

- Tobacco use status (non-user, user)
- Tobacco use history (never, former, current)
- Region (US, EU)
- Site
- Age category (<65 years, ≥65 years)
- Gender (male, female)
- Race (white, black or African American, Asian, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino).

Descriptive summaries were provided for various efficacy endpoints and TEAEs for select subgroups. If one of the subgroups had less than 5 subjects, no summary table was created, except for site and race. Sites were not pooled regardless of subject counts in the by-site subgroup analyses.

The primary efficacy endpoint in HZNP-TEP-403 was evaluated for subgroups of interest, including Tobacco use status, Age, Gender and Race.

Error probabilities, adjustment for multiplicity and interim analyses

Each of the individual trials analysed the primary and secondary efficacy endpoints in a hierarchical manner to control for multiplicity. If a statistically significant result in favour of teprotumumab was achieved for the primary efficacy endpoint at the 0.05 significance level, the secondary efficacy endpoints were analysed in a hierarchical manner to control the overall Type I error rate. For each secondary outcome measure, teprotumumab was tested against placebo at the 0.05 significance level only if the outcome measure preceding it was statistically significant in favour of teprotumumab.

No interim analysis was planned or performed in any of the studies.

Changes from protocol-specified analyses

TED01RV

The SAP version 2 included changes that were made in the protocol amendment, i.e., definition of a responder (primary endpoint) was changed, secondary endpoints were made hierarchical, and exploratory and sensitivity analyses for the primary endpoint were added.

OPTIC

The statistical analyses were conducted according to the SAP, dated 8th February 2019, for the data cut-off dated 19th February 2019. No changes from the SAP and no post-hoc analyses are apparent.

Following changes from the planned analyses in the Protocol Version 4.0 were included the SAP:

- The safety analysis population definition was changed from subjects who received at least 1 dose of study drug and had at least 1 post-dose safety assessment to require only that the subject received at least 1 dose of study drug.
- The focus of the continuous secondary endpoints (proptosis and GO-QoL) was revised to the overall treatment differences through Week 24, with the main results consisting of the overall estimated LS means, SEs and their differences with the SE, 95% CI and p-value.

OPTIC J

The statistical analyses were conducted according to the SAP, dated 23rd March 2023, which was prior to the database lock for the double-masked treatment period (14th June 2023). No post-hoc analyses are apparent. Of note, as mITT and ITT were identical, a sensitivity analysis using the mITT was omitted. Also, a tipping point analysis was not conducted as there were no missing data at Week 24.

HZNP-TEP-403

The final SAP (version 5) dated 21 March 2023, was finalized prior to database lock and unmasking (30 March 2023). Between the initial and last version of the protocol, the study design has been changed, sample size increases twice, endpoints added, and analysis methods updated. Changes from the protocol specified analyses are described in the SAP. No changes from the SAP and no post-hoc analyses are apparent.

Results

- **Participant flow**

Table 11. Participant 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).

- **Recruitment**

Refer to Table 4.

- **Conduct of the study**

All study protocols were amended, but in general no major amendments were identified. However, for study 403, the study protocol was amended 3 times and the sample size was increased twice. It is noted that 50% of subjects in the active arm had a major protocol deviation.

- **Baseline data**

Table 12. Demographic Characteristics (ITT Analysis Set)

Parameter Statistic	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)
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)

Parameter Statistic	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)
Weight (kg)										
Mean (SD)	80.8 (21.40)	80.8 (19.66)	75.8 (18.51)	75.0 (16.54)	60.0 (11.42)	61.3 (12.52)	74.0 (19.98)	73.9 (18.48)	79.2 (24.20)	81.7 (18.97)
Median	73.5	75.0	74.5	73.9	61.4	59.0	70.2	71.1	71.7	80.6
Min, max	54, 169	48, 138	45, 123	49, 110	39, 82	43, 100	39, 169	43, 138	46, 130	49, 131

AA = African American; ITT = intent-to-treat; max =maximum; min = minimum; NH/PI = Native Hawaiian or Other Pacific Islander; SD = standard deviation; TED = thyroid eye disease; Tepro = teprotumumab

a. Participants with more than 1 race indicated appear in the "Other" category.

Source: ISE Tables 2.1 and 2.2

Table 13. Baseline characteristics (ITT Analysis set)

	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

	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)**
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.

- **Numbers analysed**

See tables below presenting numbers in populations analysed

- **Outcomes and estimation**

Table 14. Primary and Secondary Efficacy Endpoints at Week 24 (TED01RV; ITT Population)

Primary Endpoint[a]	**Placebo (N = 45)**	**Teprotumumab (N = 42)**	**Odds Ratio**	**95% CI**	**p-value**
Overall responder rate at Week 24[b]					
n (%)	9 (20.0)	29 (69.0)	8.86	3.293, 23.825	< 0.001
Secondary Endpoints[c]			**Difference**	**95% CI**	**p-value**
Mean change from Baseline in GO-QoL overall score through Week 24					
LS mean (SE)	6.42 (2.242)	17.28 (2.410)	10.86 (3.207)	4.483, 17.241	0.001
Mean change from Baseline in proptosis (mm) through Week 24					
LS mean (SE)	-0.15 (0.188)	-2.46 (0.200)	-2.31 (0.269)	-2.843, -1.772	< 0.001
Mean change from Baseline in CAS (points) through Week 24					
LS mean (SE)	-1.85 (0.172)	-3.43 (0.181)	-1.59 (0.245)	-2.073, -1.098	< 0.001
Mean change from Baseline in GO-QoL visual functioning through Week 24					
LS mean (SE)	6.80 (2.656)	21.10 (2.900)	14.30 (3.841)	6.663, 21.941	< 0.001
Mean change from Baseline in GO-QoL appearance through Week 24					
LS mean (SE)	6.60 (2.656)	12.92 (2.836)	6.32 (3.810)	-1.255, 13.901	0.101

CAS = Clinical Activity Score; CI = confidence interval; CSR = clinical study report; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; SE = standard error

a. Odds ratio (teprotumumab - placebo), 95% CI and p-value were from a logistic regression with treatment and tobacco use status (non-user vs. user) as covariates.

b. Overall responders (participants with a ≥ 2-mm reduction in proptosis AND a ≥ 2-point reduction in CAS from Baseline in the study eye, without deterioration [≥ 2-mm increase in proptosis or ≥ 2-point increase in CAS] in the fellow eye at Week 24); participants missing the Week 24 evaluation were considered non-responders.

c. Results from a mixed model repeated-measures analysis with an unstructured covariance matrix using treatment, tobacco use, Baseline value, visit, treatment-by-visit and visit-by-Baseline value interaction as fixed effects.

Table 15. Primary and Secondary Efficacy Endpoints at Week 24 (OPTIC; ITT Population)

	Placebo (N = 42)	Teprotumumab (N = 41)	Difference	95% CI	p-value
Primary Endpoint:					
Proptosis responder rate at Week 24[a,b]					
n (%)	4 (9.5)	34 (82.9)	73.45 (7.43)	58.89, 88.01	< 0.001
Secondary Endpoints:					
Overall responder rate at Week 24[a,b]					
n (%)	3 (7.1)	32 (78.0)	70.82 (7.62)	55.89, 85.75	< 0.001
CAS responder rate at Week 24[a,b]					
n (%)	9 (21.4)	24 (58.5)	36.03 (9.51)	17.39, 54.67	< 0.001
Mean change from Baseline in proptosis (mm) through Week 24[c]					
LS mean (SE)	-0.54 (0.192)	-2.82 (0.191)	-2.28 (0.244)	-2.77, -1.80	< 0.001
Diplopia responder rate at Week 24[a,b,d]					
n/N (%)	8/28 (28.6)	19/28 (67.9)	39.29 (12.11)	15.55, 63.02	0.001
Mean change from Baseline in GO-QoL overall score through Week 24[c]					
LS mean (SE)	4.43 (2.102)	13.79 (2.074)	9.36 (2.651)	4.08, 14.64	< 0.001

CAS = Clinical Activity Score; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CSR = clinical study report; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; MMRM = mixed model repeated-measures; SE = standard error

a. Stratified difference is a weighted average of the difference within each stratum. Estimates from the 2 strata (tobacco user, tobacco non-user) were combined with CMH weights. Test statistic calculated by dividing the stratified difference by the SE. Two-sided p-value was calculated assuming the test statistic was distributed as a standard normal random variable.
b. Responder definitions: proptosis (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); overall (participants with a ≥ 2-mm reduction in proptosis AND a ≥ 2-point reduction in CAS from Baseline in the study eye, without deterioration [≥ 2-mm increase in proptosis or ≥ 2-point increase in CAS] in the fellow eye at Week 24); CAS (participants with a reduction to a CAS of 0 or 1 [no or minimal inflammation] as a categorical response variable at Week 24); diplopia (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). Participants missing the Week 24 evaluation were considered non-responders.
c. Results from an MMRM with an unstructured covariance matrix including the following terms: Baseline value, tobacco use status, treatment group, visit, visit-by-treatment interaction and visit-by-Baseline value interaction. A change from Baseline of 0 was imputed at the first post-Baseline visit for any participant without a post-Baseline value.
d. Denominator is number of participants who had diplopia at Baseline.

Table 16. Primary and Secondary Efficacy Endpoints at Week 24 (OPTIC-J;ITT Analysis Set)

Endpoint	Teprotumumab (N = 27)	Placebo (N = 27)	Treatment Difference (95% CI)	p-value
Primary: proptosis responder rate at Week 24, n (%)[a]	24 (88.9)	3 (11.1)	77.78 (60.7, 94.8)	< 0.0001[b]
Secondary				
Overall responder rate at Week 24, n (%)[c]	21 (77.8)	1 (3.7)	74.07 (56.9, 91.3)	< 0.0001[b]
CAS categorical responder rate at Week 24, n (%)[d]	16 (59.3)	6 (22.2)	37.04 (12.5, 61.6)	0.0031[b]
Change from Baseline in proptosis at Week 24, LS mean (SE)	-2.36 (0.302)	-0.37 (0.303)	-1.99 (-2.75, -1.22)	< 0.0001[e]
Binocular diplopia responder rate at Week 24, n (%)[f]	n = 22 14 (63.6)	n = 20 9 (45.0)	16.82 (-11.4, 45.1)	0.2430[b]
Complete binocular diplopia responder rate at Week 24, n (%)	n = 22 11 (50.0)	n = 20 4 (20.0)	29.09 (0.9, 57.3)	0.0430[b]
Change from Baseline in GO-QoL overall score at Week 24, LS mean (SE)	17.39 (3.355)	6.39 (3.351)	11.01 (2.65, 19.36)	0.0109[e]
Change from Baseline in GO-QoL appearance subscale score at Week 24, LS mean (SE)	19.35 (3.931)	8.69 (3.925)	10.66 (1.04, 20.28)	0.0306[e]
Change from Baseline in GO-QoL visual functioning subscale score at Week 24, LS mean (SE)	16.22 (3.959)	4.39 (3.968)	11.83 (1.82, 21.83)	0.0215[e]

CAS = Clinical Activity Score; CSR = clinical study report; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; SE = standard error

Note: No participant had a missing evaluation at Week 24 for the endpoints included in this table.

Note: Results shown are those for the study eye, if applicable.

a. Proptosis responders were defined as participants with a ≥ 2-mm reduction from Baseline in proptosis in the study eye, without deterioration (≥ 2-mm increase) of proptosis in the fellow eye at Week 24.
b. p-value was estimated from Cochran-Mantel-Haenszel test adjusted for the randomization stratification factor (tobacco use status).
c. Overall responders were defined as participants with a ≥ 2-mm reduction in proptosis AND a ≥ 2-point reduction in CAS from Baseline in the study eye, provided there was no corresponding deterioration (≥ 2-mm increase in proptosis or ≥ 2-point increase in CAS in the fellow eye) at Week 24.
d. CAS categorical responders were defined as participants with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) at Week 24.
e. p-value is from mixed model repeated measurements analysis with an unstructured variance-covariance matrix including change from Baseline value as the dependent variable and the following covariates: Baseline value, treatment group, tobacco use status, visit, visit-by-treatment and visit-by-Baseline value interactions.
f. Binocular diplopia responders were defined as participants with Baseline binocular diplopia > 0 who had a reduction of ≥ 1 grade at Week 24.
i. Complete binocular diplopia responders were defined as participants with Baseline binocular diplopia > 0 and a score of 0 at Week 24.

Table 17. Primary and Other Efficacy Endpoints at Week 24 (HZNP-TEP-403, ITT Analysis Set)

Endpoint	Teprotumumab (N = 42)	Placebo (N = 20)	Treatment Difference (95% CI)	p-value
Primary: change from Baseline in proptosis at Week 24 in the study eye, LS mean (SE)	-2.41 (0.228)	-0.92 (0.323)	-1.48 (-2.28, -0.69)	0.0004[a]
Other				
Proptosis responder rate at Week 24, n (%)[b]	26 (61.9)	5 (25.0)	36.9 (5.4, 59.2)	0.0134[c]
Change from Baseline in GO-QoL visual functioning subscale score at Week 24, LS mean (SE)	n = 39 8.73 (1.661)	n = 20 2.41 (2.329)	6.31 (0.57, 12.06)	0.0318[a]
Change from Baseline in GO-QoL appearance subscale score at Week 24, LS mean (SE)	n = 39 10.03 (3.592)	n = 20 7.19 (5.069)	2.85 (-9.62, 15.32)	0.6494[a]
Treatment comparison for change from Baseline in diplopia as ordinal response categories[d] Odds ratio (teprotumumab vs. placebo)/95% CI			2.13/ (0.39, 11.60)	0.3815[e]
Binocular diplopia responder rate at Week 24, n (%)[f]	n = 14 6 (42.9)	n = 4 2 (50.0)	-7.1 (-57.3, 44.3)	> 0.9999[c]
Complete binocular diplopia responder rate at Week 24, n (%)[g]	n = 14 4 (28.6)	N = 4 1 (25.0)	3.6 (-53.3, 46.1)	> 0.9999[c]

CI = confidence interval; CSR = clinical study report; GO-QoL = Graves' Ophthalmopathy Quality of Life; ITT = intent-to-treat; LS = least squares; SE = standard error

Note: For responder rates, a participant missing the Week 24 evaluation was considered a non-responder.

Note: Results shown are those for the study eye, if applicable.

a. p-value is from mixed effect repeated measurement analysis with an unstructured variance-covariance matrix including change from Baseline value as the dependent variable and the following covariates: Baseline value, treatment group, 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 participant without post-Baseline values.

b. Proptosis responders were defined as participants with a ≥ 2-mm reduction from Baseline in proptosis in the study eye, without deterioration (≥ 2-mm increase) of proptosis in the fellow eye at Week 24.

c. p-value is from Fisher exact test.

d. Change from Baseline was categorized into 5 categories: significant worsening if change score was 2 or 3; worsening if change score was 1; no change if change score was 0; improvement if change score was -1; significant improvement if change score was -2 or -3. If the Week 24 assessment was not done, the latest assessment score available for that participant was carried forward to define the Week 24 diplopia score.

e. p-value is from a proportional odds model with treatment as the model effect.

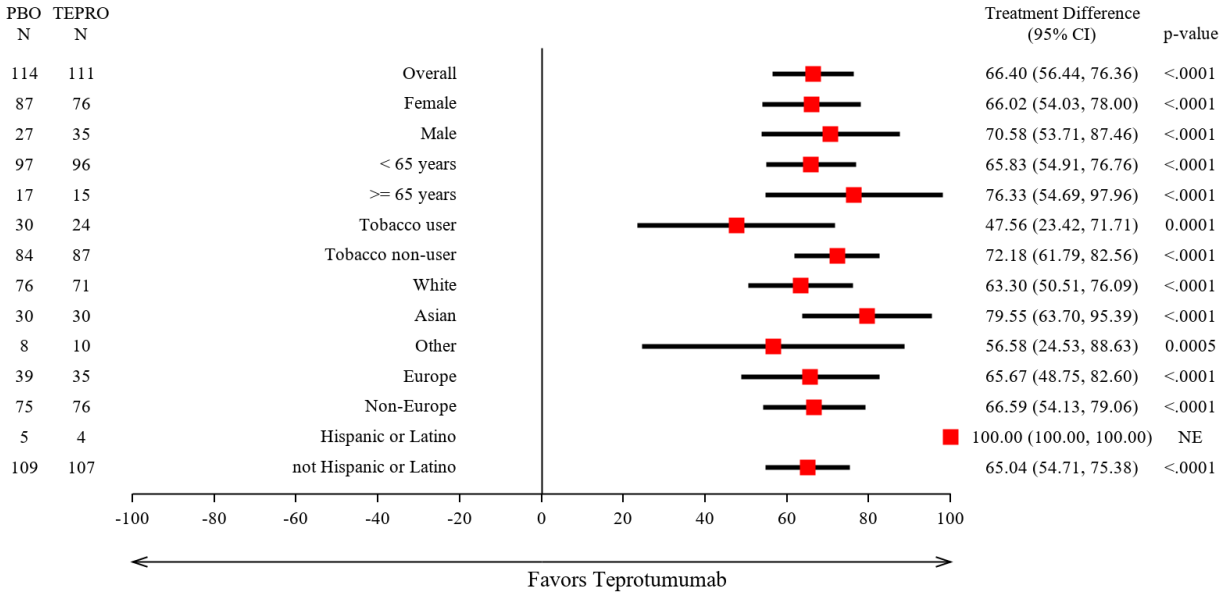
f. Binocular diplopia responders were defined as participants with Baseline binocular diplopia > 0 who had a reduction of ≥ 1 grade at Week 24.

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

- **Ancillary analyses**

The primary efficacy endpoint was examined and compared in prespecified subgroups in the acute TED studies based on gender, age, tobacco use, race and geographic location.

Figure 2. Difference in proptosis responder rate at week 24 by subgroup in the acute TED trials (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.

Table 18. Difference in Proptosis Responder Rate at Week 24 (Study Eye) by Special Population (ITT Analysis Set)

Special Population Statistic	Controlled Trial				Non-controlled Trial
	Active		Chronic		Active
	Placebo	TEPRO	Placebo	TEPRO	TEPRO
Mild Hepatic Impairment					
Responder, n/m (%)[a]	0/6 (0.0)	5/9 (55.6)	0/1 (0.0)	4/4 (100.0)	2/2 (100.0)
Non-Responder, n/m (%)	6/6 (100.0)	4/9 (44.4)	1/1 (100.0)	0/4 (0.0)	0/2 (0.0)
Stratified Difference in Response Rates (TEPRO - Placebo)[b]					
Estimate (SE)		50.0 (20.4)		NE (NE)	
95% CI		(10.0, 90.0)		(NE, NE)	
Age 65 to 74					
Responder, n/m (%)[a]	3/16 (18.8)	11/13 (84.6)	0/3 (0.0)	3/5 (60.0)	5/7 (71.4)
Non-Responder, n/m (%)	13/16 (81.3)	2/13 (15.4)	3/3 (100.0)	2/5 (40.0)	2/7 (28.6)

Special Population Statistic	Controlled Trial				Non-controlled Trial
	Active		Chronic		Active
	Placebo	TEPRO	Placebo	TEPRO	TEPRO
Stratified Difference in Response Rates (TEPRO - Placebo)[b]					
Estimate (SE)		69.0 (12.9)		60.0 (21.9)	
95% CI		(43.7, 94.2)		(17.1, 100.0)	
Age 75 to 84					
Responder, n/m (%)[a]	0/1 (0.0)	2/2 (100.0)	0/1 (0.0)	0/0 (-)	0/1 (0.0)
Non-Responder, n/m (%)	1/1 (100.0)	0/2 (0.0)	1/1 (100.0)	0/0 (-)	1/1 (100.0)
Stratified Difference in Response Rates (TEPRO - Placebo)[b]					
Estimate (SE)		NE (NE)		NE (NE)	
95% CI		(NE, NE)		(NE, NE)	

CI = confidence interval; ITT = Intent-to-treat; NE = Not Estimable; SE = Standard Error; TED = Thyroid Eye Disease; TEPRO = Teprotumumab.
Note 1: Active Controlled Trials: TED01RV, HZNP-TEP-301, HZNP-TEP-303; Chronic Controlled Trial: HZNP-TEP-403; Non-controlled Trial: HZNP-TEP-302.
[a] The proptosis responder rate is defined as the percentage of subjects with a ≥ 2 mm reduction from Baseline in proptosis in the study eye, without deterioration (≥2 mm increase) of proptosis in the fellow eye at week 24. A subject with a missing assessment at week 24 is considered as a "Non-Responder".
[b] The estimate, SE, and 95% CI are estimated from Cochran-Mantel-Haenszel test, adjusted for study if applicable.
The terms active and acute are used analogously in the submission documentation.
Source: ISE Table 14-11.2.1.

2.5.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Integrated Efficacy Analyses

The objective of the integrated efficacy analyses was to characterize the overall efficacy profile of teprotumumab compared with placebo after 24 weeks of treatment. Selected clinical data up to the Week 24 evaluation from the acute TED trials (Phase 2 trial TED01RV and Phase 3 trials OPTIC and OPTIC-J) were integrated to support this objective.

Table 19. Integrated efficacy analyses for primary and secondary efficacy endpoints week 24

	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: Responder definitions are provided in Section 1.4. 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 TED01RV, 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.

2.5.5.4. Supportive study(ies)

TED01RV

Following completion of the 24-week Double-masked Treatment Period, participants entered a follow-up period of 48 weeks with no additional trial treatment. Participants attended clinic visits at Weeks 28, 36, 48, 60 and 72. A total of 76 (87.4%) subjects (39 [86.7%] in the placebo group and 37 [88.1%] in the teprotumumab group) completed study treatment (Week 24). Of these, all but 2 subjects (1 in each treatment group) also completed study TED01RV off-treatment Follow-up Period Week 72 visit.

Table 20. Proportion of Overall Responders and Proptosis Responders at Week 24, Week 28 and Week 72 (Follow-up Period of TED01RV; ITT Population; Study Eye)

Efficacy Endpoint (Observed Cases)[a]	Week 24		Week 28		Week 72	
Overall responders, n (%)	Placebo	Tepro	Placebo	Tepro	Placebo	Tepro
Responder[b]	9/39 (23.1)	29/38 (76.3)	6/38 (15.8)	31/36 (86.1)	10/38 (26.3)	19/37 (51.4)
Non-responder	30/39 (76.9)	9/38 (23.7)	32/38 (84.2)	5/36 (13.9)	28/38 (73.7)	18/37 (48.6)
Proptosis responders, n (%)						
Responder[c]	9/39 (23.1)	30/38 (78.9)	6/38 (15.8)	31/36 (86.1)	10/38 (26.3)	19/36 (52.8)
Non-responder	30/39 (76.9)	8/38 (21.1)	32/38 (84.2)	5/36 (13.9)	28/38 (73.7)	17/36 (47.2)

14 teprotumumab-treated participants did not maintain their responder status at Week 72 after achieving proptosis response at Week 24 (including 1 participant due to missing data), but only 2 participants had a proptosis measurement that increased from Baseline.

OPTIC follow up study

Following the Double-masked Treatment Period, the durability of effect was evaluated for proptosis responders in an off-treatment Follow-up Period for 48 weeks. Participants who completed the 48-week treatment-free Follow-up Period had their final visit at Week 72 (51 weeks after their last IP infusion).

Subjects who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter an open-label extension study (HZNP-TEP-302, referred to as OPTIC-X, see below).

A total of 39 subjects [95.1%] in the teprotumumab group and 40 [95.2%] in the placebo group completed the Double-Masked Treatment Period at week 24. The majority of the subjects in the teprotumumab group (36 [87.8%]) continued into the Follow-Up Period whereas the majority of the subjects in the placebo group (36 [85.7%]) enrolled in OPTIC-X.

A total of 20 (48.8%) teprotumumab subjects completed the 48-week Follow-Up Period of the study.

