

Single Technology Appraisal

**Teprotumumab for treating thyroid eye disease
[ID6432]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

**Teprotumumab for treating thyroid eye disease
[ID6432]**

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

- 1. Company submission from Amgen:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from**
 - a. British Thyroid Foundation
 - b. British OculoPlastic Surgery Society (BOPSS)
 - c. Royal College Ophthalmic Surgeon
 - d. NHSE Commissioning group
- 4. External Assessment Report** prepared by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
- 5. External Assessment Report – factual accuracy check**
- 6. Presentation Slides**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teprotumumab for treating thyroid eye disease [ID6432]

Document B

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6432_teprotumumab_Document B [redacted]	2.0	No	26 February 2025

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Glossary

1L	First-line
2L	Second-line
AE	Adverse event
ATA	American Thyroid Association
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAS	Clinical Activity Score
CD34	Cluster of differentiation 34
CD40	Cluster of differentiation 40
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CFB	Change from baseline
CT	Computed tomography
ED	Emergency department
ESS	Effective sample size
ETA	European Thyroid Association
EUGOGO	European Group on Graves' Ophthalmopathy
FDA	US Food and Drug Administration
GO	Graves' orbitopathy or Graves' ophthalmopathy
GD-IgG	Graves' disease immunoglobulins
GO-QOL	Graves' ophthalmopathy-specific quality-of-life
HARS	Hamilton Anxiety Rating Scale
HCPs	Healthcare professionals
HDRS	Hamilton Depression Rating Sale
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFN-gamma	Interferon-gamma
IGF-1	Insulin-like growth factor-1
IL- β	Interleukin β
IPD	Individual patient-level data

ITC	Indirect treatment comparison
IV	Intravenous
ITT	Intention-To-Treat
IVMP	Intravenous methylprednisolone
LCI	Lower confidence interval
LS	Least squares
LY	Life years
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire
mITT	Modified Intention-To-Treat
MMF	Mycophenolate mofetil
MP	Methylprednisolone
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLE	Open-label extension
OR	Odds Ratio
ORT	Orbital Radiotherapy
OSDI	Ocular Surface Disease Index
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PBRER	Positive Benefit Risk Evaluation Report
PP	Per Protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival models
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
q3W	Every three weeks
QALY	Quality-adjusted life years
QoL	Quality of life
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RIT	Radioactive iodine therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan

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SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
TBII	Thyrotropin binding inhibiting immunoglobulins
TED	Thyroid eye disease
TNF	Tumor necrosis factor
TRAEs	Treatment related adverse events
TSAb	Thyrotropin receptor antibodies
TSH	TSH, thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
TSI	Thyroid stimulating immunoglobulins
UCI	Upper confidence interval
UK	United Kingdom
US	United States

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation only, that is, for the treatment of people with active moderate-to-severe thyroid eye disease (TED). The proposed population is narrower than the anticipated marketing authorisation because:

- The current evidence base on teprotumumab is mostly in this population.
- This population reflects where teprotumumab provides the most clinical benefit.

The decision problem addressed by this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People living with moderate to severe thyroid eye disease	People living with active moderate to severe thyroid eye disease	The company submission focuses on active disease
Intervention	Teprotumumab	Teprotumumab	Not applicable
Comparator(s)	Established clinical management without teprotumumab which may include: • Corticosteroids - o prednisolone - o methylprednisolone - o triamcinolone • Immunosuppressive agents - o mycophenolate - o rituximab - o tocilizumab - o ciclosporin • Orbital radiotherapy • Surgical interventions: - o eyelid surgery - o orbital decompression - o strabismus surgery	Established clinical management without teprotumumab which may include: • Corticosteroids - o prednisolone - o methylprednisolone • Immunosuppressive agents - o mycophenolate - o ciclosporin - o azathioprine • Orbital radiotherapy	Methylprednisolone, with or without mycophenolate, is the main comparator used to treat active, moderate to severe TED in UK clinical practice. • Clinical opinion indicates that azathioprine is used in the NHS (usually in combination with IVMP), so it has been suggested as an additional comparator. • Rituximab and tocilizumab are not routinely available in NHS practice and are rarely used as require individual funding requests in most centres. • Triamcinolone is not widely used. • Surgical interventions are not relevant comparators for active, moderate-to-severe TED. They are usually reserved for sight-threatening disease (for which teprotumumab will not be licensed) or chronic TED only. • The evidence base in this submission focuses on the comparison between teprotumumab and methylprednisolone, with or without mycophenolate. The other comparators

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			(azathioprine, ciclosporin, orbital radiotherapy) are used less frequently at second and later lines, and the evidence base for their use is lacking, therefore it has not been possible to do a formal comparison. We instead suggest a conservative assumption that outcomes for teprotumumab vs. methylprednisolone (with or without mycophenolate), are generalisable to other comparators (please see section B.2.12 Interpretation of clinical effectiveness and safety evidence).
Outcomes	The outcome measures to be considered include: • disease activity • disease severity • proptosis response • diplopia response • adverse effects • health-related quality of life (including psychosocial impact) • duration of treatment response • retreatment • need for rehabilitation surgery • need for subsequent surgical intervention	The outcome measures to be considered include: • disease activity • disease severity (note: although the clinical trial programme did not include a specific outcome for severity, it is captured via outcomes such as diplopia and proptosis) • proptosis response • diplopia response • adverse effects • health-related quality of life (including psychosocial impact) • duration of treatment response • retreatment	Evidence is not included about the need for rehabilitation surgery or subsequent surgical intervention, as data on these outcomes were not collected in the clinical development programme.
Subgroups to be considered	If evidence allows and where appropriate, the following may be considered: Subgroups by disease activity • Active • Inactive		Subgroup analyses have not been included due to insufficient evidence.