Table 21. Overall Responder Rate in the Follow-Up Period (Study Eye; ITT Population; Observed Cases)

Visit Response	Placebo	Teprotumumab
Week 28	n = 4	n = 35
Responder, n (%)	2 (50.0)	30 (85.7)
Non-responder, n (%)	2 (50.0)	5 (14.3)
Week 36	n = 3	n = 33
Responder, n (%)	2 (66.7)	30 (90.9)
Non-responder, n (%)	1 (33.3)	3 (9.1)
Week 48	n = 3	n = 33
Responder, n (%)	2 (66.7)	24 (72.7)
Non-responder, n (%)	1 (33.3)	9 (27.3)
Week 60	n = 3	n = 25
Responder, n (%)	2 (66.7)	19 (76.0)
Non-responder, n (%)	1 (33.3)	6 (24.0)
Week 72	n = 3	n = 21
Responder, n (%)	2 (66.7)	18 (85.7)
Non-responder, n (%)	1 (33.3)	3 (14.3)

Among the 33 teprotumumab subjects who were Week 24 proptosis responders and entered the Follow-Up Period, 10 (30.3%) subjects relapsed during the Follow-Up Period; 1 teprotumumab subject who was a Week 24 proptosis responder did not enter the Follow-Up Period.
Median time to relapse could not be estimated because <50% of subjects relapsed during the Follow-Up Period, although 25% of the subjects had relapsed by Day 253. Relapse occurred at Week 48 for 7 subjects, at Week 60 for 2 subjects, and after Week 72 for 1 subject.

Patients remaining in the study at week 72 entered the Follow-Up Contact Period (Week 96 and Week 120) of the trial, which included telephone calls and/or email to subjects after 6 months and 12 months by research staff to enquire if any treatment for TED has been received since last trial contact. Two of the 23 subjects who had data collected in the Follow-Up Contact Period received at least 1 treatment for TED during the Follow-Up Contact Period. Both subjects had received teprotumumab during the Double-Masked Treatment Period.

OPTIC X
OPTIC-X was a multicenter, open-label extension trial conducted in the US and Europe of the safety and efficacy of teprotumumab in participants who completed the 24-week double-masked treatment period in OPTIC and were proptosis non-responders or proptosis responders at Week 24 but met criteria for re-treatment due to relapse during the Follow-up Period of OPTIC.
Criteria to determine relapse were the following:
• Increase in proptosis of ≥2 mm in the study eye since Week 24 of OPTIC, or
• An increase in CAS of ≥2 points since Week 24 with an absolute CAS of ≥4 in the study eye following Week 24 of 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) in an open-label fashion. For subjects

who entered OPTIC-X because they were proptosis non-responders in OPTIC, the Treatment Period in OPTIC-X was followed by a 24-week Follow-up Period. During this Follow-up Period, trial drug was not administered, and clinic visits occurred 1, 3 and 6 months after the Week 24 Visit of the open-label Treatment Period.

Fifty-one participants entered the trial. Thirty-seven participants received placebo and 14 received teprotumumab in OPTIC. In OPTIC-X, these participants are referred to as "first-course" (participants who received placebo in OPTIC) and "second-course" (participants who received teprotumumab in OPTIC).

Table 22. Overview of Primary and Secondary Efficacy Endpoint Results Relative to Study Baseline (ITT Population)

	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)

Among the 32 first-course subjects who were proptosis non-responders in OPTIC and proptosis responders at Week 24 in OPTIC-X, the percentage of subjects with sustained proptosis response was 100% at Week 28, 96.9% at Week 36 and 90.6% at Week 48.

2.5.6. Discussion on clinical efficacy

Thyroid eye disease (TED), also known as Graves' orbitopathy (GO) is primarily a disease of the orbit where the orbital tissue undergoes inflammation, expansion and remodeling. Although most commonly associated with Graves' hyperthyroidism, TED also occurs rarely in patients with other autoimmune thyroid diseases.

The natural history of TED involves an initial progressive worsening of signs and symptoms with visible signs of inflammation known as the active/acute phase (lasts in most case 1 to 3 years). In this phase, patients may present with orbital pain, periorbital inflammation, proptosis, eyelid retraction, strabismus and diplopia. Sight-threatening disease affects 6% of TED patients.

The acute phase is followed by an inactive/chronic phase during which no further deterioration occurs, but some symptoms and remodelling of orbital tissue may remain. In this phase, the histopathology becomes increasingly fibrotic in nature.

Design and conduct of clinical studies

Five trials have been conducted to evaluate the efficacy of teprotumumab for the TED indication:

- Three independent, randomized, double-masked, placebo-controlled, parallel-group, multicenter trials that evaluated the efficacy and safety of teprotumumab for the treatment of moderate to severe acute TED: Phase 2 Trial TED01RV and Phase 3 Trial HZNP-TEP-301 (OPTIC) conducted in the US and Europe and Phase 3 Trial HZNP-TEP-303 (OPTIC-J) conducted in Japan
- A Phase 3 open-label extension of OPTIC: HZNP-TEP-302 (OPTIC-X)
- A Phase 4 randomized, double-masked, placebo-controlled, parallel-group, multicenter trial that evaluated the efficacy and safety of teprotumumab in participants with chronic TED: HZNP-TEP-403

No formal pharmacodynamic studies have been conducted with teprotumumab. Data and discussions pharmacology are included in the relevant sections of this report.

No dose response studies have been performed. The proposed posology is based on earlier clinical studies conducted in oncology indications indicating that a teprotumumab serum concentration of 20 µg/mL would result in greater than 90% saturation of target-mediated clearance (implying greater than 90% saturation of IGF-1R).

The lack of PD and dose response studies is a limitation, but not considered as crucial since the results from phase III/IV studies are available. The phase 3b/4 clinical study HZNP-TEP-402 is ongoing with the aim to evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for re-treatment in patients with TED. The study is included in the RMP and the study results are expected in late 2026.

<u>Design of pivotal studies (24 weeks treatment phase)</u>

Two studies have been performed in EU/US (TED01RV and HZNP-TEP-301 (OPTIC)) and one in Japan (HZNP-TEP-303 (OPTIC-J) to support efficacy in patients with acute TED. In addition, one follow up study has been performed (OPTIC X).

The design of the 3 studies supporting the treatment effect in patients with acute TED is to a large extent similar. All studies were placebo controlled, double blinded and randomised with a treatment phase of 24 weeks. All studies included follow-up phases. The studies are rather small, but the fact that more than one study has been performed is a strength of the dossier since results could be replicated.

Inclusion and exclusion criteria aimed at including adult patients with acute TED with a duration of maximum 9 months and with moderate/severe disease. This is agreed considering that the clinical praxis for patients with mild disease is "watch and wait".

Teprotumumab was given with an initial dose of 10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions. The treatment duration and the posology in the studies in general reflect the recommendations in the SmPC section 4.2.

The primary endpoint in study TED01RV was overall responder rate at Week 24 (decrease in overall CAS ≥2 points AND reduction in proptosis ≥2 mm, AND no deterioration in the Non-Study Eye). The primary endpoint in the OPTIC/OPTIC J studies was proptosis responder rate (percentage of subjects with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration of proptosis in the fellow eye). A reduction of >2mm is considered as clinically relevant and is expected to reduce the risk of diplopia.

Secondary endpoints included assessments of change from baseline in proptosis, diplopia, clinical activity score (CAS) and QoL (GO-QoL questionnaire). These outcome measures complement the primary endpoint including assessments of e.g., pain and eye lid swelling.

Validation information for the GO-QoL questionnaire has been submitted, and further justifications was requested in the first rounds of assessments. The measurement properties of the two subscales (i.e., Visual functioning and psychosocial functioning due to changed Appearance) showed acceptable test-retest and internal consistency reliability in the modified version published by Terwee at al. (1999). However, limitations in the convergent and discriminant validity were observed, and further study of validity was recommended by the authors. Another modified version of the questionnaire has been used in a later study (Terwee et al 2001) with the aims to define minimal clinically import difference (MCID) and to study changes over time. This study suggested that a change of at least 6% was clinically meaningful. For clarification, a change of 6% on either Visual functioning or psychosocial functioning subscale (Appearance) is in fact a change of 6.25% on a 0-100% scale (as the sum of item scores was transformed to a 0 to 100 score), which corresponds to a change of 1 point in one single item included in a GO-QoL subscale. If any of the items would change 2 points, or if 2 items would change by 1 point, this would correspond to a 12.5% change on the subscale level. There were, however, limitations in the methodology and design of the referenced study that did not allow a comprehensive and reliable determination of the MCID, why the proposed MCID was questioned. Justification of the proposed MCID was of particular concern for patients with more severe characteristics at baseline.

The applicant provided a discussion regarding previously reported limitations in construct validity of the GO-QoL subscales which seems reasonable. The applicant has also performed certain further analysis of construct validity and determination of MCID using pooled data from study ED01RV and HZNP-TEP-301. Using the EUGOGO criteria from 2021, patients who met ≥2 criteria were categorized as having a more severe disease presentation, while those meeting <2 criteria were considered to have milder form of the disease. Most patients in these studies belongs to the severity group "≥2 EUGOGO Criteria" for which higher MCID was identified using both distribution-based and anchor-based methods. Further analysis of MCID indicates that the initially suggested MCID of 6 percent is too low and that a higher MCID needs to be considered in the interpretation of the GO-QoL subscales results. Furthermore, the validity of the GO-QoL subscales relies on the literature data and the previous use of GO-QoL.

Of note, the "overall score" for the GO-QoL questionnaire was used as one of the key secondary endpoints in all main studies. Ultimately, the the GO-QoL overall score was not included in the SmPC section 5.1 since the overall score has not been independently validated.

Study 403 aimed at including a patient population with stable, chronic TED. The study was placebo controlled with a 2:1 randomisation. Posology, duration of treatment and study assessments were similar to the studies in patients with acute TED. The primary objective was to evaluate the effect of teprotumumab versus placebo on the change of proptosis measurements in the study eye from Baseline at Week 24. The study protocol was amended 3 times, and the sample size was increased twice. It is noted that 50% of subjects in the active arm had a major protocol deviation. According to the applicant, there may have been impact of incorrectly dispensed IP and missing data on the efficacy results, these deviations resulted in a decrease in the teprotumumab treatment effect, and thus not expected to overestimate the effect. The deviations related to consent/assent procedures/ documentation are not expected to influence the study results, which is agreed.

Statistical methods

The statistical analysis plan for each study was generally adequate. The primary efficacy analysis was performed on the ITT population and repeated for the mITT and PP populations as sensitivity analyses.

In the OPTIC, OPTIC J and study HZNP-TEP-403 (Study 403), the ITT population included all subjects randomized to treatment, which is endorsed. In the TED01RV, the ITT population included all subjects randomized to treatment and received at least one dose of study medication. This definition is also endorsed as only one subject, among 88 enrolled, was excluded from the ITT population.

The primary and the selected secondary endpoints were tested hierarchically in a pre-defined order which adequately controlled the Type I error at 5% (two-sided).

Each of the studies was reasonably powered to detect a relevant difference between teprotumumab and placebo.

In OPTIC J and Study 403, the primary estimand was defined to use treatment policy strategy to handle the intercurrent event of premature treatment discontinuations.

The estimand framework was not used in the OPTIC nor in the TED01RV study. No intercurrent events were defined. For the primary analysis, subjects who prematurely discontinued study drug were analysed as treatment failures (non-responders), unless an assessment at Week 24 was available.

Premature treatment discontinuation for categorical (secondary) endpoints was primarily handled using non-responder imputation.

Although different methods of primary analysis were used in the 4 studies, each of the methods seems appropriate for the selected primary endpoint. Categorical endpoints were analysed using methods of logistic regression and/or Cochran-Mantel-Haenszel (CMH) stratified proportion differences, while the continuous variables were analyses using MMRM.

Missing data in the MMRM analysis were handled differently in different studies. In the OPTIC, TED01RV and Study 403, if there were any subjects in the ITT population without post-baseline values, a change from baseline value of 0 was imputed at the first post-baseline visit (in order to avoid exclusion of these subjects from the MMRM analysis). In the OPTIC J, no such imputation was performed. Generally, amount of missing data does not seem to be of major concern in the three studies, and sensitivity analyses were prespecified to explore their impact. For example, there were only 2 participants with missing post-baseline measurements that were handled by imputation of 0 change from baseline in the MMRM analysis.

OPTIC

The primary analysis assessed the stratified difference in the proportions of proptosis responders between the treatment groups, using tobacco use as the same stratification factor, which is endorsed. Estimates from the 2 strata were combined using CMH weights, and the test statistic was calculated by

dividing the stratified difference by the standard error. A two-sided p-value was calculated assuming that the test statistic was distributed as a standard normal random variable under the null hypothesis. While the stratified CMH test would estimate an odds ratio, the methodology here applied provides a difference in proportions using the CMH weights. The analysis method for the primary endpoint is supported. Sensitivity analyses included a chi-square test (i.e., an unstratified test), which is informative.

Further, a logistic regression model that was originally defined in the protocol, prior to the amendment where the primary analysis method was changed, was also performed as part of the sensitivity analyses. This sensitivity analysis is endorsed.

Regarding handling of missing data in the primary analysis, subjects were considered treatment failures (non-responders) if they missed the Week 24 evaluation. Also, subjects who prematurely discontinued study drug dosing prior to Week 21 were analysed as treatment failures (non-responders), unless an assessment at Week 24 was available. The results show that only 2 subjects in placebo group and 2 subjects in the teprotumumab group prematurely discontinued from the double-masked treatment period, which does not raise concerns. There were only 2 missing values in placebo group and 1 missing value in the teprotumumab group that were imputed as non-response.

OPTIC J

The primary endpoint was analysed using CMH test, adjusted for the randomization stratification factor (tobacco use status). The stratified difference, which is a weighted average of the difference within each stratum, standard error (SE), its 95% confidence interval (CI) and p-value were provided. The method is similar to the analysis method in OPTIC study. Logistic regression as described for the OPTIC study was performed. There were no missing data for the primary endpoint.

TED01RV

The primary analysis was a logistic regression model with treatment group as the model effect and smoking status as a covariate. Patients missing the 24-week evaluation were considered to be treatment failures. There were few such missing values imputed (i.e., 5 and 4 subjects in placebo and teprotumumab group, respectively). No data were missing due to intercurrent events since treatment policy strategy was applied in the primary estimand.

Study 403

All efficacy analyses were based on the observed data except for categorical efficacy endpoints. Treatment policy strategy was used to account for the ICEs for defining estimands corresponding to continuous efficacy endpoints, including the primary efficacy endpoint. The primary analysis of change from baseline at Week 24 in proptosis in the study eye was using a MMRM model where for subjects without post-baseline values, a change from baseline value of 0 was imputed at the first post-baseline visit. Although acknowledged to have been used in order to avoid exclusion of these patients from the MMRM analysis, the imputation of 0-change was not in line with the pre-specification that the analysis of continuous efficacy variables was based on the observed data. There were 3 subjects with missing values for the primary endpoint in the teprotumumab group, and no missing data in placebo group. The imputation of 0-change was used only for one subject, who was randomized to teprotumumab but did not receive study drug and withdrew from the study. The 0-imputation had no impact on the efficacy results.

A tipping point sensitivity analysis for the primary endpoint was performed using placebo-based multiple imputation procedure to impute data for the 3 subjects with missing values in the teprotumumab group.

Notably, the mean difference in proptosis change between the two groups of at least 2.0 mm (deemed as clinically relevant) was expected according to the sample size calculation. This level of difference between treatment groups was not achieved in the study.

Difference in proptosis responder rates, the binocular diplopia responder rate and complete binocular diplopia responder rate was compared using a two-sided Fisher Exact test. The change from baseline at Week 24 in the GO-QoL questionnaire total scores and subscale scores was analysed using the same primary efficacy analysis method of MMRM model as specified for the primary efficacy endpoint.

Efficacy data and additional analyses

Acute TED (up to week 24)

Study population

A high proportion of patients finalized the double masked part in the OPTIC and OPTIC J studies. The proportion of patients not completing was somewhat larger in study TED01RV, but the vast majority finalized the study.

The study population with respect to age and gender represented the target population in clinical praxis with a considerably higher incidence of TED in women compared to men. Mean time from diagnosis was approximately 6 months and similar and placebo and active groups. Disease status with respect to proptosis, CAS score and diplopia was also rather similar in placebo and active groups and represents a population with moderate to severe acute TED.

One of the inclusion criteria pertaining to severity of TED was defined differently than EUGOGO guideline and requested *not sight-threatening active TED associated with 1 or more of listed signs,* although EUGOGO guideline requires 2 or more of those signs for diagnosis of moderate-to severe active TED. In order to confirm that included patients indeed had moderate-to severe TED, the proportion of patients with active TED associated with ≥2 symptoms/signs of severity was provided as well as efficacy results for this subgroup compared to patients who had only 1 of severity symptoms at baseline. Overall, proptosis response rates and difference between teprotumumab and placebo in this group were comparable to results reported in initial study reports and no significant difference between subgroups or bias in favour of participants with only one severity symptom/sign is observed.

Study results

Proptosis responder rate was the primary endpoint in the OPTIC/OPTIC J studies. More than 80% of subjects treated with teprotumumab were responders at week 24; the difference compared to placebo was 73% (95%CI 59-88) and 78% (95%CI 61-95), respectively. Subjects missing the week 24 evaluation was considered as a non-responder. The analyses are thereby considered as conservative.

Overall responder rate was the primary endpoint in TED01RV and secondary in OPTIC**/**OPTIC J studies. In study TED01RV, results were presented as odds ratio; 8.9 (95%CI 3.3-23.8), while the difference compared to placebo was 71% (95%CI 56-86) and 74% (95%CI 57-91), respectively in the OPTIC studies.

The difference compared to placebo in mean **change from baseline in proptosis** was a secondary endpoint in all studies. The difference was -2.3 (95%CI 2.8-1.8), -2.0 (95%CI 2.8-1) and -2.3 mm (95%CI 2.8-1.8), in the three studies, respectively.

Quality of life was assessed with the **GO-QoL instrument.** Based on publications from EUGOGO, clinical meaningful changes are considered as increases of ≥6 points, however higher MCID is suggested based on the analyses performed in studies TED01RV and HZNP-TEP-301. The difference compared to placebo in mean change from baseline in GO-QoL overall score was 9.4 (95%CI 4.1-14.6)

and 11.0 (95%CI 2.6-19.4) in the OPTIC studies. In study TED01RV, results were presented as odds ratio; 10.9 (95%CI 4.5-17.2).

Diplopia responder rate was a secondary endpoint in the OPTIC trial. Responders were defined as subjects with baseline diplopia grade >0 in the study eye who had a reduction of ≥ 1 grade with no corresponding deterioration in the fellow eye. Approximately 67% of subjects had diplopia at baseline. The proportion of responders in the active arm was 68% compared to 29% in the placebo arm (difference 40%, 95%CI 15.6-63.0). Based on the study reports, these are the only statistically significant and prespecified results with respect to effect on diplopia. Results on diplopia from other studies are not included in section 5.1 of the SmPC.

Only the primary efficacy endpoint was examined and compared in prespecified subgroups based on gender, age, tobacco use, race and geographic location. The results in these groups were very consistent with the results in the total population. The proportion of proptosis responders was somewhat higher in non-smokers compared to smokers. However, since the results were relevant also in smokers, there is no need to include this information in the SmPC.

Results (acute TED follow up after week 24)

In study **TED 01RV**, subjects were followed for in total 72 weeks out of which the last 48 weeks was without additional treatment with teprotumumab. Almost all of the patients completing 24 weeks of treatment entered the follow up study and also completed that part of the study. Approximately 37% of teprotumumab-treated participants did not maintain their responder status at Week 72.

Subjects that completed the 24 week part of **OPTIC** trial and were proptosis responders could enter an off-treatment follow-up period for 48 week without treatment. The majority of responders were included (36 of 39 responders). Of these, 20 subjects completed the follow up. Approximately 30% did not maintain their response.

OPTIC X included subjects who completed the 24-week double-masked treatment period in OPTIC and were proptosis non-responders or proptosis responders at Week 24 but met criteria for re-treatment due to relapse during the Follow-up Period of OPTIC.

In OPTIC X, all subjects were treated with teprotumumab (same regimen as in OPTIC). Among subjects who had their first course of teprotumumab, 90% were protoptosis responders at week 24. Fourteen subjects had a second course of teprotumumab and among these, around 50% responded. This seems to be the only reported experience with retreatment with teprotumumab. It is agreed with the applicant that there is insufficient data to support recommendations for retreatment of either non-responders or relapsers. 'Need for re-treatment' will be included as missing information in the RMP.

Results of study in chronic TED (week 24)

The study population was dominated by female subjects which is in line with the already known increased risk of TED in women. Time since diagnosis was approximately 5 years, and the baseline CAS score was low supporting that the study population indeed had chronic (inactive) TED.

The primary endpoint (change in proptosis) was met (-2.4 vs -0.9 mm, p =0.0004), but the magnitude of the effect is smaller compared to the results in patients with acute TED.

Inferential testing on other efficacy endpoints was conducted only if the primary efficacy endpoint reached statistical significance at 0.05 (2-sided) in favour of teprotumumab. With respect to secondary endpoints, the difference for proptosis responder rate was 37% (95%CI 5.4-59.2) and for change from baseline in Go-QoL visual functioning scale 6.3 (95%CI 0.6-12.1)**.**

Limited, supportive data for an effect on proptosis became available during the procedure from the 24-week open-label treatment period of Study HZNP-TEP-403. A total of 24 participants from the 24-week

randomized, double-masked period who were proptosis non-responders entered the 24-week open-label treatment period and received open-label treatment with teprotumumab; 12 placebo participants (first-course); and 12 teprotumumab participants (second-course). 10 participants in each group completed the open-label period. Mean reduction in proptosis from baseline of 2.00 mm was observed in 7/12 (58.3%) first course subjects. In second course subjects, mean reduction from teprotumumab baseline of 1.60 mm was observed. The applicant also submitted supportive literature data from additional 40 patients. Even if these data are not placebo controlled, it is not very plausible that the reported treatment results could be a result of spontaneous improvements considering the natural course of the disease. In a literature review by Dvies at al (Up to Date 2024), it is concluded that moderate-to-severe disease rarely resolves without treatment.

There is not much support from study 403 confirming the importance of the reduction of proptosis except for a limited difference in the GO-QoL vision scale. However, there is support from EUGOGO that a 2 mm reduction of proptosis is expected to reduce the risk of diplopia and other complications of TED. Some mechanistic data, albeit limited, also seems to support a treatment effect. Further, 2 studies are ongoing that include patients with chronic CAD and more information is expected in the future.

In conclusion, the totality of data presented by the applicant supports that a relevant effect of teprotumumab can be expected in patients with chronic TED.

2.5.7. Conclusions on the clinical efficacy

Overall, results of primary and secondary endpoints support a robust treatment effect of teprotumumab for the treatment of patients with acute TED. A decrease of proptosis with ≥2mm is considered as clinically relevant. In addition, the clinical relevance is supported by positive results for secondary endpoints like CAS and GO-QoL reflecting complementary benefits. Considering that active TED typically lasts 1.5 – 3 years without treatment, long term follow-up of patients after the initial 24-week treatment phase in the studies is of importance to assess relapse rate, time to relapse and the need for retreatment. Approximately 55-60 subjects have been followed up for 48 weeks after the 24-week treatment period. Of these 30-40% have relapsed and about 50% maintained their initial response. Data on retreatment and alternative treatment regimens will be achieved from the ongoing study 402.

The results in patients with chronic TED are not as convincing as in acute TED considering that there is a lack of replication from other controlled studies and support from other endpoints measuring other effects than the one on proptosis. Nonetheless, the applicant has submitted supportive data from a follow-up study, literature data and mechanistic studies. In addition, studies are ongoing in subjects with chronic TED. In conclusion, the totality of data supports that a relevant effect of teprotumumab can be expected also in patients with chronic TED.

2.5.8. Clinical safety

The clinical program evaluating the safety of teprotumumab for the treatment of thyroid eye disease (TED) includes 6 trials and constitutes the main safety database. Supportive safety data are derived from post-marketing experience, since TEPEZZA (teprotumumab) was approved by the US FDA in 2020, and from studies in other patient groups. Teprotumumab was originally evaluated in patients for the treatment of a variety of solid tumours. Small studies have also been performed with the intention to treat diabetic macular oedema (DME), and diffuse cutaneous systemic sclerosis.

Based on the mode of action and experience from studies in other patient groups, adverse events of special interest were identified.

2.5.8.1. Patient exposure

The clinical program evaluating the safety of teprotumumab for the treatment of TED includes 6 trials (Table 23 and Table 24).The safety assessment is based on a total exposure to investigational product (IP) (teprotumumab or placebo) of 285 participants, of whom 246 have received treatment with teprotumumab.