	Duration of active symptom • More than 1 year • Less than 1 year Severe proptosis Severe diplopia Severe inflammation Treated vs untreated TED		
Special considerations including issues related to equity or equality	The NICE scope discusses the limitations of the CAS score, which can rely on subjective, visual assessments which may be biased by the patient's skin colour and ethnicity.	The company agrees with NICE's scoping consultation response which states that it will be important during this appraisal to ensure any recommendations do not have a different impact on people protected by the equality legislation than on the wider population.	Not applicable

B.1.2 Description of the technology being evaluated

The draft summary of product characteristics for teprotumumab is provided in Appendix C. No European or UK public assessment report or draft is available.

Table 2: Technology being evaluated

UK approved name and brand name	Generic approved name: teprotumumab Brand name: TEPEZZA®
Mechanism of action	Teprotumumab is a first in class, fully human immunoglobulin G1 monoclonal antibody and insulin-like growth factor-1 receptor (IGF-1R) antagonist. While the exact pathogenesis of TED is not fully established, there is a substantial body of evidence within the literature that thyroid hormone stimulating receptors (TSHR) and IGF-1R are physically and functionally coupled.¹ Autoantibodies directed against this receptor complex are responsible for stimulating the downstream cellular signalling pathways that underpin the pathogenesis of thyroid eye disease (TED).^{1,2} Stimulation of the TSHR/IGF-1R complex by autoantibodies increases the release of signaling molecules (chemoattractants) by orbital fibroblasts. This results in the attraction of immune cells (T lymphocytes) and the initiation of both an inflammatory immune reaction and the pathogenic synthesis of connective (hyaluronan) and fat tissue (adipogenesis) alongside extraocular muscle hypertrophy within the orbit.^{3,4} These events lead to potentially debilitating downstream effects that are typical of TED, such as proptosis, diplopia and eyelid retraction.^{5,6} Teprotumumab blocks the stimulatory effects of auto-antibodies on orbital fibroblasts,⁵ thereby preventing muscle and tissue expansion behind the eye to reduce the symptoms of TED.^{6,7}
Marketing authorisation/CE mark status	Teprotumumab does not yet have a UK marketing authorisation for the indication covered by this submission. The Marketing Authorisation Application was submitted to the European Medicines Agency (EMA) in [REDACTED]. EMA approval is anticipated in [REDACTED]. Approval from the Medicines & Healthcare products Regulatory Agency (MHRA) is also anticipated in [REDACTED].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	TEPEZZA® is expected to be indicated in the UK [REDACTED]
Method of administration and dosage	Teprotumumab is administered by intravenous (IV) infusion. Teprotumumab (500mg) is formulated as a white to off-white lyophilised powder in a single-dose vial for reconstitution and dilution. The recommended dose of teprotumumab is 10mg/kg of body weight for the initial dose followed by 20mg/kg of body weight for 7 additional doses given once every three weeks as an IV infusion.⁸ For the first 2 infusions, the diluted solution is administered as an IV infusion over at least 90 minutes. If well tolerated, infusions 3 to 8 can be administered

	over 60 minutes every three weeks. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes. ⁸
Additional tests or investigations	Events associated with hearing impairment including hearing loss have been observed in the teprotumumab clinical trials. The draft SPC states that patients' hearing should be assessed before, during and after treatment with teprotumumab and the benefit-risk of treatment should be considered with the patient. ⁸
List price and average cost of a course of treatment	The anticipated list price is [REDACTED] per 500 mg vial.
Patient access scheme (if applicable)	A simple patient access scheme (PAS) has been approved which provides a [REDACTED] discount from the list price of teprotumumab. The PAS price is therefore [REDACTED] per 500 mg vial of teprotumumab.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Thyroid eye disease (TED), also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy or Graves' orbitopathy, is a serious and progressive autoimmune disorder that re-models the fat, muscle and connective tissues behind the eye. TED is most commonly associated with Graves' hyperthyroidism, which is an autoimmune thyroid disorder caused by the pathological stimulation of thyroid stimulating hormone receptors (TSHR) by autoantibodies; most commonly by thyroid stimulating hormone receptor antibodies (TRAb). TED also occurs rarely in a proportion of patients with other autoimmune thyroid diseases, including Hashimoto's thyroiditis (associated with hypothyroidism) and those with detectable thyroid autoantibodies in euthyroid states.^{9, 10} Furthermore, patients can rarely present with ocular symptoms of TED in the absence of detectable autoantibodies and in a euthyroid state. There is a lack of long term follow up data for such patients, but many will go on to develop detectable autoantibody levels with or without thyroid dysfunction with time.¹¹ Furthermore, the sensitivity of different assays used to detect autoantibodies has been shown to vary, with one study demonstrating positive TRAb (TSH receptor antibodies) in 7 euthyroid patients by at least one method.¹²

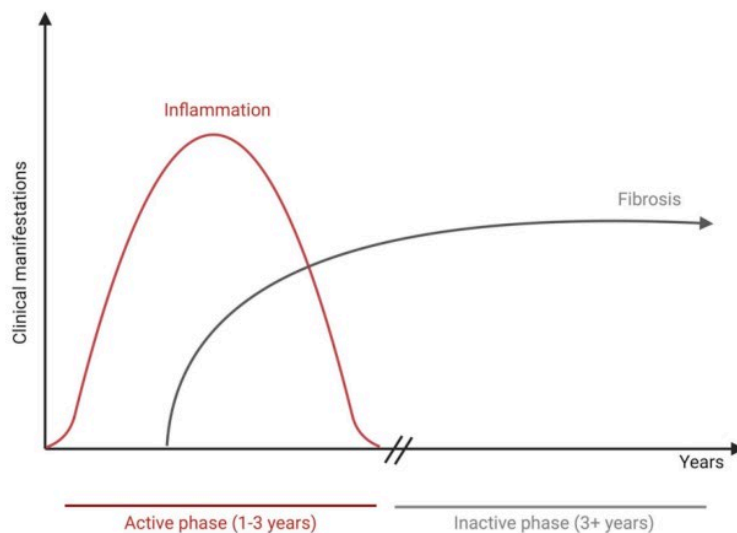
TED can cause debilitating and sight-threatening symptoms such as pain, swelling, dry eyes, redness of the lids and ocular surface, corneal ulceration (a breakdown of Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

the surface layer of the eye above the pupil and the iris due to an inability to close the eyelids) and dysthyroid optic neuropathy (dysfunction of the optic nerve, most commonly due to compression, which can cause visual loss). These symptoms can lead to disabling and disfiguring effects on the orbit including diplopia (double vision) and proptosis (unilateral or bilateral bulging of the eye anteriorly out of the orbit) due to the expansion of tissues behind the eye, and can pose a threat to vision.^{10, 13, 14}

These physical symptoms combine to produce high morbidity and marked reductions in quality of life (QoL), such as physical functioning, role functioning, social functioning, mental health, health perceptions and pain.^{15, 16} The substantial changes in patient QoL due to TED can produce profound psychosocial problems and impact various aspects of patient well-being. In particular, patients can experience anxiety and depression due to the alarming and disfiguring changes in appearance that result,¹⁷⁻¹⁹ alongside feelings of isolation and, in some cases, suicidal behaviour.^{6, 20-22}

In terms of time course, TED can be considered as two distinct conditions: active (or acute) TED, and chronic (also known as inactive) TED, and is traditionally considered to follow the trajectory of Rundle's curve (see Figure 1). Active disease is characterised by the presence of acute inflammation of the eye(s) and orbital tissues alongside enlargement of retro-orbital fat tissue and extraocular muscles (i.e., re-models the fat and muscle tissue behind the eye), leading to proptosis, diplopia, and compressive optic neuropathy, which can result in permanent visual impairment. Active TED typically lasts between 1 and 3 years, before there is regression of the active inflammation and patients move to a chronic (inactive) state,¹⁴ in which the expanded and fibrotic tissues persist as the sequelae of active disease. As a result of orbital tissue remodelling, patients are left with longstanding symptoms, such as dry eyes, decreased vision, proptosis, diplopia, excessive tearing, and pain.²³⁻²⁵ As a result of these residual symptoms, TED patients continue to report a significant impact on their QOL and psychological wellbeing long after the active phase of TED has subsided.^{24,26}

Figure 1: Schematic representation of Rundle's Curve



Note: The thyroid eye disease course is composed of an active phase, which typically lasts from 1 to 3 years and may or may not involve resolution of clinical manifestations during the disease course, and a chronic (inactive) phase of 3 years duration and more.
Source: Kulbay *et al.* (2024).²⁷

As described in more detail below, TED is divided by severity into mild, moderate-to-severe, and very severe (sight threatening) disease. Approximately 25 to 50% of people with a diagnosis of Graves' disease go on to develop TED^{9, 28, 29}, of whom approximately one-third have active moderate-to-severe disease. This submission is concerned with active TED of moderate-to-severe severity only.^{27, 30, 31} This submission is concerned with active TED of moderate-to-severe severity only.

B.1.3.1.1 Epidemiology

The epidemiological data and literature around TED are highly variable and unclear. In Europe, the incidence (rate at which new cases occur) of TED was estimated by the European Group on Graves' Orbitopathy (EUG

OGO) at 0.483 per 10,000 person-years, with the prevalence ranging from 8.97 to 15.48 per 10,000 population.³¹

EUGOGO further categorised prevalence into mild (5.83 per 10,000 population), moderate-to-severe (2.96 per 10,000 population), and sight-threatening TED (0.18 per 10,000 population).³¹ In a recent study utilising data from the EUGOGO tertiary treatment centres researchers found that, among 431 European patients with TED, Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

49.7% had moderate-to-severe TED and 61.3% were in a chronic phase of the disease.³² Therefore, whilst TED as an entity does not meet the European definition of a rare disease (prevalence of ≤ 5 per 10,000), the moderate to severe subpopulation can be regarded as rare.

TED is five or six times more common in women than in men, with incidence rates ranging from 3.3 to 16 per 100,000 in women and from 0.9 to 2.9 per 100,000 in men across the US, Europe, and Japan across all degrees of severity.¹⁰ TED frequently affects individuals in middle age, approximately 40 to 65 years old.¹⁰

In the absence of established patient registries or robust centralised datasets, the exact number of patients affected by TED within the UK remains uncertain. Using the recent European epidemiological study described above, which estimated the prevalence of TED as approximately 10/10,000 population (range 8.97 to 15.48^{31, 33-35}), this would equate to 68,000 (range 60,996 to 105,264) TED patients in the UK based on a UK population of 68 million. Previous epidemiological studies have also estimated a prevalence of 0.1% to 0.3%³⁶ (equating to 68,000 to 204,000 UK patients in total).