- Three multicenter trials evaluated the efficacy and safety of teprotumumab versus placebo (Phase 2 TED01RV, Phase 3 OPTIC and Phase 3 OPTIC-J) for the treatment of acute TED. The 24-week double-masked treatment period has been completed for all 3 trials.
- A Phase 3, open-label extension of OPTIC: HZNP-TEP-302 (OPTIC-X)
- A Phase 3b, open-label, single-arm, multicenter expanded access program (EAP) trial conducted in the US in participants with acute TED: Trial HZNP-TEP-401
- A Phase 4, randomized, double-masked, placebo-controlled, parallel-group, multicenter trial conducted in the US that evaluated the efficacy and safety of teprotumumab in participants with chronic TED: Trial HZNP-TEP-403. The 24-week double-masked treatment period has been completed for this trial. Of note, this chronic TED study did not recruit in Europe.

TEPEZZA (teprotumumab) was approved by the US FDA in 2020, and the cumulative post-authorisation patient exposure through 20 July 2023 is estimated to be 8690 patient years based on the available sales figures (Table 23).

Teprotumumab was originally evaluated in 725 participants for the treatment of a variety of solid tumors and in 5 participants for the treatment of DME and in 3 participants (1 teprotumumab, 2 placebo) with diffuse cutaneous systemic sclerosis (Table 23).

Table 23. Patient exposure

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)				
TED01RV	88	43	43	37 (w24), 36 (w72)
OPTIC	83	41	41	39 (w24), 20(w72)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
OPTIC-J – OL treatment and follow-up periods ongoing	54	27	27	26 (w24),
HZNP-TEP-403 OL treatment and follow-up periods ongoing	62	41	41	39 (w24),
Open studies				
OPTIC-X	51	51 (37 de novo, 14 previously exposed in the Optic study)	51	48 (36 de novo, 12 previously exposed) (w24), 40 (36 de novo, 4 previously exposed) (w48)
OPTIC-J – OL treatment period ongoing	26	26 (23 de novo, 3 previously exposed in the OPTIC-J study)	26	
HZNP-TEP-403 OL treatment period ongoing	24	24	24	7 (w48 as of cut-off date 30Mar2023)
Expanded Access Programme				
HZNP-TEP-401	23		23	(w28)
Post marketing				
US and Brazil		8690 PY***		
Other indications				
9 different oncology clinical trials	786 (57 placebo)	725	N/A	N/A
DME01RV (Diabetic macular edema, DME)	5	5	N/A	-
HZNP-TEP-001 (Cutanous systemic sclerosis)	3 (1 active treatment, 2 placebo)	1	N/A	-

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
*** patient-years based on sales figures (cut off 20 Jul 2023)

Table 24. Tabular Listing of Clinical Trials for Teprotumumab, including the Safety Parameters Assessed

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	Sex Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Safety Parameters Assessed
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 most 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)	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies
				48-week Follow-up Period				
				No IP administration	Teprotumumab Completed Trial 36 Placebo Completed Trial 38	NA	Completed 24-week Treatment Period	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies.

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	Sex Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Safety Parameters Assessed
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	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	**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 most 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)	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies
		48-week Follow-up Period: Completed/ 21Jan2020	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	**48-week Follow-up Period**				
				No IP administration	Teprotumumab 36/20 Placebo 4/3	NA	Completed 24-week Treatment Period	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies
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 (only 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	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies
				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	Adverse events, concomitant medications, safety laboratory tests (hematology, chemistry, thyroid panel and urinalysis), pregnancy testing, vital signs, ECGs, ophthalmic and physical examinations and anti-drug antibodies

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	Sex Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Safety Parameters Assessed
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)	Adverse events, concomitant medications, immunogenicity testing (anti-drug antibodies and possibly neutralizing antibodies), ophthalmic examinations, vital signs, clinical safety laboratory evaluations (complete blood count, fasting chemistry, including thyroid panel and glycated hemoglobin) and pregnancy testing (if applicable)
				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	Adverse events, concomitant medications, immunogenicity testing (anti-drug antibodies and possibly neutralizing antibodies), ophthalmic examinations, vital signs, clinical safety laboratory evaluations (complete blood count, fasting chemistry, including thyroid panel and glycated hemoglobin) and pregnancy testing (if applicable)
HZNP-TEP-403 Efficacy and Safety	11 US	24-week Treatment Period: 12Aug2021 Completed/ Data Cutoff 30Mar2023 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	**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 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 chronic TED with CAS ≤ 1 at Screening and Baseline; proptosis ≥ 3 mm increase from the participant's baseline (prior to diagnosis of stable TED), as estimated by treating physician, and/or proptosis ≥ 3 mm above normal for race and sex; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	Adverse events, concomitant medications, immunogenicity testing, best-corrected visual acuity, vital signs, clinical safety laboratory evaluations and pregnancy testing
				24-week OL Treatment Period				
				Teprotumumab Q3W for a total of 8 infusions	Teprotumumab 24/7 As of 30Mar2023	NA	Completed 24-week Double-masked Treatment Period and were proptosis non-responders at Week 24 of the Double-masked Treatment Period	Adverse events, concomitant medications, immunogenicity testing, best-corrected visual acuity, vital signs, clinical safety laboratory evaluations and pregnancy testing

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	Sex Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Safety Parameters Assessed
				10 mg/kg for first infusion; 20 mg/kg for subsequent infusions Administered as IV infusion				
HZNP-TEP-401 Expanded access protocol	8 US	02Dec2019 Completed/ 14Oct2020 Up to 60 planned/ 23 enrolled/ 22 treated	Open-label, 24-week Treatment Period	**24-week Open-label 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 22/19	M: 8 F: 14 W: 17 B: 1 A: 3 O: 1 52.4 years (20 - 78)	≥ 18 years of age; clinical diagnosis of moderate-to-severe acute TED with CAS ≥ 4; within ~12 months from onset of acute TED; euthyroid or mild hypo- or hyperthyroidism (FT4 and FT3 levels < 50% above or below the normal limits)	Adverse events, concomitant medication use, vital signs, clinical safety laboratory evaluations (hematology, chemistry and thyroid panel) and pregnancy testing (if applicable)

A = Asian; B = black or African American; CAS = Clinical Activity Score; CSR = clinical study report; ECG = electrocardiogram; F = female; FT3 = free triiodothyronine; FT4 = free thyroxine; IP = investigational product; IV = intravenous; M = male; NA = not applicable; NH/PI = Native Hawaiian or other Pacific Islander; O = other (participants with more than 1 race indicated appear in the "other" category); OL = Open-label; Q3W = every 3 weeks; TED = thyroid eye disease; US = United States; W = white

a. Participant 029-0002 was randomized to placebo but received teprotumumab.

b. < 2-mm reduction from Baseline in proptosis in the study eye.

Source: TED01RV CSR for 24-week Treatment Period and CSR Addendum for 48-Week Follow-up Period, OPTIC CSR for 24-week Treatment Period, OPTIC Week 72 CSR Addendum, OPTIC-J CSR for 24-week Treatment Period, OPTIC-X CSR, HZNP-TEP-403 CSR for 24-week Treatment Period and HZNP-TEP-401 CSR

Data collection

Safety assessments during the 24-week double-masked treatment period of each trial were performed at the time points indicated in Table 26. Safety assessments during the follow-up periods in acute TED trials TED01RV, OPTIC and OPTIC-X were performed at the time points indicated in Table 27. During the 30-day follow-up period in OPTIC-J and HZNP-TEP-403, safety assessments were AEs and concomitant medications; immunogenicity was also assessed in OPTIC-J during the follow-up period. Safety assessments and assessment time points in the EAP trial in participants with acute TED (HZNP-TEP-401) were similar to those in the other acute TED trials. For collection of supportive safety data from oncology studies and post-marketing, see section 2.5.8.10. and 2.5.8.11. , respectively.

Statistical methods

The following endpoints were used to assess the safety of teprotumumab:

- Exposure to IP
- AEs
- AEs of special interest (AESIs)
- Laboratory results
- Immunogenicity (anti-drug antibodies [ADA])
- Vital signs
- Prior and concomitant medications

For Follow-up period analyses, AEs were the only safety parameter summarised.

Analysis populations

Integrated safety data summary tables were generated using the following analysis populations:

Table 25. Number of Participants 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 26. Schedule of Safety Evaluations During the 24-Week Double-Masked Treatment Periods in Teprotumumab Trials

Safety Assessments	Screen [a]	Treatment Period (Trial Week)										
		BL[b]	1	3	4	6	9	12	15	18	21	24/ PW[c]
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[d]	X	X	X	RV	RV	X	RV	X	RV	X	RV	X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	302					303/ 403	X				X
12-lead ECG[f]	X	X		X		X		X				X
Ophthalmic examination[g]	X	X	X	RV	RV	X	RV	X	RV	X	RV	X
BCVA assessment (303 and 403)[h]	X	X				X		X		X		X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests												
TED01RV, OPTIC and OPTIC-X												
Chemistry (excluding glucose)	X	X		X		X	X	X		X		X
Thyroid panel	X	X		X		X	X	X		X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Glucose	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X	302						X				X
Urinalysis	X	X		X		X	X	X		X		X
ADA		X		X			X					X
Pregnancy test[i]	X	X		X		X	X	X	X	X	X	X
OPTIC-J												
Fasting chemistry	X	X				X		X		X		X
Thyroid panel	X	X						X				X
Hematology	X	X				X		X		X		X
HbA1c	X	X						X				X
ADA		X		X				X				X
Pregnancy test[i]	X	X	X	X		X	X	X	X	X	X	X
Chronic TED trial												
Fasting chemistry	X	X				X		X		X		X
Thyroid panel	X	X						X				X
Hematology	X	X				X		X		X		X
HbA1c	X	X						X				X
ADA		X		X				X				X
Pregnancy test[i]	X	X		X		X	X	X	X	X	X	X

302 = Trial HZNP-TEP-302 (OPTIC-X) only; 303 = Trial HZNP-TEP-303 only; 403 = Trial HZNP-TEP-403 only; ADA = anti-drug antibodies; BCVA = best-corrected visual acuity; BL = Baseline; ECG = electrocardiogram; HbA1c = glycated hemoglobin; PW = premature withdrawal; RV = TED01RV only; TED = thyroid eye disease

a. Applicable for TED01RV, OPTIC and HZNP-TEP-403 only.
b. At Baseline (Day 1), participants received the first dose of investigational product; Baseline assessments were performed prior to dosing. If the first day of OPTIC-X occurred on the same day as the final visit of OPTIC, final assessments from the lead-in trial served as Baseline for OPTIC-X.
c. If a participant prematurely discontinued investigational product during the Treatment Period, they returned for a clinic visit and underwent the Week 24 assessments, except for the collection of blood samples for pharmacokinetic and ADA evaluations.
d. Physical examinations were not conducted in Trial HZNP-TEP-403 or Trial HZNP-TEP-303.
e. Vital signs (heart rate, blood pressure, respiratory rate, temperature) were measured at all clinic visits. Vital signs were measured prior to and post-dosing on Day 1 and Week 3 and prior to dosing on all other infusion days in OPTIC and OPTIC-X. In TED01RV, vital signs were measured prior to and post-dosing only on Day 1. Additional vital signs were monitored if infusion-associated events occurred. In HZNP-TEP-403 and Trial HZNP-TEP-303, vital signs were measured pre- and post-infusion on Day 1 and Week 3 (all participants), pre- and post-infusion at Week 24 (proptosis non-responders who elected to receive open-label teprotumumab) and pre-infusion on all other infusion days.
f. In OPTIC and OPTIC-X, a single 12-lead ECG was performed prior to dosing at the designated time points. In TED01RV, ECGs were performed in triplicate, 1 minute apart at each time point; ECGs were performed prior to and post-dosing at Baseline, Week 6 and Week 12. ECGs were not performed in Trial HZNP-TEP-403 or Trial HZNP-TEP-303.

g. In TED01RV, OPTIC and OPTIC-X, a complete undilated ophthalmic examination was performed including the best corrected visual acuity, pupil exam, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure and slit lamp exam. If significant abnormalities were noted compared with previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including afferent pupillary defect, rise in intraocular pressure, development of corneal infiltrates or other abnormalities of concern to the ophthalmologist, further investigations of the visual function were conducted according to the ophthalmologist's decision. In HZNP-TEP-403 and Trial HZNP-TEP-303, only a BCVA assessment was performed.
h. If significant abnormalities, including any other abnormalities not otherwise specified but of concern to the ophthalmologist, were noted during BCVA assessment compared with previous visits, further investigations of visual function were conducted according to the ophthalmologist's decision.
i. Serum pregnancy test at Screening and urine pregnancy tests prior to dosing at all other visits, as applicable.

Table 27. Schedule of Safety Evaluations During the Follow-up Periods in Teprotumumab Trials in TED01RV, OPTIC and OPTIC-X

	Follow-up Period (Trial Week)				
	TED01RV, OPTIC and OPTIC-X[a]			TED01RV and OPTIC	
Safety Assessments	**28**	**36**	**48**	**60**	**72[b]**
Adverse event assessment	X	X	X	X	X
Physical examination			X		X
Vital signs	X	X	X	X	X
Weight		X	X	X	X
Single 12-lead ECG			302		X
Ophthalmic examination[c]			X		X
Prior/concomitant medications	X	X	X	X	X
Clinical laboratory tests					
Chemistry (excluding glucose)		X	302		X
Thyroid panel		X	302		X
Hematology		X	302		X
Glucose		X	302		X
HbA1c		X	302		X
Urinalysis		X	302		X
ADA		X	302		X
Urine pregnancy test	X	X	301, 302		

301 = Trial HZNP-TEP-301 (OPTIC) only; 302 = Trial HZNP-TEP-302 (OPTIC-X) only; ADA = anti-drug antibodies; ECG = electrocardiogram; HbA1c = glycated hemoglobin; TED = thyroid eye disease
a. Proptosis non-responders in OPTIC only entered Follow-up Period in OPTIC-X. Participants who completed the Week 48 Visit were contacted 6 and 12 months later via phone or email by research staff to inquire if any treatment for TED was received since last trial contact.
b. Participants who completed the Week 72 Visit in OPTIC were contacted 6 and 12 months later via phone or email by research staff to inquire if any treatment for TED was received since last trial contact.
c. A complete undilated ophthalmic examination was performed including the best corrected visual acuity, pupil exam, color vision assessment, Ishihara color plates (or equivalent) or related red desaturation, intraocular pressure and slit lamp exam. If significant abnormalities were noted compared with previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including afferent pupillary defect, rise in intraocular pressure, development of corneal infiltrates or other abnormalities of concern to the ophthalmologist, further investigations of the visual function were conducted according to the ophthalmologist decision.

Baseline

Baseline was defined in 2 ways:

- For the Double-masked Population, Baseline was defined as the last observation before the first dose of IP (teprotumumab or placebo).
- For the All Teprotumumab Population, Teprotumumab Baseline was used, defined as the last observation before the first dose of teprotumumab administered.

Disposition

Participant disposition for the Double-masked Population is presented in Table 28. More than 90% of the participants in the teprotumumab and placebo groups completed the Double-masked Treatment

Period (93.4% and 94.0%, respectively). Six (3.9%) teprotumumab participants and 3 (2.3%) placebo participants had TEAEs with onset during the Double-masked Treatment Period that led to early discontinuation.

Overall, 77.0% of participants in the teprotumumab group and 91.7% of participants in the placebo group completed the trial. 124 (81.6%) teprotumumab participants and 55 (41.4%) placebo participants had data collected in the Follow-up Period.

As of the database lock date for the trials, 26 participants (3 who had received teprotumumab, 23 who had received placebo) were ongoing in the Open-label Treatment Period of OPTIC-J and 14 (7 who had received teprotumumab, 7 who had received placebo) were ongoing in the Open-label Treatment Period of HZNP-TEP-403.

Table 28. Participant Disposition (Double-masked Population)

Disposition, n (%)	Acute TED			Chronic TED			Overall		
	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
Source: ISS Table 2.1.2.2

Extent of exposure

Extent of exposure to IP is presented for the Double-masked Population in Table 29. Most participants in the teprotumumab and placebo groups received all 8 infusions of IP (87.5% and 90.2%, respectively). The mean and median number of days on IP were similar between the treatment groups.

Twelve participants (8 teprotumumab, 4 placebo) in the Double-masked Population had an interruption of the IP infusion, 1 of whom permanently discontinued IP.

Table 29. 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.

Extent of exposure to IP is presented for the All Teprotumumab Population in Table 30.

Table 30. Extent of Exposure (All Teprotumumab Population)

	Acute TED	Chronic TED	Overall
	Teprotumumab (N = 193)	**Teprotumumab (N = 53)**	**Teprotumumab (N = 246)**
Total number of teprotumumab doses administered, n			
Mean (SD)	8.1 (2.66)	8.1 (3.08)	8.1 (2.75)
Median	8.0	8.0	8.0
Min, max	1, 16	1, 16	1, 16
Total number of teprotumumab doses administered, n (%)			
1 dose	1 (0.5)	2 (3.8)	3 (1.2)
2 doses	3 (1.6)	2 (3.8)	5 (2.0)
3 doses	4 (2.1)	1 (1.9)	5 (2.0)
4 doses	4 (2.1)	0	4 (1.6)
5 doses	4 (2.1)	2 (3.8)	6 (2.4)
6 doses	9 (4.7)	1 (1.9)	10 (4.1)
7 doses	7 (3.6)	5 (9.4)	12 (4.9)
8 doses	144 (74.6)	28 (52.8)	172 (69.9)
9 doses	0	2 (3.8)	2 (0.8)
10 doses	0	3 (5.7)	3 (1.2)
11 doses	1 (0.5)	1 (1.9)	2 (0.8)
12 doses	0	1 (1.9)	1 (0.4)
14 doses	1 (0.5)	2 (3.8)	3 (1.2)
15 doses	3 (1.6)	2 (3.8)	5 (2.0)
16 doses	12 (6.2)	1 (1.9)	13 (5.3)
Total duration of treatment with teprotumumab			
Mean (SD)	151.9 (51.53)	150.3 (63.79)	151.6 (54.27)
Median	148.0	148.0	148.0
Min, max	1, 316	1, 303	1, 316
Participants with any teprotumumab doses not administered completely, n (%)	5 (2.6)	2 (3.8)	7 (2.8)
Participants with any teprotumumab infusion interruptions, n (%)	9 (4.7)	3 (5.7)	12 (4.9)

max = maximum; min = minimum; SD = standard deviation; TED = thyroid eye disease
Total duration of treatment = summation of the number of days on teprotumumab in individual trials if a participant received teprotumumab in more than 1 trial (OPTIC and OPTIC-X) or more than 1 treatment period (the Double-masked Treatment Period and Open-label Treatment Period in OPTIC-J and HZNP-TEP-403). In a trial, the number of days on teprotumumab = last teprotumumab dose date – first teprotumumab dose date + 1 appliable to that trial. In each treatment period, the number of days on teprotumumab = last teprotumumab dose date for each treatment period – first teprotumumab dose date for each treatment period + 1.

Demographic and other characteristics of trial population

Demographic and Baseline characteristics are presented for the Double-masked Population in Table 31. Demographic characteristics at Baseline were generally comparable between the treatment groups. The majority of participants were female (69.7% teprotumumab, 78.9% placebo), consistent with TED gender distribution. The majority of the participants were white. Mean Baseline weight was similar between the treatment groups.

Overall, the acute and chronic TED groups were similar with regard to age and sex. Greater percentages of participants with acute TED than chronic TED were white (65.6% vs 55.7%), not of

Hispanic or Latino ethnicity (96.0% vs 82.0%) and tobacco users (24.6% vs 13.1%). Mean time since diagnosis of TED was 5.7 months for participants with acute TED and 61.6 months for participants with chronic TED.

Overall, the most commonly used concomitant medications included sulfur-containing imidazole derivatives (44.7% teprotumumab, 57.9% placebo), thyroid hormones (52.6% teprotumumab, 39.8% placebo) and other ophthalmologicals (29.6% teprotumumab, 39.8% placebo).

Table 31: Demographic and Baseline Characteristics (Double-masked Population)

Parameter Statistic	Acute TED			Chronic TED			Overall		
	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)
Sex, n (%)									
Female	87 (77.0)	75 (67.6)	162 (72.3)	18 (90.0)	31 (75.6)	49 (80.3)	105 (78.9)	106 (69.7)	211 (74.0)
Male	26 (23.0)	36 (32.4)	62 (27.7)	2 (10.0)	10 (24.4)	12 (19.7)	28 (21.1)	46 (30.3)	74 (26.0)
Age (years)									
Mean (SD)	51.1 (13.16)	50.2 (12.39)	50.7 (12.76)	49.0 (16.45)	48.2 (14.25)	48.4 (14.87)	50.8 (13.65)	49.7 (12.90)	50.2 (13.25)
Median	52.0	50.0	52.0	49.0	49.0	49.0	52.0	50.0	51.0
Minimum, maximum	20, 77	20, 79	20, 79	23, 75	18, 73	18, 75	20, 77	18, 79	18, 79
Age category, n (%)									
< 65 years	96 (85.0)	96 (86.5)	192 (85.7)	16 (80.0)	37 (90.2)	53 (86.9)	112 (84.2)	133 (87.5)	245 (86.0)
≥ 65 years	17 (15.0)	15 (13.5)	32 (14.3)	4 (20.0)	4 (9.8)	8 (13.1)	21 (15.8)	19 (12.5)	40 (14.0)
Race, n (%)									
Asian	30 (26.5)	30 (27.0)	60 (26.8)	1 (5.0)	7 (17.1)	8 (13.1)	31 (23.3)	37 (24.3)	68 (23.9)
Black or African American	6 (5.3)	8 (7.2)	14 (6.3)	5 (25.0)	9 (22.0)	14 (23.0)	11 (8.3)	17 (11.2)	28 (9.8)
Native Hawaiian or other Pacific Islander	0	1 (0.9)	1 (0.4)	0	0	0	0	1 (0.7)	1 (0.4)
White	75 (66.4)	72 (64.9)	147 (65.6)	12 (60.0)	22 (53.7)	34 (55.7)	87 (65.4)	94 (61.8)	181 (63.5)
Other	2 (1.8)	0	2 (0.9)	2 (10.0)	3 (7.3)	5 (8.2)	4 (3.0)	3 (2.0)	7 (2.5)
Race grouping, n (%)									
White	75 (66.4)	72 (64.9)	147 (65.6)	12 (60.0)	22 (53.7)	34 (55.7)	87 (65.4)	94 (61.8)	181 (63.5)
Non-White	38 (33.6)	39 (35.1)	77 (34.4)	8 (40.0)	19 (46.3)	27 (44.3)	46 (34.6)	58 (38.2)	104 (36.5)
Region, n (%)									
Europe	39 (34.5)	35 (31.5)	74 (33.0)	0	0	0	39 (29.3)	35 (23.0)	74 (26.0)
Non-Europe	74 (65.5)	76 (68.5)	150 (67.0)	20 (100)	41 (100)	61 (100)	94 (70.7)	117 (77.0)	211 (74.0)
Ethnicity, n (%)									
Hispanic/Latino	5 (4.4)	4 (3.6)	9 (4.0)	5 (25.0)	6 (14.6)	11 (18.0)	10 (7.5)	10 (6.6)	20 (7.0)
Not Hispanic/Latino	108 (95.6)	107 (96.4)	215 (96.0)	15 (75.0)	35 (85.4)	50 (82.0)	123 (92.5)	142 (93.4)	265 (93.0)
Study eye, n (%)									
Left eye	58 (51.3)	49 (44.1)	107 (47.8)	7 (35.0)	14 (34.1)	21 (34.4)	65 (48.9)	63 (41.4)	128 (44.9)
Right eye	55 (48.7)	62 (55.9)	117 (52.2)	13 (65.0)	27 (65.9)	40 (65.6)	68 (51.1)	89 (58.6)	157 (55.1)
Weight (kg)									
Mean (SD)	73.20 (17.943)	74.58 (20.472)	73.89 (19.207)	79.22 (24.196)	81.68 (19.208)	80.88 (20.802)	74.11 (19.029)	76.50 (20.323)	75.38 (19.732)
Median	70.10	71.10	70.35	71.69	79.90	77.56	70.10	73.70	72.12
Minimum, maximum	38.9, 122.9	43.4, 168.7	38.9, 168.7	46.2, 130.0	48.6, 130.5	46.2, 130.5	38.9, 130.0	43.4, 168.7	38.9, 168.7
Tobacco use status, n (%)									
Non-user	82 (72.6)	87 (78.4)	169 (75.4)	18 (90.0)	35 (85.4)	53 (86.9)	100 (75.2)	122 (80.3)	222 (77.9)
User	31 (27.4)	24 (21.6)	55 (24.6)	2 (10.0)	6 (14.6)	8 (13.1)	33 (24.8)	30 (19.7)	63 (22.1)

Table 31: Demographic and Baseline Characteristics (Double-masked Population)

Parameter Statistic	Acute TED			Chronic TED			Overall		
	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)
Time since diagnosis of TED (months)									
Mean (SD)	6.008 (2.3966)	5.467 (2.3199)	5.740 (2.3691)	64.565 (19.3152)	60.227 (22.1705)	61.649 (21.2143)	14.813 (22.3603)	20.238 (26.9945)	17.706 (25.0436)
Median	6.209	5.257	5.740	69.191	56.739	63.409	6.880	7.040	6.910
Minimum, maximum	1.05, 11.02	0.53, 10.13	0.53, 11.02	32.03, 94.06	26.87, 104.90	26.87, 104.90	1.05, 94.06	0.53, 104.90	0.53, 104.90

SD = standard deviation; TED = thyroid eye disease; Tepro = teprotumumab

2.5.8.2. Averse events

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. A TEAE for the Double-masked Treatment Period was an AE with an onset date between the administration of the first dose of IP and 3 weeks (21 days) after the last dose of IP. TEAEs for the Open-label Treatment Period were those AEs with an onset date on or after first dose of teprotumumab during the Open-label Treatment Period through 3 weeks (21 days) after last dose of teprotumumab during the Open-label Treatment Period. Follow-up AEs were those AEs with an onset date more than 3 weeks (> 21 days) after the last dose of IP through the completion of the Follow-up Period. Denominators for the summaries of AEs during the Follow-up Period were based on the number of participants who entered the Follow-up Period. Imputation rules for missing or incomplete dates are provided in the Statistical Analysis Plan.