B.1.3.1.2 Pathophysiology

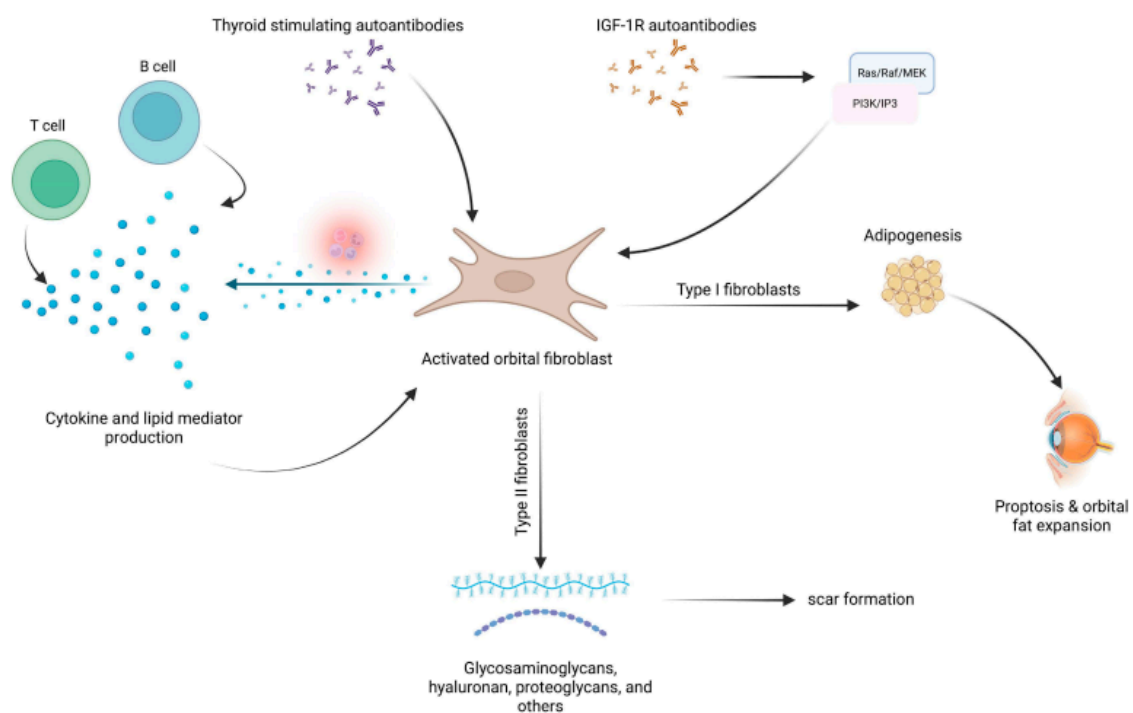
The pathogenesis of TED is not fully understood but a mounting body of literature suggests that the pathophysiology of active TED is driven by autoantibody activation of the insulin-like growth factor 1 (IGF-1) and thyrotropin receptor (TSHR) signalling complex on orbital fibroblasts.^{3, 7, 37} This activation of fibroblasts triggers an inflammatory response alongside remodelling of connective tissues, fat accumulation and muscle cell hypertrophy within the orbit.

Research highlights an overexpression of TSHR in the retro-orbital tissue of Graves' disease patients, particularly in orbital fibroblasts, which are key to the pathogenesis of TED.^{1, 2} In addition, the expression of IGF-1 receptors is also elevated in TED orbital fibroblasts, suggesting an enhanced role of these receptors in the disease.^{6, 7, 38, 39} Furthermore, a study showed that immunoglobulins from patients with Graves' disease inhibit radiolabelled IGF-1 from binding to the surface of orbital fibroblasts. Although the binding site was not identified, these studies provided insight into a role for the IGF-1 pathway in TED.⁶

The interaction between autoantigens (e.g., TSHR and IGF-1 receptor) and the autoantibodies found in Graves' disease leads to orbital fibroblast activation. Orbital fibroblasts trigger a cascade of inflammatory signalling and the release of a number of proinflammatory cytokines leading to the secretion of Th1-type cytokines and leukoregulin. The end result is over production of hyaluronan and myofibrocyte/adipocyte proliferation with retro-ocular muscle/fat expansion^{38, 40} (Figure 2).

The resulting inflammation causes extraocular muscle oedema, limiting eye movement and causing double vision. The increase in orbital fat and immune cells increases the orbital tissue volume, causing venous congestion, elevated orbital pressure and proptosis. In severe cases, this can result in compression of the optic nerve, risking neuropathy and permanent vision loss.²⁴

Figure 2: Pathophysiology of Thyroid Eye Disease



Abbreviations: IGF-1R, insulin-like growth factor 1 receptor
Source: Kulbay *et al.* (2024).²⁷

B.1.3.1.3 Clinical burden

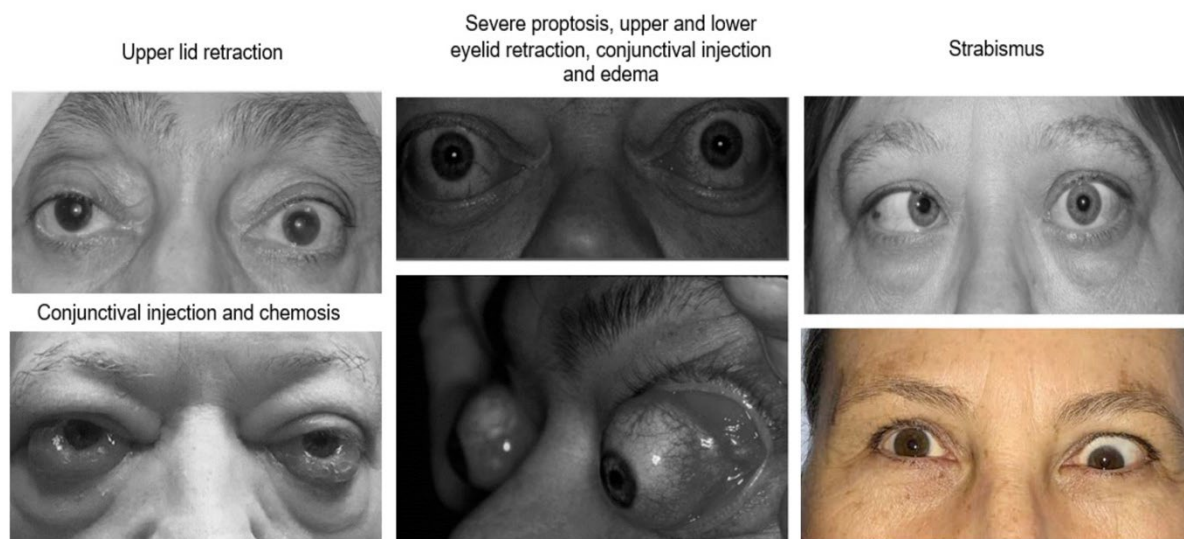
In its moderate-to-severe form, TED has high morbidity.^{9, 15, 41} In active disease, morbidity takes the form of orbital pain (due to acute inflammatory processes), disfigurement (secondary to proptosis and orbital tissue swelling) and functional disability secondary to diplopia (double vision due to malalignment of the eyes). Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

Visual involvement can progress to become sight threatening secondary to corneal ulceration (due to inability to close lids) and dysthyroid optic neuropathy (due to increased orbital tissue volume resulting in raised intra-orbital pressure and compression of the optic nerve(s)). In the chronic phase, tissue inflammation subsides and gives way to tissue fibrosis (permanent scarring of previously inflamed tissues). Consequently, symptoms such as dryness of the eyes, decreased vision, proptosis, diplopia and pain frequently continue, due to persistence of the orbital tissue remodelling that occurred during the active phase.

Common clinical presentations of TED include dry eyes, upper eyelid retraction (which can lead to wide-eyed appearance, chronic eye exposure, sensations of foreign bodies, dryness, tearing, risks of severe keratopathy, corneal scarring and ulceration), proptosis (exophthalmos or bulging eyes), lagophthalmos (inability to fully close the eyes), extraocular muscle dysfunction (which can lead to ocular misalignment [strabismus], double vision, or restricted eye movements), orbital pain, increased lacrimation (flow of tears), dyschromatopsia (loss of colour vision), visual acuity loss due to compressive optic neuropathy, oedema and erythema (swollen or reddened eyelids) conjunctival injection, and chemosis (conjunctival swelling).^{13, 25} Some of the symptoms of TED, such as eyelid retraction, proptosis, and strabismus, can cause significant facial disfigurement, challenges in looking straight ahead, and difficulties in closing the eyelids during sleep.^{25, 42}

Figure 3 demonstrates some of the typical clinical manifestations of TED.

Figure 3: Clinical Manifestations of Thyroid Eye Disease



Sources: Top left: Verity, D., Rose, G. Acute thyroid eye disease (TED): Principles of medical and surgical management. *Eye* 27, 308–319 (2013). <https://doi.org/10.1038/eye.2012.284><https://doi.org/10.3390/life12122084>
Lower left: Rashad, R.; Pinto, R.; Li, E.; Sohrab, M.; Distefano, A.G. Thyroid Eye Disease. *Life* 2022, 12, 2084. <https://doi.org/10.3390/life12122084>
Top and lower middle: Szelog J, Swanson H, Sniegowski MC, Lyon DB. Thyroid Eye Disease. *Mo Med*. 2022 Jul-Aug;119(4):343-350. PMID: 36118816; PMCID: PMC9462910.
Top right: Bothun ED, Scheurer RA, Harrison AR, Lee MS. Update on thyroid eye disease and management. *Clin Ophthalmol*. 2009;3:543-51. doi: 10.2147/ophth.s5228. Epub 2009 Oct 19. PMID: 19898626; PMCID: PMC2770865.
Lower right: Dallalzadeh LO, et al. *Ophthalmic Plast Reconstr Surg*. 2024;40:434-439.
24, 25, 43-46

B.1.3.1.4 Classification of disease activity and severity

Various measurements are used to assess clinical activity and severity of TED.