For the TEAE analysis, the following subgroups were used to present analysis results:

- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race grouping (white, Asian, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Tobacco use status (user, non-user)
- Region (Europe, Non-Europe)

Double-masked period

An overview of TEAEs experienced during the Double-masked Treatment Period is presented for the Double-masked Population in

Table 32. Summary of TEAEs During the Double-masked Treatment Period (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.

A greater percentage of teprotumumab participants than placebo participants experienced TEAEs considered treatment related by the Investigator (62.5% vs. 32.3%). No clinically meaningful differences in the overall TEAE profile were observed between the acute and chronic TED clinical trial populations. Two teprotumumab participants had severe TEAEs considered at least possibly related to IP by the Investigator: *Diarrhoea* (this event was reported in a participant with underlying IBD and is thus, likely exacerbation of pre-existing IBD) and *Conductive deafness* (participant had a history of hearing impairment that predated receipt of IP).

Follow-up period

An overview of AEs experienced during the Follow-up Period is presented for the Double-masked Population in Table 33.

Table 33. Summary of AEs During the Follow-up Period (Double-masked Population)

AE[a] Category	Number (%) of Participants					
	Acute TED		Chronic TED		Overall	
	Placebo (N = 47)	Tepro (N = 98)	Placebo (N = 8)	Tepro (N = 26)	Placebo (N = 55)	Tepro (N = 124)
Any	10 (21.3)	33 (33.7)	0	4 (15.4)	10 (18.2)	37 (29.8)
Any treatment-related	0	10 (10.2)	0	3 (11.5)	0	13 (10.5)
Any serious	2 (4.3)	2 (2.0)	0	1 (3.8)	2 (3.6)	3 (2.4)
Any treatment-related serious	0	0	0	0	0	0
Any with an intensity of Grade 3 or higher	1 (2.1)	3 (3.1)	0	0	1 (1.8)	3 (2.4)
Any leading to death	0	0	0	0	0	0

AE = adverse event; IP = investigational product; TED = thyroid eye disease; Tepro = teprotumumab

a. An AE during the Follow-Up Period was defined as any AE occurring more than 3 weeks following the last dose of IP (placebo or teprotumumab) during the Double-masked Treatment Period for participants who did not enter the Open-label Treatment Period in each trial.

In TED01RV and OPTIC, there was a 48-week Follow-up Period after Week 24. For participants who entered OPTIC-X because they were proptosis non-responders in OPTIC, the Treatment Period in OPTIC-X was followed by a 24-week Follow-up Period; for participants who entered OPTIC-X because they were OPTIC responders who subsequently relapsed, there was no Follow-up Period. In OPTIC-J and HZNP-TEP-403, there was a 30-day Follow-up Period after Week 24 for proptosis responders as well as non-responders who chose not to enroll in the Open-label Treatment Period.

Treatment-related AEs were reported during the Follow-up Period for 13 (10.5%) participants who had received teprotumumab compared to no reports among those who had received placebo. Three teprotumumab participants and 1 placebo participant had AEs with an intensity of severe or higher during the Follow-up Period. These AEs were *Optic neuropathy*, *Intercostal neuralgia* and *Hypothyroidism*, experienced by 1 teprotumumab participant each, and *Prostate cancer* in the placebo participant. None of these events was considered related to IP.

2.5.8.2.1. Adverse drug reactions

Double-masked population

All TEAEs

No clinically meaningful differences in the TEAE profile were observed between the acute and chronic TED clinical trial populations.

The most commonly reported TEAEs occurring in ≥ 5.0% of participants in the teprotumumab group and with an incidence greater than placebo (ie, ADRs) are presented in Table 34. Of note, there are 5 groupings of PTs to avoid underestimating the occurrence of the event, specifically: hearing impairment includes *Autophony*, *Conductive deafness*, *Deafness*, *Deafness unilateral*, *Eustachian tube dysfunction*, *Eustachian tube patulous*, *Hyperacusis*, *Hypoacusis*, *Neurosensory hypoacusis*, *Tinnitus* and *Tympanic membrane* disorder; hyperglycemia includes *Blood glucose increased*, *Diabetes mellitus*, *Diabetic ketoacidosis*, *Glucose tolerance impaired*, *Glycosylated haemoglobin increased* and *Hyperglycaemia*; dysgeusia includes *Dysgeusia* and *Taste disorder*; fatigue includes *Fatigue* and *Asthenia* and nail disorder includes *Ingrowing nail*, *Nail bed disorder*, *Nail discolouration*, *Nail disorder* and *Onychoclasis*.

Table 34. Summary of TEAEs Occurring in ≥ 5.0% of Teprotumumab Participants with a Greater Incidence than Placebo During the Double-masked Treatment Period by Preferred Term (Double-masked Population)

Preferred Term or Grouped Term	Number (%) of Participants	
	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. Hyperglycemia 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*.

The following commonly reported ADRs were either serious, severe or led to premature discontinuation of IP: *Diarrhoea, Conductive deafness, COVID-19, Headache, Neurosensory hypoacusis, and Diabetic ketoacidosis.* All of the other commonly reported ADRs in placebo- or teprotumumab-treated participants were nonserious, mild or moderate in intensity and did not result in discontinuation of IP.

Treatment-related TEAEs

A summary of treatment-related TEAEs occurring in ≥ 2.0% of participants in the teprotumumab group and with an incidence greater than in the placebo group overall during the Double-masked Treatment Period is presented in Table 35. The proportion of participants who experienced at least 1 treatment-related TEAE during the Double-masked Treatment Period was higher in the teprotumumab group than in the placebo group (62.5% vs. 32.3%).

Table 35. Summary of Treatment-related TEAEs Occurring in ≥ 2.0% of Teprotumumab Participants with a Greater Incidence than Placebo Overall During the 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.

Among all treatment-related TEAEs reported during the Double-masked Treatment Period, 3 were serious and led to premature discontinuation of IP in the teprotumumab group: severe *Diarrhoea* [likely exacerbation of pre-existing IBD], moderate *Infusion related reaction* and severe *Conductive deafness* reported in

1 teprotumumab participant each. The *Conductive deafness*, which occurred in a participant who had a history of hearing impairment that predated receipt of IP, led to IP discontinuation during the Open-label Treatment Period of HZNP-TEP-403. These events are further discussed in Section 2.5.8.3.3. as they are AESIs. One placebo participant had a serious TEAE of *Diabetic ketoacidosis* after receiving teprotumumab for the first infusion in error, that was considered severe and related to IP, but the dose of IP was not changed. All other treatment-related TEAEs during the Double-masked Treatment Period were considered mild or moderate in intensity.

Two infectious events were considered related to IP (*Influenza* in a placebo participant and *Periodontitis* in a teprotumumab participant). A serious TEAE of *Escherichia sepsis* (verbatim: systemic *E coli* sepsis) that was considered severe, unrelated to IP and led to discontinuation of IP was reported in a teprotumumab participant. A serious TEAE of *COVID-19* that was considered severe and unrelated to IP was reported in a teprotumumab participant. None of the other TEAEs within the *Infections and infestations* SOC were serious, led to discontinuation of IP or were considered severe in intensity.

AEs during the Follow-up period

The overall incidence of AEs during the Follow-up Period was 29.8% among participants who had received teprotumumab (N = 124) and 18.2% among participants who had received placebo (N = 55). AEs associated with the *Skin and subcutaneous tissue disorders* SOC were more commonly observed in participants who had received teprotumumab compared with those who had received placebo (8.9% vs. 1.8%). AEs reported during the Follow-up Period by 2 or more participants who had received teprotumumab included *Onychoclasis* (5.6%) and *Fatigue*, *Upper respiratory tract infection, Urinary tract infection*, *Blood cholesterol increased*, *Hepatic enzyme increased* and *Headache* (1.6% each). *Fatigue* (3.6%) was the only AE reported during the Follow-up Period by 2 or more participants who had received placebo.

AEs during the Follow-up Period that were considered severe in intensity by the Investigator were experienced by 3 (2.4%) participants who had received teprotumumab (*Hypothyroidism*, *Optic neuropathy* and *Intercostal neuralgia* in 1 participant each) and 1 (1.8%) participant who had received placebo (*Prostate cancer*). The *Optic neuropathy*, *Intercostal neuralgia* and *Prostate cancer* were serious. Treatment-related AEs were reported during the Follow-up Period for 13 (10.5%) participants who had received teprotumumab. No treatment-related AEs were recorded during the Follow-up Period for participants who had received placebo.

<u>All Teprobumumab population</u>

All TEAEs

TEAEs during any treatment period for 'All teprotumumab population' are summarised in Table 36.

Table 36. TEAEs during any treatment period for 'All teprotumumab population'

Table 2.2.2.1
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During Any Treatment Period
(All Teprotumumab Population)

	Acute TED		Chronic TED		Overall	
	TEPRO N=193		TEPRO N=53		TEPRO N=246	
System Organ Class Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAEs	164 (85.0)	921	43 (81.1)	260	207 (84.1)	1181

A total of 77 events belonging to 'Ear and labyrinth disorders' were reported for 57/246 subjects. Five these events were vertigo/vertigo positional. One Chronic TED patient was diagnosed with malignant melanoma,

and one Acute TED patient was diagnosed with squamous cell carcinoma during the clinical studies. No other cancer was diagnosed.

2.5.8.3. Serious adverse event/deaths/other significant events

2.5.8.3.1. Serious adverse events

Nine (5.9%) teprotumumab participants and 2 (1.5%) placebo participants in the Double-masked Population experienced serious TEAEs during the Double-masked Treatment Period. No specific TEAE (PT) was reported for > 1 participant.

Among the serious TEAEs reported in the teprotumumab group in the Double-masked Population, 5 were considered severe (*Diarrhoea*, *Escherichia sepsis*, *Inflammatory bowel disease*, *COVID-19* and *Conductive deafness*) and 1 was considered life-threatening (*Pneumothorax)*. *Diarrhoea, Hashimoto's encephalopathy*, *infusion related reaction, Diabetes ketoacidosis* and *Conductive deafness* were considered related to IP.

Diabetic ketoacidosis in one participant (placebo) who had undiagnosed diabetes mellitus, was not receiving any medication to control glucose and experienced this TEAE after receiving teprotumumab for the first infusion in error.

In OPTIC-X, the EAP Trial and Open-label Treatment Period of OPTIC-J, serious TEAEs of *Cerebral haemorrhage*, *Appendicitis* and *Calculus urinary* were reported.

2.5.8.3.2. Deaths

There were no deaths during the conduct of the teprotumumab clinical program in TED.

2.5.8.3.3. Adverse events of special interest (AESIs)

Infusion-related reactions (IRRs)

Infusion-associated events (including hypersensitivity and anaphylactic reaction) are anticipated for all monoclonal antibodies and IRRs were previously observed in the clinical oncology development program. Therefore, IRRs were defined as AESIs for the TED clinical studies.

Infusion-related reactions (IRRs) were identified based on a Sponsor-adjudicated process for TED01RV, OPTIC and OPTIC-X, while IRRs were reported on the AE electronic case report form for OPTIC-J and HZNP-TEP-403. Note that no IRR was reported in the EAP trial.

In the Double-masked Population, during the double-masked treatment period, IRRs were observed in 6 of 152 (3.9%) participants who received teprotumumab and 4 of 133 (3.0%) participants who received placebo across the acute and chronic TED trials.

Two teprotumumab participants experienced IRRs (one serious and one non-serious) leading to discontinuation of IP. One placebo participant experienced IRR with symptoms of chest pain, leading to discontinuation of IP. In the open-label trials and open-label treatment periods of OPTIC-J and HZNP-TEP-403, no IRRs which were considered serious and/or led to discontinuation of IP were recorded. In summary, IRRs were reported in 8 (3.3%) participants who received teprotumumab. The reactions were considered

mild or moderate in intensity and managed with antihistamines and/or corticosteroids, if needed. No IRRs in TED trials were reported as anaphylactic reactions.

Hyperglycaemia

Insulin and IGF-1 receptors are highly homologous and share many downstream signalling pathways but have unique biological effects. Disturbing these pathways has been shown to increase insulin resistance, glucose intolerance and dyslipidaemia. For participants in oncology teprotumumab clinical studies, hyperglycaemia events were recorded, especially for those with known diabetes or prediabetes. Hyperglycaemia was thus identified as an AESI.

Hyperglycemia was identified using the standardised MedDRA query (SMQ) narrow term of *Hyperglycaemia/new onset diabetes mellitus*.

To further understand the glycaemic effects of teprotumumab, participants were categorized according to Baseline glycaemic status based on Baseline HbA1c and history of diabetes according to the American Diabetes Association criteria as follows:

- Normoglycemia: Baseline HbA1c $\leq$ 5.6% and no history of diabetes or prediabetes
- Prediabetes: 5.7% $\leq$ Baseline HbA1c $\leq$ 6.4% and no history of diabetes
- Diabetes: Baseline HbA1c $\geq$ 6.5% or known history of diabetes

Of all 285 participants in the Double-masked Population, 24 (8.4%) had diabetes at Baseline, 68 (23.9%) had prediabetes at Baseline and 180 (63.2%) were normoglycemic at Baseline (Table 37).

Among teprotumumab participants with diabetes or prediabetes at Baseline, 9 of 13 (69.2%) and 7 of 38 (18.4%), respectively, experienced an AESI of hyperglycaemia. The remaining 4 teprotumumab participants who experienced an AESI of hyperglycaemia were normoglycemic at Baseline, none of whom had received corticosteroids during the trial.

In contrast, 4 of the 133 (3.0%) placebo-treated participants experienced an AESI of hyperglycaemia even though 11 (8.3%) and 30 (22.6%) participants had been identified as diabetic or prediabetic, respectively, at Baseline. Of these 4 participants, 1 had diabetes at Baseline and experienced *Diabetic ketoacidosis* after receiving teprotumumab as the first dose of IP in error. None of the other 3 placebo participants had received corticosteroids during the trial.

Table 37. Summary of TEAEs of Special Interest Occurring During the Double-masked Treatment Period Overall and by Baseline Glycaemic Status: Hyperglycaemia (Double-masked Population)

	Number (%) of Participants					
	Acute TED		**Chronic TED**		**Overall**	
Hyperglycemia **Preferred Term**	**Placebo** **(N = 113)**	**Tepro** **(N = 111)**	**Placebo** **(N = 20)**	**Tepro** **(N = 41)**	**Placebo** **(N = 133)**	**Tepro** **(N = 152)**
All participants						
Any AESI of hyperglycemia	2 (1.8)	14 (12.6)	2 (10.0)	6 (14.6)	4 (3.0)	20 (13.2)
Blood glucose increased	1 (0.9)	4 (3.6)	0	1 (2.4)	1 (0.8)	5 (3.3)
Diabetes mellitus	0	2 (1.8)	1 (5.0)	2 (4.9)	1 (0.8)	4 (2.6)

Table 37. Summary of TEAEs of Special Interest Occurring During the Double-masked Treatment Period Overall and by Baseline Glycaemic Status: Hyperglycaemia (Double-masked Population)

Hyperglycemia Preferred Term	Number (%) of Participants					
	Acute TED		Chronic TED		Overall	
	Placebo (N = 113)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 41)	Placebo (N = 133)	Tepro (N = 152)
Diabetic ketoacidosis	0	0	1 (5.0)	0	1 (0.8)	0
Glucose tolerance impaired	0	1 (0.9)	1 (5.0)	1 (2.4)	1 (0.8)	2 (1.3)
Glycosylated haemoglobin increased	0	0	0	3 (7.3)	0	3 (2.0)
Hyperglycaemia	1 (0.9)	7 (6.3)	0	1 (2.4)	1 (0.8)	8 (5.3)
Participants with diabetes at Baseline	**n = 10**	**n = 10**	**n = 1**	**n = 3**	**n = 11**	**n = 13**
Any AESI of hyperglycemia	0	8 (80.0)	1 (100)	1 (33.3)	1 (9.1)	9 (69.2)
Blood glucose increased	0	1 (10.0)	0	0	0	1 (7.7)
Diabetes mellitus	0	2 (20.0)	1 (100)	1 (33.3)	1 (9.1)	3 (23.1)
Diabetic ketoacidosis	0	0	1 (100)	0	1 (9.1)	0
Hyperglycaemia	0	5 (50.0)	0	0	0	5 (38.5)
Participants with prediabetes at Baseline	**n = 25**	**n = 28**	**n = 5**	**n = 10**	**n = 30**	**n = 38**
Any AESI of hyperglycemia	0	3 (10.7)	0	4 (40.0)	0	7 (18.4)
Blood glucose increased	0	2 (7.1)	0	1 (10.0)	0	3 (7.9)
Diabetes mellitus	0	0	0	1 (10.0)	0	1 (2.6)
Glucose tolerance impaired	0	0	0	1 (10.0)	0	1 (2.6)
Glycosylated haemoglobin increased	0	0	0	3 (30.0)	0	3 (7.9)
Hyperglycaemia	0	1 (3.6)	0	0	0	1 (2.6)
Participants with normoglycemia at Baseline	**n = 71**	**n = 67**	**n = 14**	**n = 28**	**n = 85**	**n = 95**
Any AESI of hyperglycemia	1 (1.4)	3 (4.5)	1 (7.1)	1 (3.6)	2 (2.4)	4 (4.2)
Blood glucose increased	1 (1.4)	1 (1.5)	0	0	1 (1.2)	1 (1.1)
Glucose tolerance impaired	0	1 (1.5)	1 (7.1)	0	1 (1.2)	1 (1.1)

Table 37. Summary of TEAEs of Special Interest Occurring During the Double-masked Treatment Period Overall and by Baseline Glycaemic Status: Hyperglycaemia (Double-masked Population)

Hyperglycemia Preferred Term	Number (%) of Participants					
	Acute TED		Chronic TED		Overall	
	Placebo (N = 113)	Tepro (N = 111)	Placebo (N = 20)	Tepro (N = 41)	Placebo (N = 133)	Tepro (N = 152)
Hyperglycaemia	0	1 (1.5)	0	1 (3.6)	0	2 (2.1)

AESI = adverse event of special interest; TEAE = treatment-emergent adverse event; TED = thyroid eye disease; Tepro = teprotumumab

The event of hyperglycaemia in 1 participant in the placebo group was serious and severe. In HZNP-TEP-403, on participant with undiagnosed diabetes mellitus and not receiving any medication to control glucose, experienced a serious TEAE of *Diabetic ketoacidosis* after receiving teprotumumab as the first dose of IP in error, with onset on Day 21. The Investigator assessed the *Diabetic ketoacidosis* as severe in intensity and related to IP.

Events of hyperglycaemia were also detected for participants in the OPTIC-X trial, the EAP Trial, and Open-label Treatment Periods of OPTIC-J and HZNP-TEP-403.

Safety Laboratory Value Data Pertaining to Hyperglycaemia

Overall, during the Double-masked Treatment Period, mean increases from Baseline in fasting blood glucose were greatest among participants with diabetes at Baseline, followed by participants with prediabetes at Baseline and those with normoglycemia at Baseline. In each Baseline glycaemic status category, the mean increases from Baseline were greater among teprotumumab participants than placebo participants at each visit.

Summary of Hyperglycaemia

In summary, a higher incidence of hyperglycaemia 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 prediabetes (18.4% [7/38] teprotumumab vs. 0% [0/30] placebo) at Baseline are at greatest risk of experiencing hyperglycaemia. One serious adverse event of *Diabetic ketoacidosis* was reported in a placebo participant with undiagnosed diabetes who was mistakenly administered teprotumumab as the first infusion. The majority of hyperglycaemia events were nonserious. Participants with pre-existing diabetes and prediabetes showed a greater elevation in fasting glucose and HbA1c levels compared with normoglycemic participants at Baseline over the Double-masked Treatment Period.

Hearing impairment

Insulin-like growth factor-1, which binds the IGF-1R, is an important regulator of cochlear development, and its mutations are associated with hearing loss in mice and humans.

Teprotumumab inhibits signaling through the IGF-1R, and understanding of the pharmacologic impact on hearing is still evolving. Events of hearing impairment were observed in the oncology development program for teprotumumab.

Hearing impairment was identified using the sub-SMQ term of *Hearing impairment* (under SMQ *Hearing and vestibular disorders*) and the High-Level Term (HLT) term *Hearing losses*.

A summary of the time to the first AESI of hearing impairment and the number of infusions received before the first AESI of hearing impairment for those participants with an AESI of hearing impairment was provided for the Double-Masked Population.

Across the TED clinical program, a total of 43 (43/246, 17.5%) participants experienced 57 events of hearing impairment (reported as *Autophony*, *Conductive deafness*, *Deafness*, *Deafness neurosensory*, *Deafness unilateral*, *Eustachian tube dysfunction*, *Eustachian tube patulous*, *Hyperacusis*, *Hypoacusis*, *Neurosensory hypoacusis*, *Tinnitus* or *Tympanic membrane disorder*) while receiving teprotumumab or during the Follow-up Period after receipt of teprotumumab, as of the cut-off date of 16 October 2024 .

Double-masked Treatment Period

In the Double-masked Population, 21 (13.8%) participants in the teprotumumab group experienced 28 TEAEs of hearing impairment (reported as *Autophony*, *Conductive deafness*, *Deafness*, *Deafness unilateral*, *Eustachian tube dysfunction*, *Eustachian tube patulous*, *Hyperacusis*, *Hypoacusis, Neurosensory hypoacusis*, *Tinnitus* or *Tympanic membrane disorder*) during the Double-masked Treatment Period compared with 3 (2.3%) participants in the placebo group who experienced 4 TEAEs of hearing impairment (Table 38).

Table 38. AESIs by Preferred Term during the double-masked treatment period (double-masked population)

	Acute TED				Chronic TED			
	Placebo N=113		TEPRO N=111		Placebo N=20		TEPRO N=41	
AESI Category Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
New Onset IBD or Exacerbation of IBD	0	0	1 (0.9)	2	0	0	0	0
Inflammatory bowel disease	0	0	1 (0.9)	2	0	0	0	0
Hearing Impairment	1 (0.9)	1	12 (10.8)	16	2 (10.0)	3	9 (22.0)	12
Autophony	0	0	1 (0.9)	1	0	0	1 (2.4)	1
Conductive deafness	0	0	0	0	0	0	1 (2.4)	1
Deafness	0	0	2 (1.8)	2	0	0	0	0
Deafness unilateral	0	0	0	0	0	0	1 (2.4)	2
Eustachian tube dysfunction	0	0	1 (0.9)	1	0	0	1 (2.4)	1
Eustachian tube patulous	0	0	2 (1.8)	2	0	0	0	0
Hyperacusis	0	0	1 (0.9)	1	0	0	0	0
Hypoacusis	0	0	4 (3.6)	4	0	0	4 (9.8)	4
Neurosensory hypoacusis	1 (0.9)	1	2 (1.8)	2	0	0	0	0
Tinnitus	0	0	3 (2.7)	3	2 (10.0)	3	2 (4.9)	2
Tympanic membrane disorder	0	0	0	0	0	0	1 (2.4)	1

Abbreviations: TEPRO = Teprotumumab; TEAEs = treatment-emergent adverse events; AESI = Adverse Event of Special Interest; IBD = Inflammatory Bowel Disease.
Note: Includes studies of TED01RV, HZNP-TEP-301, HZNP-TEP-303, AND HZNP-TEP-403. Percentages are based on the number of subjects in the Double-Masked Population in each treatment group within each disease activity group. Adverse events are coded using MedDRA version 26.0. At each level of summarization, subjects who experienced more than one event are counted only once. Within each AESI category, events are sorted alphabetically by preferred term. TEAEs are defined as adverse events occurring after the first dose (placebo or teprotumumab) on Day 1 through 3 weeks following the last dose of study drug in each study.
[1] Includes TEAEs assessed by the Sponsor to be adjudicated Infusion-Related Reactions for TED01RV and HZNP-TEP-301. For HZNP-TEP-303 and HZNP-TEP-403, Infusion-Related Reactions are collected in the AE electronic case report form.
[2]/[3]/[4] Denominator for percentages is the number of subjects in the Double-Masked Population with pre-existing diabetes/prediabetes/normoglycemia.

Mean time to first hearing impairment event relative to the participant's first dose of IP was 77.9 days (range: 3 to 153 days) among teprotumumab-treated participants and 96.0 days (range: 6 to 161 days) among placebo-treated participants, with an average of 4.2 infusions received before onset in the teprotumumab group and 5.0 infusions received before onset in the placebo group.

In two participants in teprotumumab treatment groups and one placebo-treated participant, events of hearing impairment led to premature withdrawal of IP.

Open-label treatment

In OPTIC-X, 6 (11.8%) participants (4 first-course [received placebo in OPTIC], 2 second-course [received teprotumumab in OPTIC]) had nonserious TEAEs related to hearing impairment during the Treatment Period and one additional first-course participant had a nonserious AE (Deafness neurosensory) during the Follow-up Period. In OPTIC-J, one participant, who had a history of presbycusis and received placebo during the Double-masked Treatment Period, experienced Hypoacusis during the Open-label Treatment Period that led to premature discontinuation of teprotumumab. Another participant experienced first tinnitus and later mild hypoacusis which led to withdrawal of IP, in the open-label treatment period. During follow-up, hypoacusis was noted as moderate. In HZNP-TEP-403 and the EAP trials, 3 and 9 participants have experienced a hearing impairment TEAE, respectively, during the Open-label Treatment Period. In addition, 1 teprotumumab participant experienced Deafness during the Follow-up Period.

Summary of Hearing Impairment

In the Double-masked Population, 21 (13.8%) participants in the teprotumumab group and 3 (2.3%) participants in the placebo group experienced a hearing impairment TEAE during the Double-masked Treatment Period. 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 database lock 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.

<u>New onset IBD and exacerbation of IBD</u>

In Phase 2 TED01RV, a serious TEAE was reported for one participant (*Inflammatory bowel disease*), who received teprotumumab; this participant had underlying IBD. In the same trial, the only placebo participant with IBD (Crohn's disease) did not experience exacerbation of IBD. Therefore, participants with a history of IBD were excluded from Phase 3 OPTIC and the EAP trial. In OPTIC-J and HZNP-TEP-403, 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.

For this AESI, relevant cases were retrieved from the integrated safety dataset using the HLT *Colitis (excl infective)*.

New-onset IBD or exacerbation of IBD (*Inflammatory bowel disease*) was reported for 1 of 152 participants who received teprotumumab and no participants who received placebo. The severe, serious event of *Inflammatory bowel disease* occurred in resulted in discontinuation of IP. Although the database search for IBD exacerbation did not retrieve the serious event of *Diarrhoea* for another participant, this event is also considered exacerbation of IBD because of the participant's underlying history of colitis and subsequent diagnosis of ulcerative colitis. No event of diarrhea or IBD exacerbation was reported in the Follow-up Period for the Double-masked Population.

In summary, IBD exacerbation (severe, serious) was reported in two participants exposed to teprotumumab who had a history of IBD. No events of new-onset IBD have been observed in the TED trials.

2.5.8.4. Laboratory findings

Laboratory results were presented using the International System of Units. Clinical laboratory test results (hematology, chemistry and thyroid panel) and changes from Baseline were summarized for the Double-masked Population by treatment group within disease activity group at each scheduled analysis visit.

Changes in fasting glucose and HbA1c values from Baseline at scheduled analysis visits were summarized by baseline glycemic status. In addition, Sankey plots depicting changes in hyperglycemia CTCAE grade and HbA1c based on normal range category by Baseline glycemic status were provided.

A summary of liver function tests was provided for the Double-masked Population, including the number and percentage of participants with the following values at each visit and the number and percentage of participants with the following values at any post-Baseline visit:

- Alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN)
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- Aspartate aminotransferase (AST) ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- Total bilirubin ≥ 2 × ULN
- ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (at the same visit)

Laboratory results were summarized only for the Double-masked Population in integrated safety analyses. No clinically meaningful differences between the acute and chronic TED clinical trial populations were observed for laboratory results; therefore, discussion of results is based on the overall Double-masked Population. All integrated safety statistical summary tables and figures provide data overall and by TED activity (acute TED, chronic TED).

Haematology

Haematology laboratory tests were taken. Shifts from normal at Baseline to above the normal range in percentage of lymphocytes were consistently greater in the teprotumumab group (range: 7.1% to 16.7%) compared with the placebo group (range: 0% to 4.7%) during the Double-masked Treatment Period. However, no clinically meaningful shifts were observed to above the normal range in absolute lymphocytes (range: 0% to 2.0% for teprotumumab, 0% to 0.8% for placebo) or to below the normal range in absolute neutrophil count (range: 0% to 5.3% for teprotumumab, 0% to 1.5% for placebo). Differences between the groups were also observed for shifts from normal Baseline in haemoglobin and percentage of platelets, but the differences were less consistent and smaller in magnitude. No clinically meaningful difference between treatment groups was observed for the percentage of participants with TEAEs associated with abnormal haematology results (ie, *Anaemia* [0.7% teprotumumab, 0.8% placebo]), *Haemoglobin decreased* [0.7% teprotumumab, 0% placebo]). None of these TEAEs was severe, serious or led to premature discontinuation of IP.

Chemistry

No clinically significant mean changes from Baseline were observed at any time point for any chemistry parameter. No clinically meaningful differences between treatment groups were observed for the percentage of participants with TEAEs associated with abnormal chemistry results (ie, *Alanine aminotransferase increased* [0% teprotumumab, 0.8% placebo], *Blood bilirubin increased* [0.7% teprotumumab, 0% placebo], *Blood creatinine increased* [0.7% teprotumumab, 0% placebo], *Gamma-glutamyltransferase increased* [1.3% teprotumumab, 0.8% placebo], *Hepatic enzyme increased* [0% teprotumumab, 0.8% placebo], *Hepatic function abnormal* [0.7% teprotumumab, 0% placebo], *Hypokalaemia* [0.7% teprotumumab, 0% placebo]). None of these TEAEs was serious or led to premature discontinuation of IP. All hepatic-related TEAEs recorded during the Double-masked Treatment Period were mild or moderate in severity, with the exception of a TEAE of *Gamma-glutamyltransferase increased*. One participant in OPTIC-J had a severe TEAE of *Gamma-glutamyl transferase increased* on Days 163-188. The participant received all 8 infusions of IP and completed the trial. Other liver enzymes and bilirubin remained in the normal range during the Double-masked Treatment Period except for a slight increase in ALT and alkaline phosphatase at Week 24. This 57-year-old male participant was an alcohol user (168 ounces of beer per week) and GGT is the most sensitive liver enzyme to alcohol intake.

Thyroid panel

No clinically significant differences were observed between the placebo and teprotumumab groups for changes from Baseline in thyroid function values, with no consistent trends noted during the Double-masked Treatment Period. No clinically meaningful differences between treatment groups were observed for the percentage of participants with TEAEs associated with abnormal thyroid test results. None of these TEAEs was severe, serious or led to premature discontinuation of IP.

2.5.8.5. Vital signs

Vital sign results (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature and weight) and changes from Baseline were summarized for each scheduled analysis visit using descriptive statistics for the Double-masked Population by treatment group within disease activity group. A summary of weight loss was also provided based on CTCAE criteria (Table 39).

Table 39. CTCAE Grades for Weight Loss

	Grade 1	**Grade 2**	**Grade 3**
Weight loss	5 to < 10% decrease from Baseline	10 to < 20% decrease from Baseline	≥ 20% decrease from Baseline

CTCAE = Common Terminology Criteria for Adverse Events

Vital sign results (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature and weight) and changes from Baseline were summarized for each scheduled analysis visit using descriptive statistics for the Double-masked Population by treatment group within disease activity group. Vital sign results were summarized only for the Double-masked Population in integrated safety analyses. No clinically meaningful differences between the acute and chronic TED clinical trial populations were observed for vital sign results; therefore, discussion of results is based on the overall Double-masked Population.

No clinically significant differences were observed between the placebo and teprotumumab groups for mean changes from Baseline in temperature, systolic and diastolic blood pressure, heart rate or respiratory rate.

During the Double-masked Treatment Period, small mean increases in body weight measurement were observed in the placebo group at Weeks 12 (0.95 kg) and 24 (1.07 kg), whereas small mean decreases in body weight measurement were observed in the teprotumumab group at Weeks 12 (-0.84 kg) and 24 (-1.18 kg). A TEAE of *Weight decreased* was reported for 3.3% of teprotumumab-treated participants and no placebo-treated participants.

2.5.8.6. Safety in special populations

TEAEs were summarized by intrinsic and extrinsic factors, including age (< 65, ≥ 65 years), sex (female, male), race grouping (white, non-white), ethnicity (Hispanic or Latino, not Hispanic or Latino), tobacco use status (user, non-user) and region (Europe, non-Europe) for the Double-masked Population. The TEAE data presented in this section focus on TEAEs (individual PTs) occurring in ≥ 5.0% of participants in the teprotumumab treatment group overall and with a higher incidence than placebo in the Double-masked Population.

Incidence of TEAEs by Age

A summary of TEAEs occurring in ≥ 5.0% of participants in either treatment group overall during the Double-masked Treatment Period is presented by age in Table 40. Analysis of TEAEs by age did not suggest any clinically relevant differences from the overall analysis of TEAEs although the majority of participants were <65 years of age. Overall, the numbers of participants in the age groups of 65 to 74 years and 75 to 84 years were small and there were no participants ≥ 85 years of age. Summary of treatment-emerging adverse events overall by age group during double-masked treatment period (double-masked population) by age is found in

Table *41*.

Table 40. Summary of TEAEs Occurring in ≥ 5.0% of Participants in Either Treatment Group Overall During the Double-masked Treatment Period by Age (Double-masked Population)

	Number (%) of Participants			
	Overall			
	< 65 years		**≥ 65 years**	
Preferred Term	**Placebo (N = 112)**	**Teprotumumab (N = 133)**	**Placebo (N = 21)**	**Teprotumumab (N = 19)**
Any TEAE[a]	80 (71.4)	112 (84.2)	17 (81.0)	15 (78.9)
Muscle spasms	6 (5.4)	39 (29.3)	2 (9.5)	3 (15.8)
Diarrhoea	12 (10.7)	19 (14.3)	0	3 (15.8)
Alopecia	7 (6.3)	18 (13.5)	0	2 (10.5)
Fatigue	7 (6.3)	15 (11.3)	1 (4.8)	2 (10.5)
Nausea	8 (7.1)	15 (11.3)	1 (4.8)	1 (5.3)

Preferred Term	Number (%) of Participants			
	Overall			
	< 65 years		≥ 65 years	
	Placebo (N = 112)	Teprotumumab (N = 133)	Placebo (N = 21)	Teprotumumab (N = 19)
Headache	9 (8.0)	16 (12.0)	1 (4.8)	0
Dry skin	0	14 (10.5)	0	1 (5.3)
COVID-19	3 (2.7)	10 (7.5)	2 (9.5)	0
Dysgeusia	1 (0.9)	11 (8.3)	0	0
Ear discomfort	2 (1.8)	10 (7.5)	0	0
Hyperglycaemia	1 (0.9)	5 (3.8)	0	3 (15.8)
Hypoacusis	0	7 (5.3)	0	1 (5.3)

COVID-19 = coronavirus disease 2019; IP = investigational product; TEAE = treatment-emergent adverse event

Note: Preferred terms included in this table are those occurring in ≥ 5.0% of participants in the teprotumumab treatment group overall and with a higher incidence than placebo in the Double-masked Population.

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 41. Summary of treatment-emerging adverse events overall by age group during double-masked treatment period (double-masked population)

MedDRA Terms	Teprotumumab (N = 152)				Placebo (N = 133)			
	Age < 65 (N = 133) n (%)	Age 65-74 (N = 17) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)	Age < 65 (N = 112) n (%)	Age 65-74 (N = 19) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)
Total TEAEs	112 (84.2)	13 (76.5)	2 (100.0)	NA	80 (71.4)	16 (84.2)	1 (50.0)	NA
Serious AEs – Total	7 (5.3)	2 (11.8)	0	NA	2 (1.8)	0	0	NA
- Fatal	0	0	0	NA	0	0	0	NA
- Hospitalization/prolong existing hospitalization	5 (3.8)	2 (11.8)	0	NA	1 (0.9)	0	0	NA
- Life-threatening	0	1 (5.9)	0	NA	0	0	0	NA
- Disability/incapacity	1 (0.8)	0	0	NA	0	0	0	NA

MedDRA Terms	Teprotumumab (N = 152)				Placebo (N = 133)			
	Age < 65 (N = 133) n (%)	Age 65-74 (N = 17) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)	Age < 65 (N = 112) n (%)	Age 65-74 (N = 19) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)
- Other (medically significant)	1 (0.8)	0	0	NA	1 (0.9)	0	0	NA
AE leading to drop-out	5 (3.8)	2 (11.8)	0	NA	3 (2.7)	1 (5.3)	0	NA
Psychiatric disorders [a]	5 (3.8)	1 (5.9)	0	NA	7 (6.3)	1 (5.3)	0	NA
Nervous system disorders [b]	35 (26.3)	2 (11.8)	1 (50.0)	NA	21 (18.8)	3 (15.8)	1 (50.0)	NA
Accidents and injuries [c]	9 (6.8)	0	0	NA	7 (6.3)	1 (5.3)	0	NA
Cardiac disorders [d]	6 (4.5)	0	0	NA	3 (2.7)	0	0	NA
Vascular disorders [e]	5 (3.8)	1 (5.9)	0	NA	4 (3.6)	0	0	NA
Cerebrovascular disorders [f]	1 (0.8)	0	0	NA	1 (0.9)	0	0	NA
Infections and infestations [g]	45 (33.8)	5 (29.4)	0	NA	25 (22.3)	8 (42.1)	0	NA
Anticholinergic syndrome [h]	0	0	0	NA	0	0	0	NA
Quality of life decreased [i]	0	0	0	NA	0	0	0	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [j]	4 (3.0)	1 (5.9)	0	NA	6 (5.4)	3 (15.8)	0	NA
Other AE appearing more frequently in older patients								
Blood and lymphatic system disorders								
- Anaemia	1 (0.8)	0	0	NA	0	1 (5.3)	0	NA
- Polycythaemia	0	0	0	NA	0	1 (5.3)	0	NA
Ear and labyrinth disorders								
- Deafness	1 (0.8)	0	1 (50.0)	NA	0	0	0	NA
- Deafness unilateral	0	1 (5.9)	0	NA	0	0	0	NA
- Ear pain	2 (1.5)	0	0	NA	0	1 (5.3)	0	NA
- Eustachian tube patulous	1 (0.8)	1 (5.9)	0	NA	0	0	0	NA
- Neurosensory hypoacusis	1 (0.8)	1 (5.9)	0	NA	0	1 (5.3)	0	NA
- Tinnitus	4 (3.0)	1 (5.9)	0	NA	2 (1.8)	0	0	NA
- Vertigo	1 (0.8)	0	0	NA	0	1 (5.3)	0	NA
Endocrine disorders								
- Hypothyroidism	0	1 (5.9)	0	NA	0	0	0	NA
Eye disorders								

MedDRA Terms	Teprotumumab (N = 152)				Placebo (N = 133)			
	Age < 65 (N = 133) n (%)	Age 65-74 (N = 17) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)	Age < 65 (N = 112) n (%)	Age 65-74 (N = 19) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)
- Cataract subcapsular	0	0	0	NA	0	1 (5.3)	0	NA
- Corneal epithelium defect	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Corneal erosion	0	0	1 (50.0)	NA	0	0	0	NA
- Diplopia	0	1 (5.9)	0	NA	0	0	0	NA
- Ocular hypertension	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Punctate keratitis	0	0	0	NA	0	1 (5.3)	0	NA
- Visual acuity reduced	0	0	0	NA	0	1 (5.3)	0	NA
Gastrointestinal disorders								
- Abdominal distension	0	1 (5.9)	0	NA	0	0	0	NA
- Abdominal pain lower	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Dry mouth	1 (0.8)	1 (5.9)	0	NA	2 (1.8)	0	0	NA
General disorders and administration site conditions								
- Feeling hot	3 (2.3)	1 (5.9)	0	NA	2 (1.8)	0	0	NA
- Malaise	1 (0.8)	0	0	NA	0	1 (5.3)	0	NA
Hepatobiliary disorders								
- Hepatic function abnormal	0	1 (5.9)	0	NA	0	0	0	NA
- Hepatic steatosis	0	1 (5.9)	0	NA	0	0	0	NA
Immune system disorders								
- Allergy to chemicals	0	1 (5.9)	0	NA	0	0	0	NA
- Seasonal allergy	4 (3.0)	1 (5.9)	0	NA	1 (0.9)	0	0	NA
Infections and infestations								
- Bronchitis	4 (3.0)	1 (5.9)	0	NA	2 (1.8)	0	0	NA
- Cystitis	3 (2.3)	1 (5.9)	0	NA	0	1 (5.3)	0	NA
- Gastroenteritis	1 (0.8)	0	0	NA	0	1 (5.3)	0	NA
- Influenza	2 (1.5)	1 (5.9)	0	NA	4 (3.6)	1 (5.3)	0	NA
- Pneumonia chlamydial	0	1 (5.9)	0	NA	0	0	0	NA

MedDRA Terms	Teprotumumab (N = 152)				Placebo (N = 133)			
	Age < 65 (N = 133) n (%)	Age 65-74 (N = 17) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)	Age < 65 (N = 112) n (%)	Age 65-74 (N = 19) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)
- Sinusitis	2 (1.5)	1 (5.9)	0	NA	0	0	0	NA
- Tooth infection	1 (0.8)	0	0	NA	0	1 (5.3)	0	NA
- Upper respiratory tract infection	1 (0.8)	0	0	NA	4 (3.6)	2 (10.5)	0	NA
Injury, poisoning and procedural complications								
- Fall	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Joint injury	0	0	0	NA	0	1 (5.3)	0	NA
Investigations								
- Blood glucose increased	4 (3.0)	1 (5.9)	0	NA	0	1 (5.3)	0	NA
- Blood pressure increased	1 (0.8)	1 (5.9)	0	NA	3 (2.7)	0	0	NA
- Human chorionic gonadotrophin increased	0	0	0	NA	0	1 (5.3)	0	NA
- Vitamin D decreased	0	0	0	NA	0	1 (5.3)	0	NA
- Weight decreased	4 (3.0)	0	1 (50.0)	NA	0	0	0	NA
Metabolism and nutrition disorders								
- Decreased appetite	3 (2.3)	0	1 (50.0)	NA	0	1 (5.3)	0	NA
- Hyperglycaemia	5 (3.8)	3 (17.6)	0	NA	1 (0.9)	0	0	NA
Musculoskeletal and connective tissue disorders								
- Arthralgia	1 (0.8)	1 (5.9)	0	NA	1 (0.9)	1 (5.3)	0	NA
- Back pain	1 (0.8)	0	0	NA	3 (2.7)	1 (5.3)	0	NA
- Joint swelling	0	1 (5.9)	0	NA	0	0	0	NA
- Musculoskeletal chest pain	0	0	0	NA	0	1 (5.3)	0	NA
- Myalgia	3 (2.3)	1 (5.9)	0	NA	2 (1.8)	0	0	NA
- Osteoarthritis	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Rotator cuff syndrome	0	0	0	NA	0	1 (5.3)	0	NA
- Spinal pain	0	0	1 (50.0)	NA	0	0	0	NA
Neoplasms benign, malignant and unspecified (incl cysts)								
- Lipoma	0	0	0	NA	0	1 (5.3)	0	NA
Nervous system disorders								

MedDRA Terms	Teprotumumab (N = 152)				Placebo (N = 133)			
	Age < 65 (N = 133) n (%)	Age 65-74 (N = 17) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)	Age < 65 (N = 112) n (%)	Age 65-74 (N = 19) n (%)	Age 75-84 (N = 2) n (%)	Age 85+ (N = 0) n (%)
- Dizziness	4 (3.0)	1 (5.9)	0	NA	5 (4.5)	2 (10.5)	0	NA
- Hypoaesthesia	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
- Hypogeusia	0	0	1 (50.0)	NA	0	0	0	NA
- Hyposmia	0	0	1 (50.0)	NA	0	0	0	NA
- Loss of consciousness	0	1 (5.9)	0	NA	0	0	0	NA
- Paraesthesia	3 (2.3)	1 (5.9)	0	NA	0	0	0	NA
- Somnolence	0	0	0	NA	3 (2.7)	1 (5.3)	0	NA
Psychiatric disorders								
- Abnormal behaviour	0	0	0	NA	0	1 (5.3)	0	NA
- Nightmare	0	1 (5.9)	0	NA	0	0	0	NA
Renal and urinary disorders								
- Dysuria	1 (0.8)	0	1 (50.0)	NA	0	0	0	NA
Reproductive system and breast disorders								
- Benign prostatic hyperplasia	0	1 (5.9)	0	NA	0	0	0	NA
- Vaginal haemorrhage	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
Respiratory, thoracic, and mediastinal disorders								
- Cough	6 (4.5)	0	0	NA	2 (1.8)	2 (10.5)	0	NA
- Pneumothorax	0	1 (5.9)	0	NA	0	0	0	NA
- Respiratory tract congestion	0	0	0	NA	1 (0.9)	1 (5.3)	0	NA
Skin and subcutaneous tissue disorders								
- Dermatitis	0	1 (5.9)	0	NA	0	0	0	NA
- Nail disorder	2 (1.5)	0	0	NA	0	1 (5.3)	0	NA
- Night sweats	0	1 (5.9)	0	NA	0	0	0	NA
- Petechiae	0	1 (5.9)	0	NA	0	0	0	NA
- Pruritus	0	1 (5.9)	0	NA	3 (2.7)	0	0	NA
Vascular disorders								
- Hypertension	4 (3.0)	1 (5.9)	0	NA	2 (1.8)	0	0	NA

MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable (no participants in this age group); NEC = not elsewhere classified; PT = preferred term; SOC = system organ class; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event

[a] Includes all events with any PT from the Psychiatric disorders SOC

[b] Includes all events with any PT from the Nervous system disorders SOC

[c] Includes all events with any PT from the Accidents and injuries SMQ

[d] Includes all events with any PT from the Cardiac disorders SOC

[e] Includes all events with any PT from the Vascular disorders SOC
[f] Includes all events with any PT from the Central nervous system haemorrhages and cerebrovascular conditions SMQ
[g] Includes all events with any PT from the Infections and infestations SOC
[h] Includes all events with PT Anticholinergic syndrome
[i] Includes all events with PT Quality of life decreased
[j] Includes all events with PTs ataxia, dizziness, fall, loss of consciousness, orthostatic hypotension, syncope; and all events with any PT from the fractures and dislocations NEC high level term
Includes studies of TED01RV, HZNP-TEP-301, HZNP-TEP-303, and HZNP-TEP-403, and includes the open-label data for HZNP-TEP-303 and HZNP-TEP-403.
Percentages are based on the number of senior people in the Double-masked Population in each treatment group within each disease activity group and in the specific subgroup.
Adverse events are coded using MedDRA version 26.0. At each level of summarization, participants who experienced more than 1 event are counted only once. Events are sorted alphabetically by system organ class and by preferred term within system organ class.
TEAEs are defined as adverse events occurring after the first dose on day 1 (placebo or teprotumumab) through 3 weeks after the last dose of study drug (placebo or teprotumumab) in each study.