Activity measures usually focus on the presence or absence of inflammatory signs, while severity assessments involve evaluating the extent of lid retraction, soft tissue involvement, proptosis, diplopia, optic nerve status, and corneal exposure.^{47, 48}

The Clinical Activity Score (CAS), recommended by the EUGOGO clinical practice guidelines as the standard of care indicator of disease activity, is used to assess the activity of TED and distinguish between its active (acute) and chronic (inactive) stages.^{39, 47} The CAS consists of seven criteria related to inflammatory orbital symptoms such as pain, redness, and swelling (Table 3). The score at each efficacy assessment is the sum of all items present (i.e., giving a range of 0-7). A score of three or higher indicates active (acute) TED, whilst a score of less than three indicates chronic (inactive) TED. A change of >2 points is considered clinically meaningful.⁴⁹ In practice, the CAS score needs to be interpreted in the context of the patient's disease course. For example, patients presenting in the initial early stages

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of the disease process may have CAS scores <3 that would be expected to rise in the near future. Such patients would require close monitoring for progression and an increase in their CAS score.⁴⁹ Additionally, a 10-item CAS, which includes an increase in proptosis ≥ 2 mm, a decrease of eye movements in any direction of gaze $\geq 8^\circ$, and a decrease of visual acuity ≥ 1 line on the Snellen chart during a period of 1-3 months, aids in monitoring TED progression after initial evaluation.⁴⁷

Table 3: Clinical Activity Score

Assessment of activity
1. Spontaneous retrobulbar pain 2. Pain on attempted upward or downward gaze 3. Redness of eyelids 4. Redness of conjunctiva 5. Swelling of caruncle or plica 6. Swelling of eyelids 7. Swelling of conjunctiva (chemosis)
Follow-up (1-3 months) 8. Increase in proptosis of ≥ 2 mm 9. Decrease in eye motility of $\geq 8^\circ$ 10. Decrease of acuity equivalent to 1 Snellen line
Note: This score is calculated as the sum of each item, with each item having the same value of 1. CAS <3 indicates chronic TED; CAS ≥ 3 indicates acute TED. Abbreviation: CAS, Clinical Activity Score; TED, thyroid eye disease Source: Bartalena <i>et al.</i> (2021), Campi <i>et al.</i> (2022).^{47, 50}

Over the years, the CAS has become the established measure of disease activity in patients with TED and, although it has some limitations, is widely used in clinical practice and clinical research due to its simplicity, ease of use, and low cost when compared to imaging. However, the CAS includes parameters that are subjective and can lead to poor inter-observer agreement.⁵¹

Magnetic resonance imaging (MRI) assessment of patients with TED is becoming more common and MRI using a signal intensity ratio and T2-relaxation time has been shown to correlate with CAS and accurately identify the phase of the disease.⁵² However, the CAS lacks sensitivity compared to MRI; some patients with low CAS on clinical assessment have also been shown to demonstrate abnormal signal on MRI, consistent with active inflammation. These patients were also demonstrated to derive clinical benefit from treatment for active TED despite low CAS scores. These findings highlight the limitations of using CAS as the sole determinant of disease activity in TED.⁵³

People with TED are categorised as having mild, moderate-to-severe, or sight-threatening (very severe) disease, based on the presence and degree of specific symptoms and signs.⁴⁷ Table 4 lists the EUGOGO classification of severity of TED.

Table 4: EUGOGO Classification of Severity of TED

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

Abbreviation: TED, thyroid eye disease

Source: Bartalena *et al.* (2021).⁴⁷

Table 5 lists common signs and symptoms of TED by disease severity.

Table 5: Signs and Symptoms of Thyroid Eye Disease

Mild: Early-stage TED	
Symptoms	• Foreign body sensation • Dry eye • Excessive tearing • Conjunctival or eyelid redness and swelling • Blurred vision • Retro-orbital pain
Clinical signs	• Mild, soft tissue inflammation • Dilated conjunctival vasculature • Keratoconjunctivitis • Corneal staining
Moderate-to-Severe: Progression of orbital inflammation and advanced TED	
Symptoms	Symptoms in mild stage (e.g., pain, dry eye and excessive tearing), plus: • Pulling sensation around the eye • Eyelid redness and swelling • Eyelid retraction and bulging eyes • Horizontal, vertical, and torsional strabismus with double vision • Deteriorating blurred vision • Fading colour vision in one or both eyes

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	• Decrease in visual acuity, visual field, and colour vision (signs of optic neuropathy)
Clinical signs	• Swelling of extraocular muscles • Chemosis • Eyelid oedema • Proptosis • Extraocular muscles may be visible • Progressive proptosis with eyelid retraction and meibomian gland inflammation • Corneal ulceration and proliferation • Inflammation of extraocular muscles and scarring leading to strabismus and ophthalmoplegia • Increased intraocular pressure • Dysthyroid optic neuropathy

Abbreviation: TED, thyroid eye disease

Source: Patel *et al.* (2019).⁶

Teprotumumab is expected to be indicated in the UK for the treatment of [REDACTED] [REDACTED]. [REDACTED]. [REDACTED]. This NICE submission is concerned with patients who have active, moderate-to-severe TED only.