Incidence of TEAEs by sex

Analysis of TEAEs by sex did not suggest any clinically relevant differences from the overall analysis of TEAEs although the majority of participants were female. A more pronounced difference between the teprotumumab and placebo groups for the SOC *Infections and infestations* was observed for females (36.8% teprotumumab, 24.8% placebo), whereas the incidence for this SOC was similar among males in the placebo and teprotumumab groups (23.9% teprotumumab, 25.0% placebo).

Among female participants of childbearing potential, menstrual disorders (*Amenorrhea*, *Dysmenorrhoea*, *Heavy menstrual bleeding*, *Hypomenorrhoea*, *Menstruation irregular*) were reported by 13.0% (7 of 54) of teprotumumab-treated participants and 2.2% (1 of 45) of placebo-treated participants during the Double-masked Treatment Period.

Incidence of TEAEs by Race and by Ethnicity

Analysis of TEAEs by race did not suggest any clinically relevant differences from the overall analysis of TEAEs although the majority of participants were white. Very few participants treated in the Double-masked Population were of Hispanic or Latino ethnicity (10 [0.8%] placebo and 10 [0.7%] teprotumumab).

Incidence of TEAEs by tobacco use status

Analysis of TEAEs by tobacco use status did not suggest any clinically relevant differences from the overall analysis of TEAEs although the majority of participants were non-users of tobacco.

Incidence of TEAEs by region

A summary of TEAEs occurring in ≥ 5.0% of participants in either treatment group overall during the Double-masked Treatment Period is presented by region in Table 42. Analysis of TEAEs by region did not suggest any clinically relevant differences from the overall analysis of TEAEs although the majority of participants were not in Europe.

Table 42. Summary of TEAEs Occurring in ≥ 5.0% of Participants in Either Treatment Group Overall During the Double-masked Treatment Period by Region (Double-masked Population)

	Number (%) of Participants			
	Overall			
	Europe		**Non-Europe**	
Preferred Term	**Placebo (N = 39)**	**Teprotumumab (N = 35)**	**Placebo (N = 94)**	**Teprotumumab (N = 117)**
Any TEAE[a]	20 (51.3)	27 (77.1)	77 (81.9)	100 (85.5)
Muscle spasms	2 (5.1)	7 (20.0)	6 (6.4)	35 (29.9)
Diarrhoea	1 (2.6)	4 (11.4)	11 (11.7)	18 (15.4)
Alopecia	3 (7.7)	5 (14.3)	4 (4.3)	15 (12.8)
Fatigue	3 (7.7)	3 (8.6)	5 (5.3)	14 (12.0)
Nausea	3 (7.7)	3 (8.6)	6 (6.4)	13 (11.1)
Headache	2 (5.1)	4 (11.4)	8 (8.5)	12 (10.3)
Dry skin	0	3 (8.6)	0	12 (10.3)
COVID-19	0	0	5 (5.3)	10 (8.5)
Dysgeusia	0	2 (5.7)	1 (1.1)	9 (7.7)
Ear discomfort	0	1 (2.9)	2 (2.1)	9 (7.7)
Hyperglycaemia	0	0	1 (1.1)	8 (6.8)
Hypoacusis	0	2 (5.7)	0	6 (5.1)

COVID-19 = coronavirus disease 2019; IP = investigational product; TEAE = treatment-emergent adverse event

Note: Preferred terms included in this table are those occurring in ≥ 5.0% of participants in the teprotumumab treatment group overall and with a higher incidence than placebo in the Double-masked Population.

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

Use in Pregnancy and lactation

The use of teprotumumab in pregnant or lactating women has not been evaluated in clinical trials. Given the teratogenic effects of teprotumumab noted in a monkey embryo-fetal development toxicity trial and the pharmacokinetic profile of teprotumumab, all participants (men and women) in OPTIC, OPTIC-X and TED01RV were required to use adequate contraception during trial participation and for a specified period of time after the last dose of IP. In OPTIC-J and HZNP-TEP-403, all female participants of childbearing potential who were sexually active with a non-vasectomized male partner were required to use adequate contraception for at least 6 months after the last dose of IP; male participants were not required to use contraception. Participants were also required to report any pregnancies for at least 4 or 6 months after the last dose of IP. No participants became pregnant in the teprotumumab clinical program.

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

Withdrawal and Rebound

No significant increase in disease severity was observed following completion of therapy. The durability of the effectiveness of teprotumumab was demonstrated after approximately 1 year off-treatment in the 2 trials with long-term Follow-up Periods, TED01RV and OPTIC. In addition, AEs reported by participants in the off-treatment Follow-up Periods of the acute TED trials showed no evidence of withdrawal or rebound effects.

2.5.8.7. Immunological events

Results for ADA testing are summarised for the Double-masked Population by treatment group within disease activity group. The incidence of positive ADA results was summarized by visit and overall. In addition, the number and percentage of participants with a negative result at Day 1 (Baseline) and a positive result at any post-Baseline visit were presented.

A summary of ADA results is presented for the Double-masked Population inImmunogenicity of teprotumumab was assessed in serum samples using a stepwise ADA analysis approach. Only the result from HZNP-TEP-301 is presented as the results from other studies are considered unreliable (e.g. problem with drug tolerance). Among 41 acute TED participants who received teprotumumab treatment, there were 2 participants confirmed ADA-positive at post-Baseline visits. Two participants were confirmed positive at Week 72 for anti-teprotumumab antibodies. However, both samples did not have sufficient antibodies (titer <1) for quantitative assessment following titer analysis.

Table 9.

No clinically relevant immunogenic response was observed after administration of teprotumumab. The results from TED01RV are excluded in the summary due to unreliable data. Among 67 acute TED participants (HZNP-TEP-301, and HZNP-TEP-303) who received teprotumumab treatment, there were 2 participants confirmed ADA-positive at post-Baseline visits. These two participants were from Study HZNP-TEP-301. Both Participants 101-003 and 122-002 were confirmed positive at Week 72 for anti-teprotumumab antibodies. However, both samples did not have sufficient antibodies (titer <1) for quantitative assessment following titer analysis. No teprotumumab-treated participants from Studies HZNP-TEP-302, HZNP-TEP-102, or HZNP-TEP-303 had detectable anti-teprotumumab antibodies at post-Baseline visits. Among 41 chronic TED patients (HZNP-TEP-403) who received teprotumumab treatment, there was 1 participant (US-106-002) confirmed ADA-positive at post-baseline visits. The participant was confirmed positive at Week 3 for anti-teprotumumab antibodies and had low titer value (1:4).

2.5.8.8. Safety related to drug-drug interactions and other interactions

No *in vitro* or *in vivo* drug-drug interaction trials have been conducted with teprotumumab. Drug-drug interactions between teprotumumab and thyroid medications (eg, levothyroxine, propylthiouracil) commonly taken by TED patients are not expected, as teprotumumab and small molecule drugs do not share common or overlapping clearance pathways. As a monoclonal antibody, teprotumumab is primarily cleared by proteolytic catabolism and broken down into peptide fragments as endogenous immunoglobulin G, thus it is not subject to modulation of drug-metabolizing enzymes. Monoclonal antibodies are not expected to directly affect the hepatic, renal or biliary elimination of small molecules.

Teprotumumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers or inhibitors of cytochrome P450 enzymes are unlikely.

2.5.8.9. Discontinuation due to adverse events

Double-masked Treatment Period

Seven (4.6%) teprotumumab participants and 4 (3.0%) placebo participants in the Double-masked Population experienced TEAEs with onset during the Double-masked Treatment Period that led to discontinuation of IP. One additional teprotumumab participant was discontinued from IP due to a severe AE of Confusional state reported more than 21 days after the sixth dose of IP.

Among the TEAEs with onset during the Double-masked Treatment Period that led to discontinuation of IP in the teprotumumab group, events considered severe in intensity and/or related to IP were:

- *Diarrhoea* in Participant was considered severe and related to IP. This event is considered exacerbation of IBD because of the participant's underlying history of colitis and subsequent diagnosis of ulcerative colitis.
- *Escherichia sepsis* and *Dehydration* in Participant were considered severe and unrelated to IP.
- *Conductive deafness* in Participant was considered severe and related to IP. The event led to IP discontinuation during the Open-label Treatment Period of HZNP-TEP-403 and occurred in a participant with a history of hearing impairment that predated receipt of IP.
- *Inflammatory bowel disease* in Participant was considered severe and unrelated to IP. This participant had underlying IBD; thus, the event is likely exacerbation of pre-existing IBD.
- *Infusion related reaction* in Participant was considered related to IP.
- *Neurosensory hypoacusis* in Participant, who had a history of Eustachian tube disfunction and sensorineural hearing loss in both ears, was considered related to IP.

All of the TEAEs in the Double-masked Population that led to discontinuation of IP in the teprotumumab group were noted as recovered/resolved or recovered/resolved with sequelae, with the exception of *Conductive deafness* and *Neurosensory hypoacusis*, which were not recovered/not resolved as of the database lock for the primary Week 24 analysis in the ongoing trials, and *Escherichia sepsis,* for which the outcome was indicated as unknown.

Open-label treatment

During open-label treatment, TEAEs which led to discontinuation of teprotumumab included *Muscle spasms, Cerebral haemorrhage, Hypoacusis, COVID-19* and *Hyperglycaemia.* Additionally, one participant received 7 infusions of teprotumumab but refused the final infusion due to mild TEAEs of *Erythema* and *Dry eye*.

2.5.8.10. Other safety experience with teprotumumab

In addition to TED, teprotumumab has been studied in patients with cancer, patients with DME and patients with diffuse cutaneous systemic sclerosis.

Teprotumumab in oncology populations

Teprotumumab was investigated under the names R1507 or RO4858696 in 9 oncology clinical trials. The oncology clinical development program was terminated by the sponsor in Dec 2009 and all trials were concluded.

The studies included a total of 782 participants with a variety of advanced malignancies. Of the 782 participants studied, 727 received at least 1 dose of teprotumumab and 55 received placebo. Trial drug for the oncology program was derived from 1 of 2 cell lines, with the majority of participants (n = 632) exposed to the Chinese hamster ovary (CHO) cell line-derived product (the same cell line used for the TED program) and 95 participants exposed to a murine myeloid (SP2/0) cell line-derived product. A total of 94 pediatric participants (2 to 17 years of age) were evaluated in 2 of the 9 trials (NO21200 [n = 34] and NO21157 [n = 60]).

Oncology trial NO21160B

The only oncology trial which was randomised and placebo-controlled, included 171 participants. It was designed to investigate the effect of teprotumumab in patients with small cell lung cancer with disease progression after first- or second-line chemotherapy. All patients received erlotinibe in combination with IP. Overall, a total of 66% (77/116) and 76% (42/55) of participants in the teprotumumab and placebo groups, respectively, died during the trial. Disease progression (including non-small cell lung cancer [NSCLC] and lung neoplasm malignant), the most commonly reported cause of death, was reported for 59% (68/116) of the teprotumumab-treated participants and 71% (39/55) of the placebo-treated participants. Deaths for 7% (8/116) and 4% (2/55) of the participants in the teprotumumab and placebo groups, respectively, were attributed to TEAEs. In 5 of the 8 deaths attributed to TEAEs in the teprotumumab groups, the underlying cause of death was attributed to the underlying lung cancer.

Table 43. Serious and Commonly reported TEAEs by MedDRA SOC

	Teprotumumab	**Placebo**
Serious TEAEs	28% (32/116)	15% (8/55)
Infections and infestations	8% (9/116)	5% (3/55)
Respiratory, thoracic and mediastinal disorder	7% (8/116)	4% (2/55)
Myocardial infarction	3% (3/116)	0% (0/55)
Angina pectoris	<1% (1/116)	0% (0/55)
Common TEAEs		
Skin and subcutaneous tissue disorders	82% (95/116)	71% (39/55)
Gastrointestinal disorders	75% (87/116)	60% (33/55)
General disorders and administrative site conditions	66% (77/116)	40% (22/55)
	Fatigue 39% [45/116]	*Fatigue* 20% [11/55]
	Mucosal inflammation 16% [18/116]	*Mucosal inflammation* 7% [4/55]
Respiratory, thoracic and mediastinal disorders	52% (60/116)	36% (20/55)
	Epistaxis (19% [22/116]	2% [1/55]

TEAEs with frequency approx. 3 times higher for teprotumumab		
Investigations	31% (36/116)	9% (5/55)
	Weight decreased (21% [24/116]	*Weight decreased* 4% [2/55]
Vascular disorders	14% (16/116)	5% (3/55)
	Deep vein thrombosis 4% (5/116)	*Deep vein thrombosis* 0% (0/55)
Hearing losses	3,5% (4/116)	0% (0/55)

Oncology trial NO21157

The open-label study was performed in 317 patients with sarcomas. Overall, 11% (34/317) of the participants died during the trial. Causes of death included disease progression or a clinical condition that would be anticipated in the underlying sarcoma populations. The primary cause of death for 6 participants included: *Respiratory failure* (2 participants), *Acute respiratory failure*, *Sepsis*, *Cardiopulmonary failure* and *Renal failure* (1 participant each). The most commonly reported TEAEs by MedDRA SOC (≥ 50% of participants) were *General disorders and administrative site conditions* were 62% (192/310), *Gastrointestinal disorders* 56% (175/310) (including *Nausea*, *Diarrhoea*, *Vomiting* and *Constipation*) and *Musculoskeletal and connective tissue disorders* 51% (157/310) (including *muscle spasms*). Three participants (from 24 – 39 years old) reported events categorized under the HLT *Hearing losses.* Their diagnosis and causality cannot be confirmed, and events were ongoing for all 3 participants. Hearing impairment was not reported in the pediatric participants in this trial. For one patient, an event of *Anaphylactic reaction* was reported. This was the only explicitly reported anaphylactic reaction in the oncology clinical development program.

Seven other oncology studies

Seven other oncology studies were performed in patients with different malignant diseases. All seven studies were open-label and considered small in comparison to the studies mentioned above. Selected data from these studies include the fact that in one trial, hyperglycaemia occurred in higher frequency in patient group treated with the CHO-derived medicinal product, than the group treated with murine cell line-derived medicinal product. Hearing-loss occurred in four of these studies. In one study with 11 patients, TEAEs of hypercalcemia, diarrhoea and infection were reported.

Teprotumumab in DME trial

A phase 1 open-label safety and pharmacodynamic study was performed (conducted by River Vision Development Corporation). The trial investigated short-term safety (3 infusions) in participants with DME. Ten participants were planned; however, the trial was terminated due to difficult enrollment and only 5 participants were enrolled. 4 experienced events related to hyperglycaemia (*Blood sugar increased* [2 participants], *Blood glucose increased* [1 participant] and *Hyperglycaemia* [1 participant]). All events were nonserious, and 2 participants discontinued trial drug with events resolving 114 and 62 days after their second (final) infusion, respectively.

Teprotumumab in diffuse cutaneous systemic sclerosis

Three participants (1 teprotumumab, 2 placebo) were randomized in the Phase 1 trial (HZNP-TEP-001) (conducted under IND 147532, sponsored by Horizon). This trial was terminated early by the Sponsor due to low enrolment. No TEAEs were recorded for the teprotumumab participant.

2.5.8.11. Post marketing experience

TEPEZZA (teprotumumab) was first approved worldwide by the US FDA on 21 January 2020 (International Birth Date) for the treatment of TED and was approved in Brazil in June 2023. It is currently only marketed in the US. The cumulative post-authorization patient exposure through 20 July 2023 is estimated to be 8690 patient years based on the available sales figures.

From the International Birth Date through 20 July 2023, a total of 4,728 ADRs (475 serious and 4253 nonserious) have been received from spontaneous sources. In addition, 1309 serious ADRs from solicited sources have been received that were considered related by the Sponsor.

Important identified risks for TEPEZZA include infusion reactions (hypersensitivity), hyperglycemia, exacerbation of IBD and hearing impairment. New onset of IBD is considered an important potential risk. No post-marketing subgroup analysis was performed.

Infusion reactions (hypersensitivity) are commonly associated with monoclonal antibodies. Search parameters include SMQs *Anaphylactic Reaction (algorithmic)* and *Hypersensitivity* (narrow). Cumulatively, 214 ADRs were received, of which 10 were serious and 204 were nonserious. Events were primarily *Pruritis*, *Rash* and *Infusion related reaction*. No ADRs of *Anaphylactic reaction* were reported from spontaneous sources, and the 1 solicited ADR did not meet the Sampson criteria for anaphylaxis.

Hyperglycemia is searched using SMQ *Hyperglycaemia/new onset diabetes mellitus* (narrow) and PTs *Blood glucose abnormal, Blood glucose fluctuation, Glucose tolerance decreased* and *Glucose tolerance test abnormal*. 253 ADRs were received, of which 92 were serious and 161 were nonserious. In Jan2022, a signal of severe diabetic complications with TEPEZZA was opened after receipt of a literature case (Shah and Charitou, 2022) of hyperglycemic hyperosmotic state. This patient responded to treatment and remained on TEPEZZA without further complications. In the signal assessment dataset, there were several cases of *Diabetic ketoacidosis* and coma, with high glucose values in patients with no reported history of diabetes and no identified confounders. Given the biologic plausibility, the signal of severe diabetic complications was confirmed, with subsequent update of the US prescribing information.

Exacerbation of, and new-onset **IBD** are both searched using HLT *Colitis (excl infective)*, with the 2 distinguished based on reported medical history. 10 ADRs of IBD exacerbation (5 serious, 5 nonserious) and 2 of new-onset IBD (both serious) have been received. The 2 cases presenting as new onset (both solicited) had no medical history or physician confirmation and were described as starting at an unknown time after completion of TEPEZZA therapy; insufficient information precludes better representation of these events.

Hearing impairment, which may be associated with alteration of the IGF-1R signaling pathway, is searched using SMQ *Hearing impairment* (broad and narrow) and HLT *Hearing losses*. Cumulatively, 437 ADRs were reported, of which 127 were serious and 310 were nonserious. In November 2022, a signal of potential increased severity of hearing impairment was opened and a comprehensive signal assessment was performed with a focus on the following: patients who underwent audiometric evaluation or were referred to an audiologist or specialist irrespective of the results, changes to TEPEZZA dosing, including withdrawal or

pausing treatment due to hearing impairment, and events meeting CTCAE Grade 3 criteria. The review identified several notable cases in which the patient had a negative medical history of hearing issues, audiometry identified hearing impairment, there was permanent loss or lack of improvement after stopping treatment and/or medical intervention, such as hearing aid, was needed. The review demonstrated that there are some cases suggestive of increased severity than what was seen in clinical trials, and the signal was confirmed, with subsequent update of the US prescribing information. No clear risk factors for hearing impairment were identified.

No new important risks have been identified post-marketing. It is notable that post-marketing reports suggest increased severity of the known risks of hyperglycaemia and hearing impairment compared to the clinical trial experience. New-onset IBD was also identified post-marketing, although with limited information provided.

2.5.9. Discussion on clinical safety

The clinical safety analysis is based on data from 6 clinical trials. In four of the trials, the efficacy and safety of teprotumumab were investigated versus placebo in 24-week double-masked treatment periods. Some patients were included in follow-up safety investigations. Open label treatment periods followed for some of the patients in three of the studies. In addition, one separate open-label study was performed.

Supportive safety data are derived from post-marketing experience, and clinical studies in patients with other diseases. Based on the mode of action and experience from studies in other patient groups, adverse events of special interest were identified.

Safety data collection: Safety assessments during the 24-week double-masked treatment period were performed at various time points. Adverse event assessment, vital signs, concomitant medication, haematology and glucose were investigated at screening, baseline, and every 3 weeks *i.e.* at each trial visit. Other parameters, such as 12-lead ECG, ophthalmic examination, and blood analyses, were tested more seldom. In some studies, the 72 weeks follow-up included evaluation of adverse events, vital signs and concomitant medication at weeks 28, 36, 48, 60 and 72.

The design of the clinical trials with numerous predefined safety assessment timepoints and the statistical methods are considered adequate for the giving reliable data for safety assessment. The applicant pooled safety data from the double-masked treatment period of the placebo-controlled clinical studies. Summaries were provided by the treatment group (placebo or teprotumumab). Safety data were also pooled in an 'All teprotumumab population', consisting of data from patients receiving teprotumumab in any of the 6 clinical trials. The strategy of pooling data is considered adequate.

Patient exposure: The safety assessment is based on a total exposure to investigational product (IP) (teprotumumab or placebo) of 285 participants, of whom 246 have received treatment with teprotumumab. Demographic and baseline characteristics of the double-masked study population are considered representative of the patient population of TED. In the TED studies, a majority of the participants were white, and a majority of participants were recruited outside Europe. Of note, chronic TED study did not recruit in Europe.

The patient exposure in the clinical trials with the indication TED is considered of sufficient size to enable safety assessment. For 56 participants, long-term safety data from week 72 are available. Follow-up study periods and open-label study periods are still ongoing for some of the studies. The length of the follow-up is considered sufficient for the TED indication. However, no TED studies have included patients for a 3rd

treatment period of infusions. The number of participants who had infusion interruptions and the number of participants who prematurely discontinued IP were considered small and not affecting the overall safety assessment.

A majority of the participants in TED studies received 8 doses or less. Extent of exposure in Double-masked population, both for acute and chronic TED, is limited to a total of 8 administrations of teprotumumab. Total duration of exposure in All population ranged from 1 to approximately 300 days. But some participants received 9-16 infusions.

Sixteen patients received 9-15 infusions, and 13 patients received 16 infusions. In the patients who received 9-15 infusions, approximately 30% of the TEAEs were reported after the 9th infusion. The TEAE pattern for the patients who received more than 8 infusions is comparable to the pattern for the patients who received 8 infusions or fewer. Glycated haemoglobin (HbA1c) increased with the number of infusions, which is already observed for the patients receiving 8 infusions or fewer. Otherwise, the laboratory values and vital signs were not notably different for the group of patients who received more than 8 infusions, compared to the group who were treated with 8 infusions or fewer. The applicant concludes that safety concerns related to long-term use are not anticipated to be different from the known safety profile. Nevertheless, studies are ongoing, in which there are patients receiving more than one treatment course (8 infusions) of teprotumumab and the collection of safety data from these patients is considered important.

22.5% in teprotumumab discontinued early from the trial in acute TED population, with most prominent reasons being disease relapse (9%) and AE (5.4%). 7.3% in teprotumumab discontinued early from the trial in chronic TED population, with a reason lost to follow-up.

Adverse events: For the 'Double-masked population', the treatment-emerging adverse events (TEAEs) from the double-masked treatment period, and the adverse events (AEs) from the follow-up period were presented for the teprotumumab and the placebo groups. Separate data on acute vs chronic TED patients were also presented. This grouping of TEAEs and AEs is considered adequate. For eight participants, TEAEs led to treatment interruption. With these events, no alarming pattern is seen.

AEs reported during the Follow-up period were not negligible. There were 24 participants with 37 treatment-related AEs reported during the follow-up period. The final clinical study report for Study HZNP-TEP-403 has been submitted. During the follow-up period, there were no events with fatal outcome, anaphylactic reactions or any serious events. There were no AEs of infusion-related reactions, hearing impairment, or exacerbation of inflammatory bowel disease reported with onset during the follow-up period after the OLE treatment period. Overall, there were no new safety issues identified during the follow-up period of the study HZNP-TEP-403.

Two adverse events, onychoclasis and muscle spasm, were considered long-lasting with duration greater than 90 days. The most commonly reported late-appearing event was muscle spasm (N=3). This has been reflected in the product information.

Infections have been reported as TEAEs, and for Covid-19, a difference between teprotumumab and placebo groups exists. The difference is considered small, and not alarming.

Several participants with hearing impairment also have reported TEAEs of 'Ear discomfort'. In theory, the ear discomfort could be of a sensory character without physical explanation, only because of the hearing impairment. But for others, there might have been cerumen or similar explanation. Ear discomfort is more prevalent in the treatment group than in the placebo group, but since ear discomfort is not a serious symptom, the aetiology and frequency of this TEAE are not further discussed.

IGF-1 signalling has been implicated in the function of keratinocytes, which are responsible for nail formation. Thus, nail disorders have a possible biologic explanation. But nail problems do not seem strikingly prevalent, nor are they considered as great health problems. Therefore, it is acknowledged that nail disorders are not listed on beforehand as TEAEs of special interest. The effect of IGF-1 on alopecia has also been discussed in literature. A possible biologic link might be part of the explanation to the observed differences in alopecia cases between the teprotumumab and the placebo groups in the acute TED population. Grouping of the PTs 'Alopecia', 'Hair growth abnormal' and 'Madarosis' would also have been possible, in order not to underestimate the prevalence. Some patients with alopecia suffer a lot, although alopecia/hair loss/madarosis is not considered an objectively severe condition.

Overall, 53 events of alopecia were observed in teprotumumab-treated participants (7 events in the placebo) and 27/53 events (51%) had not resolved at the time of last follow-up. Although a high background incidence of alopecia, hair loss and madarosis is a given for patients with hyperthyroidism, that is, patients who can be indicated for treatment with teprotumumab, information has been included in the SmPC regarding the possibility of alopecia, hair loss and madarosis to be permanent.

The 'All teprotumumab population' shows similar pattern in the TEAEs as the 'Double-masked population'. The applicant has submitted a table with cases that corresponds to serious events according to IME/DME list. A total of 39 events (26 in the teprotumumab group) with PTs on IME/DME list were reported in the DM treatment period of the teprotumumab clinical studies. The applicant states that five events (rectal haemorrhage [2 events in 1 participant], haematochezia, diabetes mellitus, muscle rupture) were related and not described in the initial submission due to being nonserious, grade 1, with most resolved (3 of 5), and none had action taken with study drug. However, this analysis of AEs as per the IME/DME list revealed significant safety information as two cases belonging to HLGT Gastrointestinal haemorrhages NEC are recorded. Therefore, the applicant performed a cumulative review and analysis of all HLGT Gastrointestinal haemorrhages NEC cases reported with teprotumumab from all available sources. Three events in 2 subjects were identified in clinical trials: rectal haemorrhage (n = 2), and haematochezia (n = 1) all confounded by significant medical history. A cumulative search of post-marketing data using all sources up to 31 January 2025 revealed a total of 124 cases containing 128 events (PTs: haematochezia [n = 84], rectal haemorrhage [n = 24], gastrointestinal haemorrhage [n = 8], melaena [n = 6], anal haemorrhage, haematemesis, large intestinal haemorrhage, lower gastrointestinal haemorrhage, small intestinal haemorrhage, upper gastrointestinal haemorrhage [each n = 1]). Positive dechallenge was reported for 3 cases, and positive rechallenge for 1 case. The majority of cases were not medically confirmed and medical history relevant for GI hemorrhage was provided for only 34 cases. As there is currently insufficient information to draw conclusions, these events should continue to be monitored using routine pharmacovigilance.

The data on serious adverse events contribute to the total knowledge on safety, and many of the events belong to the ADRs of special interest, as expected. Two malignant diseases were diagnosed during studies. This is not considered alarming. There were no deaths during the conduct of the teprotumumab clinical program in TED.

TEAEs of special interest (AESIs): TEAEs of special interest were identified based on biologic rationale, observation in oncology studies and/or post-marketing experience.

Infusion-related reactions: Infusion-associated events (including hypersensitivity and anaphylactic reaction) are anticipated for all monoclonal antibodies (Vogel, 2010). IRRs were observed in 8 patients (3.3 %) in the teprotumumab groups and in 4 patients (3.0%) in the placebo groups in the double-masked treatment period. One IRR was considered serious in the teprotumumab groups. No IRR was reported as anaphylactic reaction, and the IRRs noted do not show an alarming pattern. However, since monoclonal antibodies are

associated with IRRs, and IRRs are identified in TED studies, it is considered adequate to include IRR as an identified risk in the RMP and to include information in the SmPC, section 4.4. IRRs are constituted of the following symptoms: feeling hot, rash, hypertension, tachycardia, diarrhoea and abdominal pain upper, temperature, headache and nasal congestion, haptic hallucinations, sleep paralysis, urticaria.

Hyperglycemia/new onset diabetes mellitus: Insulin and IGF-1 receptors are highly homologous and share many downstream signalling pathways but have unique biological effects. Disturbing these pathways has been shown to increase insulin resistance, glucose intolerance and dyslipidaemia. Hyperglycaemia has been observed in oncology studies and post-marketing. The hyperglycaemia-associated TEAEs reported for the teprotumumab treated groups in the double-masked periods and the open-label studies and the follow-up periods, are more frequent than in the placebo groups. For patients with diabetes at baseline, 69,2% of the teprotumumab participants had any event of hyperglycaemia, compared to 9,1% of the placebo participants. The laboratory values of fasting glucose and HbA1c confirm the TEAE pattern. The importance of identifying diabetic status before start of, and during, treatment with teprotumumab has been included in the SmPC.

Hyperglycaemia has been observed during follow-up in TED studies in the double-masked population. Hyperglycaemia was observed to resolve within 3-6 months in the clinical studies. A total of 7 diabetes mellitus cases have been identified in clinical trials. All subjects had baseline glycaemic status of prediabetes or diabetes. Cumulatively to 31 January 2025, 396 teprotumumab cases of the HLT Diabetes mellitus (including subtypes) have been received from post-marketing sources. One case was fatal (the patient had multiple contributing comorbid conditions). Positive dechallenge was reported in 10 cases, and positive rechallenge in 2 cases. Of the 396 cases, 14 cases included a medical history of glucose intolerance which included: glucose tolerance impaired (n = 7); Type 2 diabetes mellitus (n = 1); diabetes mellitus (n = 4), pre diabetes (n = 1), blood glucose increased (n = 2), blood glucose abnormal (n = 1).

The applicant has added appropriate risk minimizing statements in section 4.4 and 4.8 of the SmPC, including a recommendation to Section 4.4 of the SmPC that blood glucose should be monitored for 6 months after completion of treatment. The applicant further plans to continue studying hyperglycaemia in a post-authorisation study.

New-onset IBD and Exacerbation of IBD: No new onset IBD was found in the TED trials. Two serious events of exacerbation of IBD (one registered as 'diarrhoea', and one registered as 'IBD') were found in the double-masked treatment period. The placebo participant with known IBD did not experience an exacerbation. It is noted that patients with known IBD were excluded from some of the clinical studies, which might have influenced the number of exacerbation events. Since the events of exacerbation of IBD were considered serious, it is acknowledged to include in the SmPC, section 4.4, and to define as 'Important identified risk' in summary of safety concerns in the RMP.

Hearing impairment: Insulin-like growth factor-1, which binds the IGF-1R, is an important regulator of cochlear development, and its mutations are associated with hearing loss in mice and humans. As teprotumumab inhibits signalling through the IGF-1R, understanding of the pharmacologic impact on hearing is still evolving.

Hearing impairment is noted for teprotumumab treated participants in both double-masked periods of studies, during follow-up periods, as well as in open-label studies. Across the TED clinical program, a total of 40 (40/246, 16.3%) participants experienced 52 events of hearing impairment (reported as *Autophony*, *Conductive deafness*, *Deafness*, *Deafness neurosensory*, *Deafness unilateral*, *Eustachian tube dysfunction*, *Eustachian tube patulous*, *Hyperacusis*, *Hypoacusis*, *Neurosensory hypoacusis*, *Tinnitus* or *Tympanic membrane disorder*) while receiving teprotumumab or during the Follow-up Period after receipt of

teprotumumab. In the Double-masked Population, 21 (13.8%) participants in the teprotumumab group experienced 28 TEAEs of hearing impairment compared with 3 (2.3%) participants in the placebo group who experienced 4 TEAEs of hearing impairment.

The frequency of hearing impairment in the acute TED participants is approximately 6 times higher in the teprotumumab treated groups than in the placebo groups. For the chronic TED patients, the frequency is two times higher in the teprotumumab group compared to the chronic TED placebo groups, although the frequencies are higher in both groups than in the corresponding acute TED patient groups. Most of the hearing impairment events were mild or moderate, but approximately one third of the hearing impairment events in the teprotumumab treated participants were not resolved as of the database lock for the trial or the primary week 24 analysis. The applicant states that the majority of hearing impairment events were nonserious. Only one case of Conductive deafness was assessed as serious. However, there are 8 other deafness cases that are assessed as non-serious, although PT terms Conductive deafness, Deafness neurosensory, Deafness unilateral, and Deafness belong to EMA Important medical event (IME) terms list (MedDRA version 27.0, 18 March 2024), and therefore always serious. It is agreed that 'patients with medical history of hearing impairment or tinnitus' is not warranted as a contraindication. Data were too limited to draw conclusions on risk in patients with a previous history of hearing impairment vs. patients without such history. A statement has been included in section 4.4 of the SmPC, however, that for patients with pre-existing hearing impairment, worsening of hearing impairment symptoms during or after the completion of the treatment with teprotumumab can occur.

Considering the relatively young TED population, hearing impairment is of great impact to the patient, especially if permanent. The risk of permanent hearing impairment is considered the factor contributing most negatively to the B/R balance.

In the assessment of the B/R balance, the AESIs of IRRs, hyperglycaemia, and exacerbation of IBD are also considered to contribute negatively, but not to the same extent. With adequate handling according to the labelling information, the B/R balance could be positive for the individual patient regarding the separate other AESIs.

The AESIs were chosen on beforehand, and the data concerning these events motivate the special focus given to them. They are all included in the RMP as safety concerns, and warning texts concerning IRR, hyperglycaemia, hearing impairment, and exacerbation of IBD are included in the SmPC 4.4 with instructions how to mitigate the risk and how to minimise the effect if the event should occur.

Safety in special populations:

Age: TEAEs are summarised by two age groups: <65 and ≥ 65 years. TED, especially acute TED, often occurs in patients younger than 65. A slightly higher percentage of the older patient group placebo-treated participants had TEAEs than the younger placebo participants. No clear differences between the age groups were seen, and no clinically important conclusions can be drawn by this presentation, also taken in account the difference in number of participants in each age group.

The number of participants 65 years and older is limited. Overall, 11.2 % of the teprotumumab treated participants and 14.3% of the placebo treated participants were 65-74 years old. Only two participants in each group were 75-84 years old, representing 1.3% and 1.5%, respectively. No participant was > 84 years old. The applicant concludes that it is difficult to compare the safety profiles of the different age groups because of the small number of participants in the older age groups. A trend towards more serious AEs is seen, but no conclusion can be drawn. In the teprotumumab-treated group of participants 65-74 years, the

only AEs reported by more than one participant were nervous system disorders (2, placebo 3), infections and infestations (5, placebo 8), and hyperglycemia (3, placebo 0). This is not considered a concern.

Hepatic and Renal impairment: No study participants had renal impairment. Of the hepatically impaired (Child-Pugh score B or C) teprotumumab treated subjects, 85.7% had any TEAE, and of the hepatically impaired placebo treated subjects, 83.3% had any TEAE. These are frequencies comparable to the frequencies observed in the double-masked treatment period for the double-masked study population with acute TED (84.7% for tepro-treated and 71.7% for placebo-treated). These data do not seem worrying as they are comparable to the overall data from the teprotumumab treated participants in the double-masked treatment periods.

Data on TEAEs by BMI and/or body weight showed significantly higher incidences of TEAEs pertaining to the SOC Ear and labyrinth disorders and SOC Gastrointestinal disorders, and other TEAEs by PTs (alopecia, dry skin, stomatitis, COVID-19, abdominal pain upper, weight decreased, decreased appetite, dizziness, urinary tract infection) in teprotumumab-treated patients in the lowest body weight category compared to other body weight groups. These events were further discussed in terms of association with body weight, but no conclusions could be drawn.

Sex and tobacco use: No exceptional pattern is seen in the difference of TEAEs between men and women. Menstrual disorders were reported in a frequency 6 times higher in teprotumumab-treated women than for placebo. This difference is notable, and is reflected in the SmPC, section 4.8. The frequency of menstrual disorders not resolved, together with the fact that menstrual disorders are common in the context of thyroid diseases, does not motivate information in the SmPC regarding reversibility. Differences are seen in the TEAE pattern between tobacco non-users vs tobacco users. But these differences are not consistent, and no special concerns arise.

Race and geographic region: No notable differences were seen in the TEAE pattern by race. The non-Europe participants had a higher prevalence of TEAEs than the Europe participants, most notable difference in the placebo group (81.9% vs 51.3%). The greatest difference observed between the two regions are noted for Covid-19 (15 non-Europe patients vs 0 Europe patients). No clinically important conclusions can be drawn from these data, except that Covid-19 probably was more spread and/or detection was more intense outside Europe when the studies were ongoing.

Use in pregnancy and lactation: Teprotumumab has shown teratogenic effects in a study in monkeys. The pharmacokinetic profile of teprotumumab also indicate teratogenicity. Therefore, various measures to minimise the risk of pregnancy during studies were implicated. No pregnancies occurred during clinical studies. The ways of avoiding pregnancy during the studies are considered adequate. The risk of teratogenicity is reflected in the SmPC. There are no human data on the use during breast-feeding.

Safety related to drug-drug interactions: The absence of drug-drug interaction trials is acknowledged since teprotumumab is a monoclonal antibody, not expected to affect the hepatic or renal elimination, neither influence the cytochrome P450 enzyme systems.

However, since there are risks of hearing impairment, muscle spasms and onset of inflammatory bowel diseases, it might be of interest to avoid concomitant medication with known risks of hearing loss, muscle spasms and muscle toxicity. A text regarding caution with concomitant ototoxic medications is included in the SmPC section 4.4.

Laboratory findings, vital signs and electrocardiograms: Laboratory results associated with TEASs confirmed the observed TEAE pattern. For the other laboratory results, no clinically meaningful differences between the teprotumumab and placebo groups were observed.

No clinically relevant immunogenic response was observed after administration of teprotumumab. The results from TED01RV are excluded in the summary due to unreliable data. Among 67 acute TED participants who received teprotumumab treatment, there were 2 participants confirmed ADA-positive at post-Baseline visits. However, both samples did not have sufficient antibodies (titre <1) for quantitative assessment following titre analysis. Among 41 chronic TED patients (HZNP-TEP-403) who received teprotumumab treatment, there was 1 participant confirmed ADA-positive at week 3 post-baseline visits and had low titre value (1:4).

Decreased weight was reported as TEAE for teprotumumab participants, but not for placebo-treated participants. This is in line with the weight measurements. For teprotumumab, the effect on weight is not considered alarming. No alarming differences were detected in the ECGs between the teprotumumab and placebo groups.

The selection and collection of laboratory results, vital signs, and ECG are considered adequate. The overall safety results on laboratory and other findings are not considered alarming.

Other safety experience with teprotumumab: Hyperglycaemia, hearing impairment and gastro-intestinal events were reported in the oncology clinical trials. The number of deaths in these studies are not considered attributed to the teprotumumab treatment. Many groups of adverse events of importance in the oncology program are associated with the different malignant diseases or chemotherapies included in the trials. None of these TEAEs, nor the deaths, are alarming in the TED context. The oncology program safety data are considered supportive for teprotumumab in the TED population.

Post-marketing data: In post-marketing experience, the number of reported cases of hyperglycaemia and hearing impairment suggested an increased safety concern compared with the clinical trial experience. The US prescribing information was therefore updated in order to emphasise these risks. No new important identified/potential risks were identified in the post-marketing data. Two cases of new onset IBD were found post-marketing, which justifies the inclusion of new onset IBD as an important potential risk in the RMP. Off-label use (in patients < 18 years) has occurred post-marketing. The applicant explains that due to the limitations of the ICD code convention, the degree of off-label use is not easy to determine. This is agreed, and it is assumed that many patients with diagnoses as 'toxic goiter' or 'Graves' disease' registered as receiving medication off-label, also had TED, although not registered. One case of treatment of an adolescent patient was described. The ADRs described for this patient are known for the adult population and were transient. Therefore, no further action is considered necessary.

Non-clinical study results: In studies in cynomolgus monkeys, reduced bone ALP, reduced erythrocyte mass, and reversible thymus atrophy were seen. Clinical studies have not shown reduced lymphocytes. On the contrary, shifts from normal at baseline to above normal range were observed for participants treated with teprotumumab. But the shifts were not of clinically meaningful levels. Haemoglobin shifts were also observed, but smaller in magnitude and less consistent. Possible linked adverse events such as 'anaemia' were not observed in notable extent in the teprotumumab groups compared to placebo. Difference between teprotumumab groups vs placebo groups regarding infections are not considered alarming. The preclinical study results on bone mass density are not considered alarming for the human patient population, as children

and adolescents are excluded. In summary, it is not foreseen that these preclinical study results have implications for humans in the proposed indication and the suggested dosage.

Product information: Pregnancy is listed in section 4.3 as a contraindication. Given the biologic action of teprotumumab and the teratogenicity observed in animal studies, this is considered adequate. Information stressing the importance of measures to avoid pregnancy is also provided in section 4.6. In section 4.4, information on the identified AESIs is present, with instructions how to mitigate the risk and how to minimise the effect if the event should occur. Additional RMMs in terms of a healthcare professionals' guide and a patient guide are being implemented to further minimise this risk. In section 4.8, the applicant included ADRs occurring in >5% of Teprotumumab Participants with a Greater Incidence than Placebo Overall during the Double-masked Treatment Period (Double-masked Population). In addition, AESIs are included, menstrual disorders and weight decreased. The statements by the are also included the SmPC sections concerning ability to drive or operate machinery (4.7) and overdose (4.9) are supported. Overall, the product information is considered acceptable.

2.5.10. Conclusions on the clinical safety

The safety data on teprotumumab for the treatment of TED are considered reliable, given the design, and presentation of data from the 6 clinical studies. The size of the safety population may be considered as limited, but acceptable considering the rarity of the condition. The incidence of anti-teprotumumab antibodies was low for participants who received teprotumumab treatment, and no safety issue has been identified in that respect.
The most important safety issues concern the AESIs identified in advance based on scientific evidence and prevalence in teprotumumab oncology studies and post-marketing events. The AESIs of IRR, hyperglycaemia, exacerbation of IBD and new onset IBD constitute identified or potential risks. The AESI of Hearing impairment is considered as the most serious adverse event as it is frequent in clinical studies, post-marketing data having suggested an even higher prevalence, and some permanent cases have been observed. The risk of permanent hearing impairment is considered the factor contributing most negatively to the B/R balance. Comprehensive precautionary risk minimisation text in Section 4.4 of the SmPC is of utmost importance. But routine RMMs are not considered sufficient to address the risk of hearing impairment. Additional RMM tools, such as the implementation of guides for health care professionals and for patients has been agreed to ensure that all necessary information regarding the risks and actions for risk minimization is known by the healthcare professional, and adequately and thoroughly provided to the patient. In addition, the applicant has agreed to conduct a drug utilisation study to evaluate the effectiveness of these additional risk minimisation measures.

The inclusion of the AESIs IRRs, hyperglycaemia, hearing impairment and exacerbation of IBD in the RMP as Important identified risks, and new onset IBD and embryofoetal toxicity as Important potential risks, is supported.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 44. Summary of safety concerns

Important identified risks	• Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment
Important potential risks	• New onset inflammatory bowel disease • Embryofetal toxicity
Missing information	• Safety in retreated patients

2.6.2. Pharmacovigilance plan

Table 45. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study HZNP-TEP-402 A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab Category 3 Ongoing	• To evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for retreatment.	• Hyperglycemia • Exacerbation of inflammatory bowel disease • Infusion-related reactions • Hearing impairment • New onset inflammatory bowel disease • Safety in retreated patients	Final CSR	August 2026
Study HZNP-TEP-402 hearing evaluation substudy Category 3 Ongoing	• 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	• Hearing impairment	Final CSR	August 2026
Drug utilization study to evaluate the effectiveness of teprotumumab aRMMs (study number TBD) Planned	• To quantify indicators of adherence to measures aimed at minimizing the risks of hearing impairment and embryofetal toxicity among patients being prescribed teprotumumab, where fit-for-purpose data are available.	• Hearing impairment • Embryofetal toxicity	Draft protocol and feasibility report submission	October 2025
			Final CSR	April 2033

aRMM = additional risk minimization measure; CSR = clinical study report; TBD = to be determined; TED = thyroid eye disease

2.6.3. Risk minimisation measures

Table 46. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Hyperglycemia	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion as well as during treatment, ensure that patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab, and to monitor blood glucose for 6 months after completion of treatment with teprotumumab is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402
Exacerbation of inflammatory bowel disease	Routine risk minimization measures: • SmPC Section 4.4, where a recommendation to monitor patients with IBD for flare of disease and to consider discontinuation treatment if IBD exacerbation is suspected is provided. • SmPC Section 4.8 • PL Sections 2 and 4 • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

Infusion-related reactions	Routine risk minimization measures: • SmPC Sections 4.2 and 4.4, where a recommendation to premedicate and/or administer all subsequent infusions at a slower rate in patients experiencing immediate hypersensitivity is provided. • SmPC Section 4.4, where instructions to monitor patients throughout infusion and for 90 minutes after treatment, to interrupt or discontinue the infusion based on severity of the infusion-related reaction, and to manage the reaction appropriately is included. • SmPC Section 4.8 • PL Section 2, where guidance on signs and symptoms of infusion-related reactions and the importance of reporting to the physician or seeking medical help immediately is provided. • PL Section 4, where guidance on the importance of reporting infusion-related reactions to the physician or nurse straight away is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

Hearing impairment	Routine risk minimization measures: • SmPC Section 4.4, where recommendations are provided: - to advise patients to report symptoms of altered hearing promptly to their healthcare professional - to consider the benefit-risk of treatment in patients with pre-existing hearing impairment - to assess patients' hearing using audiometry before starting treatment (first infusion), during treatment (around the third or fourth infusion), and after completing treatment with teprotumumab - to perform additional audiometric assessments as necessary if a patient experiences subjective hearing changes during treatment, and to monitor hearing in these patients for up to 6 months after completion of treatment - to discontinue teprotumumab in patients experiencing hearing loss that requires intervention, limits their ability to self-care, or is considered profound - to advise patients to stop smoking and avoid high intensity noises during treatment, and that blood pressure should be appropriately controlled before and while receiving teprotumumab - to use caution when co-administering teprotumumab in patients who are receiving concomitant therapies known to cause ototoxicity • SmPC Section 4.8 • PL Sections 2 and 4 where guidance on the importance of reporting any changes in hearing to the physician as soon as possible is provided. • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402 • Substudy HZNP-TEP-402 • Drug utilization study (study number TBD)

New onset inflammatory bowel disease	Routine risk minimization measures: • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402
Embryofetal toxicity	Routine risk minimization measures: • SmPC Section 4.3 where use of teprotumumab in pregnancy is contraindicated. • SmPC Section 4.4 where a recommendation that women of childbearing potential should use effective contraception during and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 4.6 where a recommendation that women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) prior to initiation, during treatment, and for at least 6 months after the last administration of teprotumumab is included. • SmPC Section 5.3 • PL Section 2 • Legal Status: prescription only medicine Additional risk minimization measures: • Healthcare Professional Guide • Patient Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Drug utilization study (study number TBD)
Safety in retreated patients	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation that additional doses should not be administered if response is not achieved with the treatment regimen for teprotumumab is included. • Legal Status: prescription only medicine Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study HZNP-TEP-402

IBD = inflammatory bowel disease; PL = package leaflet; SmPC = Summary of Product Characteristics; TBD = to be determined

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did <not> request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.01.2020 The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons: the product is not intended to be delivered directly to the patient, and space constraints have been demonstrated on the vial label, particularly for the multilingual version.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tepezza (Teprotumumab) is included in the additional monitoring list as a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Thyroid eye disease (TED) is also known as Graves' orbitopathy (GO) or thyroid-associated orbitopathy. It is primarily a disease of the orbit where the orbital tissue undergoes inflammation, expansion and remodelling. Although most commonly associated with Graves' hyperthyroidism, TED also occurs rarely in patients with other autoimmune thyroid diseases. The estimated incidence in Europe is 0.54–1.9 cases/100,000/year in men and 2.67–8 cases/100,000/year in women. TED is most commonly mild and non-progressive, with moderate-to-severe forms accounting for only 5–6% of cases.