B.1.3.1.5 Risk factors

Genetic predisposition, combined with environmental factors like smoking and previous radioactive iodine therapy, contribute to the development and/or severity of TED.⁵⁴⁻⁵⁶ There are several other risk factors for TED, with the most significant non-modifiable risk factors being female sex and middle age (40-69 years of age). Concurrent endocrine disorders, such as type 1 diabetes, may also play a role in its development.⁵⁷ The most important modifiable risk factors include untreated thyroid dysfunction, thyrotropin receptor antibodies (TRAb) levels, treatment with radioactive iodine, and most notably, smoking^{10, 25, 48}

- **Age.** The median age for TED diagnosis is 43 years. Peak incidence rates occur in women aged 40-44 years and 60-64 years, and in men aged 45-49 years and 65-69 years. The likelihood of developing TED increases by 17% with each advancing decade of age.^{58, 59}
- **Sex.** Women are more affected than men, with the incidence of TED being approximately five times higher in women.³⁹ This disproportionate burden of TED across genders can lead to inequalities for women in terms of work opportunities and enjoying a full and healthy personal life.^{60, 61}

- **Untreated thyroid dysfunction.** TED is primarily associated with Graves' disease, as well as other autoimmune thyroid diseases, including Hashimoto's thyroiditis and euthyroid states. In fact, both hyperthyroidism and hypothyroidism are risk factors for TED. Approximately 33-50% of patients with Graves' disease develop eye symptoms. Among those with TED, 85-90% have hyperthyroid Graves' disease; however, a small percentage of TED patients are either euthyroid or hypothyroid, with rates ranging from 0.2-11% across various studies.^{10, 24, 25, 62} Guidelines strongly recommend the rapid restoration and stable maintenance of euthyroidism, without fluctuations in thyroid status, as an important preventive measure.¹⁰
- **TRAb levels.** TRAbs are the only specific biomarker for Graves' disease and TED. Levels of TRAbs with stimulating activities were found to be three times higher in patients with TED than those without and strongly correlated with the disease's activity and severity. TRAbs were shown to be an independent risk factor for TED and a predictor of its severity and outcome.¹⁰
- **Smoking.** Cigarette smoking is the strongest modifiable risk factor for TED. Smokers have a significantly higher risk of developing TED compared to non-smokers (odds ratio [OR] 7.7 [95% CI: 4.3-13.7]), and the risk increases with the number of cigarettes smoked daily. In smokers with TED, the disease is more likely to be severe and less responsive to immunosuppressive therapies. The link between TED and smoking suggests the involvement of other toxic factors, including the direct effects of cigarette smoke and the heat transmitted from the ethmoid sinuses through the lamina papyracea (the thin medial orbital wall).^{10, 37}

B.1.3.1.5 Humanistic burden and impact on quality of life

Humanistic burden

TED is a painful, debilitating and disfiguring condition that can significantly impact a patient's quality of life (QoL) and physical functioning, psychological and emotional wellbeing, and ability to carry out daily activities including reading, driving and socialising.^{42, 63}

Patients with TED can experience significant burden from various aspects. The most profound effects on QoL are due to the physical symptoms of pain, proptosis and diplopia. Data from an online survey regarding chronic TED symptoms and patient QoL were retrospectively examined. The data showed that, compared to patients with a high QoL score, those with low QoL scores experienced significantly more pain (39% vs. 13%), blurry vision (30% vs. 17%), and diplopia (27% vs. 3%) (all $p \leq 0.025$).²³

Proptosis can dramatically change a patient's appearance and, in severe cases, may decrease or threaten vision. Moreover, TED symptoms can restrict daily activities such as driving, working, watching television, reading and sleeping. These can negatively affect employment, relationships, and self-confidence, often leading to social withdrawal. The substantial changes in QoL due to TED can impact various aspects of patient well-being, including feelings of isolation, anxiety or depression, dealing with the psychosocial burdens associated with the condition, and in some cases, leading to suicidal behaviour.^{6, 20, 21}

Diagnosis

TED can impose a significant patient burden, starting with challenges in diagnosis. Some patients report encountering difficulties early on, facing uncertain diagnoses, prognoses, and treatment decisions^{42, 64}:

“It also took many months and many doctor visits to get an accurate diagnosis, which is demoralising and terribly frustrating.”

“I was diagnosed with Thyroid Eye Disease in August of 2020. I’d actually never heard of the disease before. It took 3 doctors to finally diagnose me and find a doctor who specialised in it.”

Physical symptoms

Symptoms of TED, such as dry or gritty eyes, light sensitivity, bulging eyes, and pressure or pain profoundly impact patients⁴²:

“Eyes do not look straight ahead, comfortable eye position for me after TED is much lower than neutral so to lift my eye up hurts, driving more than 15 minutes is difficult and then this creates tremendous neck pain and ... migraines.”

“When I felt increased pressure at work and home, my symptoms got worse.”

A survey found that dry/gritty eye (65%), light sensitivity (56%), proptosis (43%), and pressure or pain behind the eye (42%) were the most burdensome symptoms reported by 443 patients with acute and chronic TED.⁴²

Impact on daily activities

Moreover, TED imposes significant restrictions on daily activities such as reading, driving, socialising, and working due to impaired visual function.^{65, 66} These restrictions can negatively affect employment, relationships, and self-confidence, often leading to social withdrawal. Other noted challenges include difficulty driving and moving around outdoors, particularly with light sensitivity, uneven surfaces, and depth perception issues^{42, 67-71}:

“I am worried about crossing roads and definitely don’t go out on my own. I always go out with my sister. I wouldn’t dream of going shopping on my own.”