The natural history of TED involves an initial progressive worsening of signs and symptoms with visible signs of inflammation known as the active/acute phase (lasts in most case 1 to 3 years). In this phase, patients may present with orbital pain, periorbital inflammation, proptosis, eyelid retraction, strabismus and diplopia. Sight-threatening disease affects 6% of TED patients.

The acute phase is followed by an inactive/chronic phase during which no further deterioration occurs, but some symptoms and remodelling of orbital tissue may remain. In this phase, the histopathology becomes increasingly fibrotic in nature.

Teprotumumab is a human monoclonal antibody that targets and inhibits the insulin-like growth factor-1 receptor (IGF-1R)/thyroid-stimulating hormone receptor signalling complex, thereby blocking the autoimmune activation of orbital fibroblasts, potentially inhibiting the underlying pathogenesis of TED.

The claimed indication is:
Tepezza is indicated in adults for the treatment of moderate to severe Thyroid Eye Disease (TED).

3.1.2. Available therapies and unmet medical need

Most patients with mild GO or TED experience spontaneous resolution of eye manifestations. Therefore, a watchful strategy and local treatments are sufficient. Conversely, sight-threatening TED is an emergency that should be treated immediately.

Combination of a moderate cumulative dose of i.v. methylprednisolone + a moderate daily dose of oral enteric-coated mycophenolate sodium is the EUGOGO recommended first-line treatment for patients with moderate-to-severe and active/acute TED. An alternative first-line treatment is the administration of high single doses of i.v. methylprednisolone starting with 0.75 g per day and week for six consecutive weeks. This regimen is recommended for patients with constant/inconstant diplopia, severe proptosis, and severe inflammatory soft-tissue changes. Once TED is in inactive/chronic phase, surgery can be performed to repair the sequelae of TED.

Considering few treatment options, a claim for an unmet need is justified.

3.1.3. Main clinical studies

Six trials have been conducted to evaluate the efficacy and safety of teprotumumab for the TED indication:

- Three randomized, double-masked, placebo-controlled, parallel-group, multicenter trials that evaluated the efficacy and safety of teprotumumab for the treatment of moderate to severe acute TED: Phase 2 Trial **TED01RV** and Phase 3 Trial HZNP-TEP-301 (**OPTIC**) conducted in the US and Europe and Phase 3 Trial HZNP-TEP-303 (**OPTIC-J**) conducted in Japan
- A Phase 3 open-label extension of OPTIC: HZNP-TEP-302 (**OPTIC-X**)
- A Phase 3b, open-label, single-arm, multicenter expanded access program (EAP) trial conducted in the US in participants with acute TED: Trial HZNP-TEP-401
- A Phase 4 randomized, double-masked, placebo-controlled, parallel-group, multicenter trial that evaluated the efficacy and safety of teprotumumab in participants with chronic TED: **HZNP-TEP-403**

In all studies, teprotumumab was given with an initial dose of 10 mg/kg on Day 1 followed by 20 mg/kg for the remaining 7 infusions. The double masked period of the studies had a duration of 24 weeks.

3.2. Favourable effects

Acute TED

Protoptosis responder rate (percentage of subjects with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration of proptosis in the fellow eye) was the primary endpoint in the OPTIC/OPTIC J studies. More than 80% of subjects treated with teprotumumab were responders at week 24; difference compared to placebo 73% (95%CI 59-88) and 78% (95%CI 61-95), respectively. Subjects missing the week 24 evaluation was considered a non-responder. The analyses are thereby considered as conservative.

Overall responder rate (decrease in overall CAS ≥2 points and reduction in proptosis ≥2 mm without deterioration in fellow eye) was the primary endpoint in TED01RV and secondary in OPTIC/OPTIC J studies. In study TED01RV, results were presented as odds ratio; 8.9 (95%CI 3.3-23.8), while the difference compared to placebo was 71% (95%CI 56-86) and 74% (95%CI 57-91), respectively in the OPTIC studies.

The difference compared to placebo in mean change from baseline in proptosis was a secondary endpoint in all studies. The difference was -2.3 (95%CI 2.8-1.8), -2.0 (95%CI 2.8-1) and -2.3 mm (95%CI 2.8-1.8), in the three studies, respectively.

Quality of life was assessed with the GO-QoL instrument. The difference compared to placebo in mean change from baseline in GO-QoL overall score was 9.4 (95%CI 4.1-14.6) and 11.0 (95%CI 2.6-19.4) in the OPTIC studies. In study TED01RV, results were presented as odds ratio; 10.9 (95%CI 4.5-17.2).

Diplopia responder rate was a secondary endpoint in the OPTIC trial. Responders were defined as subjects with baseline diplopia grade >0 in the study eye who had a reduction of ≥ 1 grade with no corresponding deterioration in the fellow eye. Approximately 67% of subjects had diplopia at baseline. The proportion of responders in the active arm was 68% compared to 29% in the placebo arm (difference 40%, 95%CI 15.6-63.0).

Chronic TED

The primary endpoint in study 403 was the change from Baseline at Week 24 in proptosis in the study eye. The difference compared to placebo was -1.5 mm (95%CI 2.3-0.7).

With respect to secondary endpoints, the difference compared to placebo for proptosis responder rate was 37% (95%CI 5.4-59.2) and for change from baseline in Go-QoL visual functioning scale 6.3 (95%CI 0.6-12.1). Limited data is available from the 24-week OLE of the study. A total of 24

participants from the 24-week randomized, double-masked period who were proptosis non-responders entered the 24-week open-label treatment period and received open-label treatment with teprotumumab; 12 placebo participants (first-course); and 12 teprotumumab participants (second-course). 10 participants in each group completed the open-label period. Mean reduction in proptosis from baseline of 2.00 mm was observed in 7/12 (58.3%) first course subjects. In second course subjects, mean reduction from teprotumumab baseline of 1.60 mm was observed. The applicant has also submitted supportive literature data from additional 40 patients.

3.3. Uncertainties and limitations about favourable effects

No dose response studies have been performed. The proposed posology is based on findings in literature that a teprotumumab serum concentration of 20 µg/mL would result in greater than 90% saturation of target-mediated clearance. The lack of PD and dose response studies is a limitation but not considered crucial since the results from phase III/IV studies are available. A study is ongoing evaluating other treatment regimens.

The GO-QoL subscales are not considered fully validated. Limitations in regard to construct validity and determination of MCID of 6% is noted. The post-hoc analysis of construct validity appeared to be of limited value, why uncertainties in the construct still remain. Further analysis of MCID indicated that the initially suggested MCID of 6 percent was too low and that a higher MCID should be considered in the interpretation of the results. The validity of the GO-QoL subscales currently relies on the previous frequent use of GO-QoL as reflected in the literature. Therefore, data can be included in section 5.1 of the SmPC.

There is insufficient data to support recommendations for retreatment with teprotumumab in non-responders and relapsers. Thus, the SmPC only recommends one treatment course. Study HZNP-TEP-402 is ongoing, evaluating the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for re-treatment in participants with TED. The study is included in the RMP and the study results are expected in late 2026. 'Safety in retreated patients' is also included as missing information in the RMP.

3.4. Unfavourable effects

The TEAEs of special interest which were identified based on biologic rationale, observation in oncology studies and/or post-marketing experience, are considered key unfavourable effects after assessment of the safety results of the clinical studies. Furthermore, other unfavourable effects which were identified in the assessment of the clinical studies, are listed below.

Infusion-related reactions: IRRs were observed in 8 patients (3.3 %) in the teprotumumab groups and in 4 patients (3.0%) in the placebo groups in the double-masked treatment period. One IRR was considered serious in the teprotumumab groups. Teprotumumab is a monoclonal antibody (mAb), and mAbs are generally associated with IRRs.

Hyperglycaemia/new onset diabetes mellitus: The hyperglycaemia-associated TEAEs reported in the double-masked periods are more frequent for the teprotumumab treated groups (13.2%) than in the placebo groups (3.0%). For patients with diabetes at baseline, 69,2% of the teprotumumab participants had any event of hyperglycaemia, compared to 9,1% of the placebo participants. The laboratory values of fasting glucose and HbA1c confirm the TEAE pattern. One placebo-treated participant with undiagnosed diabetes was given teprotumumab by mistake and developed serious hyperglycaemia with ketoacidosis. Other serious hyperglycaemia events were also observed for other participants. For participants > 65 years of age, 15.1% of teprotumumab treated participants had

hyperglycaemia events, compared to none of the placebo-treated in the same age group. Insulin and IGF-1 receptors are highly homologous and share many downstream signalling pathways. Disturbing these pathways has been shown to increase insulin resistance, glucose intolerance and dyslipidaemia.

A cumulative review of HLT Diabetes mellitus (incl.subtypes) cases from clinical trials, spontaneous/solicited cases, and literature case reports was completed. A total of 7 diabetes mellitus cases have been identified in clinical trials. All subjects had baseline glycaemic status of prediabetes or diabetes. Cumulatively to 31 January 2025, 396 teprotumumab cases of the HLT Diabetes mellitus (incl. subtypes) have been received from post-marketing sources.

Hyperglycaemia and negative effects of hyperglycaemia can be reduced by assessing glycaemic status prior to initiation of teprotumumab treatment, and by actively adjusting glucose-lowering treatment, if necessary, during teprotumumab treatment.

Exacerbation of IBD: Two serious events of exacerbation of IBD (one registered as 'diarrhoea', and one registered as 'IBD') were found in the double-masked treatment period. The placebo participant with known IBD did not experience an exacerbation. It is noted that patients with known IBD were excluded from some of the clinical studies, which might have influenced the number of exacerbation events.

Hearing impairment: Insulin-like growth factor-1, which binds the IGF-1R, is an important regulator of cochlear development, and its mutations are associated with hearing loss in mice and humans (Munillo Cuesta et al, 2011). As teprotumumab inhibits signaling through the IGF-1R, understanding of the pharmacologic impact on hearing is still evolving. Hearing impairment is noted for teprotumumab treated participants in both double-masked periods of studies, during follow-up periods, as well as in open-label studies. Across the TED clinical program, a total of 43 (43/246, 17.5%) participants experienced 57 events of hearing impairment while receiving teprotumumab or during the Follow-up Period after receipt of teprotumumab. In the Double-masked Population, 21 (13.8%) participants in the teprotumumab group experienced 28 TEAEs of hearing impairment compared with 3 (2.3%) participants in the placebo group who experienced 4 TEAEs of hearing impairment. Most of the hearing impairment events were mild or moderate, but approximately one third (n=7) of the hearing impairment events in the teprotumumab treated participants were not resolved as of the database lock for the trial or the primary week 24 analysis.

Alopecia: The effect of IGF-1 on alopecia has been discussed in literature. A possible biologic link might be part of the explanation to the observed differences in alopecia cases between the teprotumumab (10,5%) and the placebo (2,3%) groups. In the acute TED population, the difference between the teprotumumab group (12.6%) and the placebo group (2.7%) is bigger than in the chronic TED population. Events of alopecia as TEAEs that were not resolved at the last follow-up, have been observed.

Menstrual disorders: In women of childbearing potential, menstrual disorders were reported by 13.0% (7 of 54) of teprotumumab-treated participants and 2.2% (1 of 45) of placebo-treated participants during the Double-masked Treatment Period.

Use in pregnancy and lactation: Teprotumumab has shown teratogenic effects in a study in monkeys. The pharmacokinetic profile of teprotumumab also indicate teratogenicity. Therefore, various measures to minimise the risk of pregnancy during studies were implicated. No pregnancies occurred during clinical studies.

3.5. Uncertainties and limitations about unfavourable effects

Biologic plausibility for an effect of teprotumumab on at least some aspects of hearing is known, has been seen in clinical trials, and is included in the current labelling. However, 2 years post-

commercialisation, post-marketing data suggest the potential for increased severity beyond what was seen in clinical trials. Clinical study cases and post-marketing cases show a large number of cases were the hearing impairment-related AE was not resolved during the follow up period.

Ongoing and planned clinical studies, as well as continuous routine pharmacovigilance activities, as outlined by the applicant, are acknowledged as ways to increase the available knowledge of hearing impairment associated with teprotumumab. The results from the hearing substudy of Study HZNP-TEP-402, which will follow participants for between 15 and 33 weeks may provide additional valuable data. In addition, as requested, the applicant has included clear recommendations in the SmPC for hearing assessment using audiometry before, during, and after treatment with teprotumumab. Specifically, the prescriber is instructed to do so before starting treatment (first infusion), during treatment (around the third or fourth infusion), after completing treatment with teprotumumab and if a patient experiences subjective hearing changes during treatment. Clear stopping criteria have also been included. At a later stage, this information may be amended, as appropriate, when additional data become available.

The applicant was asked to perform a cumulative review and analysis of all HLGT Gastrointestinal haemorrhages NEC cases reported with teprotumumab from all available sources (i.e. spontaneous notification, clinical trials and literature data) up to 31 January 2025. Three events in 2 subjects were identified in clinical trials: all were nonserious, mild, and confounded by significant medical history. A cumulative search of post-marketing data revealed 124 cases containing 128 events. As these cases provided insufficient information to draw solid conclusions, events of gastrointestinal haemorrhage should continue to be monitored using routine pharmacovigilance.

Data on TEAEs by BMI and/or body weight showed significantly higher incidences of TEAEs pertaining to the SOC Ear and labyrinth disorders and SOC Gastrointestinal disorders, and other TEAEs by PTs (alopecia, dry skin, stomatitis, COVID-19, abdominal pain upper, weight decreased, decreased appetite, dizziness, urinary tract infection) in teprotumumab-treated patients in the lowest body weight category compared to other body weight groups. The applicant discussed these observed differences in certain incidences of TEAEs by the patient's body weight group, but no clear explanation was found; while some differences could be attributable to thyroid disease, no firm conclusions could be drawn.

Serious embryofetal development toxicity was reported in the non-clinical trial program and the product is contraindicated in pregnancy (SmPC 4.3 and 4.6). It is therefore of paramount importance that appropriate routine RMMs are in place, and routine RMMs are not deemed sufficient. Additional risk minimisation measures in the form of a healthcare professionals' guide and a patient's guide are warranted to further mitigate the risk. The applicant has included the key elements for these aRMMs in PI Annex IID and RMP Annex 6.

3.6. Effects Table

Table 47. Effects Table for Tepezza in TED

Effect	Short Description	Unit	Treatment	Control	Difference compared to control	References
Favourable Effects						
Proptosis responder rate	(percentage of subjects with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration of proptosis in the fellow eye)	%	82.9 88.9	9.5 11.1	73% (95%CI 59-88) 78% (95%CI 61-95)	OPTIC OPTIC J
Change from Baseline at Week 24 in proptosis in the study eye.		mm	-2.4	-0.9	-1.5 mm (95%CI 2.3-0.7)	Study 403
Overall responder rate	(decrease in overall CAS ≥2 points and reduction in proptosis ≥2 mm)	%	78.0 77.8	7.1 3.7	71% (95%CI 56-86) 74% (95%CI 57-91)	OPTIC OPTIC J
GO-QoL Overall score	Mean change from baseline	points	13.8 17.4	4.4 6.4	9.4 (95%CI 4.1-14.6) 11.0 (95%CI 2.6-19.4)	OPTIC OPTIC J
Unfavourable Effects						
Infusion-related reactions (IRRs)	incidence	%	3.3	3.0		(1)
Hyperglycaemia	incidence	%	13.2	3.0	Incidence in patient population aged >65 years uncertain	(1)
Hearing impairment	incidence	%	13.8	2.3		(1)

Effect	Short Description	Unit	Treatment	Control	Difference compared to control	References
Exacerbation of IBD	incidence	%	2.4	0		(1)
New-onset IBD	incidence	%	0	0	2 post-marketing cases	(1)
Alopecia	incidence	%	10.5	2.3		(1)
Menstrual disturbances	incidence	%	13.0	2.2		(1)
Teratogenicity	plausible		NA	NA	Biological plausibility, studies in monkeys	

Notes: (1) Pooled data from 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

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

Four trials have been conducted to evaluate the efficacy of teprotumumab in patients with acute TED. The number of subjects were limited, but it is a strength that 3 of the studies were placebo controlled and that results were replicated in the different studies. The primary and secondary endpoints are considered to measure clinically relevant outcomes such as reduction of proptosis, diplopia as well as disease activity (CAS which includes aspects of pain relief) and QoL.

Overall, results of primary and secondary endpoints support a relevant treatment effect of teprotumumab for the treatment of patients with acute TED. A decrease of proptosis with ≥2mm is considered as clinically relevant as it is associated with reduced risk of diplopia and improvement of corneal safety. In addition, the clinical relevance is supported by positive results for secondary endpoints like CAS and GO-QoL subscales.

Considering that active TED typically lasts 1.5 – 3 years without treatment, long term follow-up of patients after the initial 24-week treatment phase in the studies is of importance to assess relapse rate, time to relapse and the need for retreatment. Approximately 55-60 subjects have been followed up for 48 weeks after the 24-week treatment period. Of these 30-40% have relapsed. It is agreed with the applicant that there are insufficient data to support recommendations for retreatment of non-responders or relapsers. 'Need for re-treatment' will be included as missing information in the RMP. Study HZNP-TEP-402 is ongoing. The primary objective of the study is to evaluate the safety and tolerability of 3 treatment durations of teprotumumab (4, 8, and 16 infusions) and the need for re-treatment in participants with TED. The study is included in the RMP and the study results are expected in late 2026.

The proposed target population also includes patients with inactive/chronic TED. Data in this group is based on one single, placebo-controlled study with 24 weeks duration. Considering the lack of replication, additional data (external or additional studies) was requested in the first round of assessments. Limited, supportive data for an effect on proptosis is available from the completed follow

up study. The applicant has also submitted supportive literature data from additional 40 patients. There is not much support from the pivotal study confirming the importance of the reduction of proptosis except for a limited difference in the GO-QoL vision scale. However, there is support from EUGOGO that a 2 mm reduction of proptosis is expected to reduce the risk of diplopia and other complications of TED. Some mechanistic data, albeit limited, also seems to support a treatment effect. In conclusion, the totality of data presented supports that a relevant effect of teprotumumab can be expected in patients with chronic TED. Proptosis can have severe consequences for the patients and there is an unmet medical need as surgery often is the only alternative treatment.

Unfavourable effects

The safety data on teprotumumab for the treatment of TED are considered reliable, given the design, and presentation of data from the 6 clinical studies. The size of the safety population may be considered as limited, but acceptable considering the rarity of the condition.

The most important safety issues concern the AESIs identified in advance based on scientific evidence and prevalence in teprotumumab oncology studies and post-marketing events. The AESIs of IRR, hyperglycaemia, exacerbation of IBD and new onset IBD constitute identified or potential risks.

The AESI of Hearing impairment is considered as the most serious adverse event and was reported in 17% of the patients in the clinical studies albeit that the majority of events were considered as mild and nonserious. Considering that a substantial number of the events were not resolved at the end of follow up, there may be a risk for permanent hearing impairment which is considered as an important side effect of treatment with teprotumumab. Additional informative will be generated in the planned hearing sub-study of Study HZNP-TEP-402, but it is of outmost importance that prescribers and patients are clearly informed about this risk to be able to make an informed decision if treatment should be initiated or not, and if patients develop any symptoms of hearing impairment, to ensure that the benefit-risk of continued treatment is carefully considered. Therefore, the use of guides for healthcare professionals and for patients as an additional RMMs are considered a requirement. In addition, some updates to the warning in section 4.4 have been made, including requirements for audiometry. With respect to patients with a medical history of hearing impairment, it is difficult to draw conclusions if these subjects have higher risk of permanent hearing impairment compared to subjects without such history. Since the data is limited, it is agreed that existing hearing impairment or tinnitus do not need to be included as contraindications, considering other precautionary wordings in the SmPC. However, more detailed instructions in the SmPC regarding the monitoring for hearing impairment symptoms prior to, during, and after treatment, have been implemented. Hearing impairment is included int the safety specification as an important identified risk.

Embryofoetal toxicity is documented based on non-clinical observations and biological rationale. Information on embryofoetal toxicity is therefore also included in the above-mentioned HCP and patient guides and in the safety specification as an important potential risk. Tepezza is contraindicated during pregnancy and women of childbearing potential should use effective contraception during and for at least 6 months, after the last administration of teprotumumab.

Hyperglycaemia and exacerbation of IBD are also included in the safety specification as important identified risks while new onset IBD is an important potential risk. Precautionary wordings are included in section 4.4 of the SmPC.

3.7.2. Balance of benefits and risks

A relevant treatment effect has been documented in patients with acute TED. The results include beneficial effects on both objective and subjective measurements and have been replicated in 3 separate studies.

The results in patients with chronic TED are less convincing. An effect on proptosis has been documented in the pivotal study and is supported by some follow up data and literature references. It is considered plausible that a relevant effect can also be achieved also in patients with chronic TED.

Available data indicate a risk for permanent hearing impairment, which is considered to be a serious side effect of treatment with teprotumumab. However, adequate routine and additional risk minimisation measures are implemented to mitigate the risk of hearing impairment. It is of outmost importance that prescribers and patients are clearly informed, to be able to come to an informed decision whether treatment should be initiated or not. In addition, the risks associated with embryofoetal toxicity will also be mitigated using routine and additional risk minimisation measures.

3.7.3. Additional considerations on the benefit-risk balance

Data has been provided from five separate prospective, randomised and controlled studies. The data is considered as comprehensive.

3.8. Conclusions

The overall benefit/risk balance of Tepezza is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tepezza is favourable in the following indication(s):

for the treatment of moderate to severe Thyroid Eye Disease (TED) in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the use of TEPEZZA in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at:

- Provision of information to healthcare professionals for the risks of hearing impairment and embryo-foetal toxicity.
- Provision of information to patients for the risks of hearing impairment and embryo-foetal toxicity.

The MAH shall ensure that in each Member State where TEPEZZA is marketed, all healthcare professionals involved in the care of patients who will be treated with TEPEZZA have access to the following educational package:

- Healthcare professional educational material
- Patient information pack

<u>Healthcare professional educational material:</u>

- The Summary of Product Characteristics
- Healthcare professional guide

Healthcare professional guide

- What is known about the safety of TEPEZZA as it relates to hearing impairment and embryo-foetal toxicity.
- Management of early signs and symptoms of hearing impairment.
- Before a decision is made about treatment with TEPEZZA the doctor will discuss with the patient the following:
    - TEPEZZA may cause hearing impairment and details on the signs and symptom to look for.
    - Requirement for monitoring for hearing impairment and appropriate management.
    - The patient should seek medical advice as soon as possible if they experience changes in hearing.
    - TEPEZZA may cause harm to the unborn foetus.

- Patients who are considering TEPEZZA treatment should inform the doctor if they are pregnant.
- The importance of using appropriate contraception during treatment with TEPEZZA.
- Patients being treated with TEPEZZA should notify the doctor without delay if they become pregnant.
- The healthcare professional will provide the Patient Guide and the Package Leaflet to the patient.

Patient information pack:

- Package Leaflet
- Patient Guide

Patient Guide:

- Description of the risk of hearing impairment and the key signs and symptoms.
- Description of what to do if signs and symptoms of hearing impairment occur.
- Information about the physician's assessment of hearing before, during, and after treatment with TEPEZZA.
- Instructions to seek medical attention if they have hearing problems or worsening of existing hearing problems.
- Information on the risk of harm to an unborn child.
- Instructions to inform the doctor if they are pregnant before starting treatment with TEPEZZA.
- Instructions on appropriate contraception while being treated with TEPEZZA.
- Instructions to notify the doctor without delay if they become pregnant while taking TEPEZZA.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that teprotumumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 20 September 2024