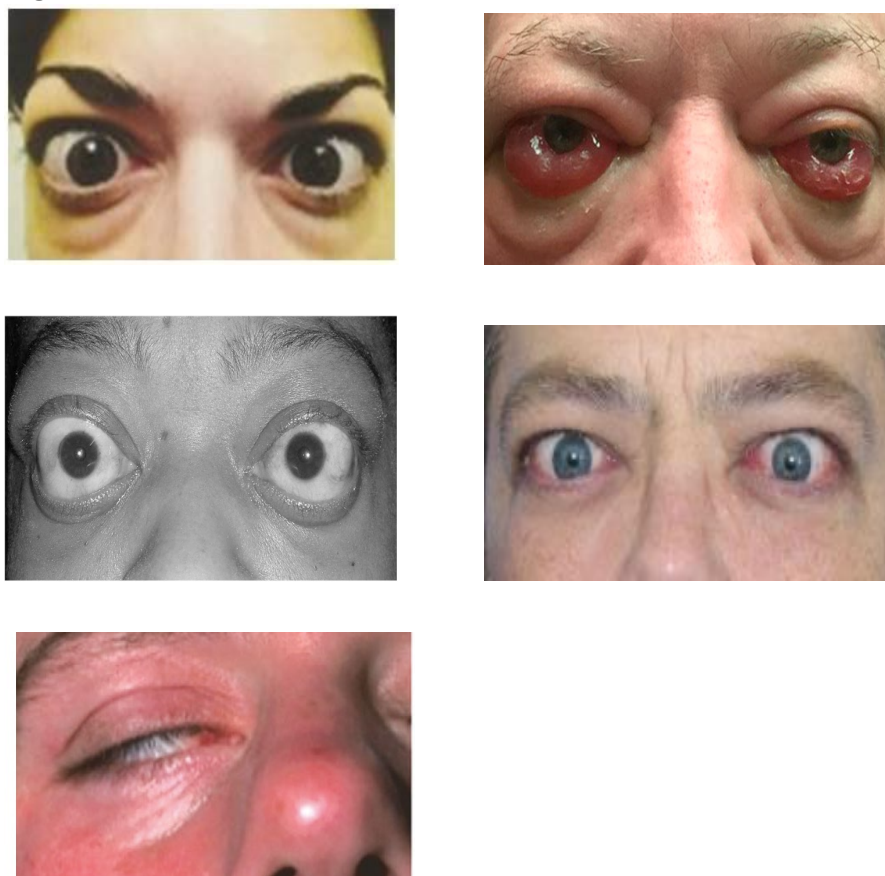
“I started experiencing visual problems which affected my daily life. I slowly stopped reading because I couldn’t track the words on the page. Eventually, I stopped driving, relying on others for transportation.”

“I started having problems completing everyday activities. Driving also became difficult. I drove with one eye closed due to severe double vision. I quit driving long distances and anywhere I was not familiar.”

Impact of altered appearance

As well as causing visual dysfunction and, in severe cases, threatening sight altogether, proptosis can dramatically change a patient's appearance (see Figure 4). This can have a profound effect on patients' quality of life.

Figure 4: The impact of TED on facial appearance



Sources: Top left, Smith & Hegedus, 2016⁷²; Top right, Rashad R, et al. *Life*. 2022;12:2084; Middle left, Verity, 2016⁷³; Middle right, Novaes et al, 2016⁷⁴; Bottom left, Burch HB, et al. *Thyroid*. 2022;32:1439-1470.

More than 70% of TED patients reported that the disease interfered with their visual function, and 60-95% felt that changes in their appearance significantly affected their psychosocial functioning.⁶⁷⁻⁶⁹

In a UK study to investigate the demographic, clinical and psychosocial factors associated with quality of life in TED patients presenting for orbital decompression surgery, Wickwar *et al.* reported higher levels of potential cases of clinical anxiety (37%) and depression (26%) in the study sample than in patients with other chronic diseases or facial disfigurements. Appearance-related quality of life and mood were particularly affected.⁷⁵ Other studies have reported how the impact of an altered appearance due to TED leads to social withdrawal, isolation, and a decrease in confidence and self-esteem^{42, 66}:

“...My confidence has taken a huge knock because of my eyes that are bulging and teary and nose that’s runny.”

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“I lost all my confidence, I’d been very outgoing, confident and popular but I just did not want to go out; I didn’t want to see anybody.”

Psychosocial effects

The substantial changes in QoL due to TED can impact various aspects of patient well-being, including feelings of isolation, anxiety or depression, dealing with the psychosocial burdens associated with the condition, and in some cases, leading to suicidal behaviour.^{6, 20-22}

The most commonly reported psychosocial effects were changes in appearance and effects on self-confidence, which were associated with mental health issues. A US study by Smith et al. found that the emotional and psychological impacts reported by 394 patients with TED included a decline in confidence and/or feelings of well-being (49%), depression and/or anxiety (45%), and concerns about appearance (44%). Additionally, patients reported experiencing a decline in achieving goals (20%) and avoiding public situations (19%).⁴² Patients report appearance impairment and psychological impact long after the active inflammatory phase of TED has subsided.²³

Patients with TED showed higher levels of anxiety and depression compared to healthy controls. A Chinese study found significantly higher scores for both the Hamilton Anxiety Rating Scale (HARS) and the Hamilton Depression Rating Scale (HDRS), suggesting higher level of anxiety and depression among TED patients compared to healthy individuals (HARS: 15.39 [SD: ±8.51] vs. 2.68 [SD: ±2.61]; HDRS: 15.25 [SD: ±9.96] vs. 2.23 [SD: ±1.93]; $p < 0.001$).⁷⁶

Further, a Danish study found that there was a significantly increased risk of death from suicide in patients with TED compared with an age- and sex-matched control group (hazard ratio [HR]=2.71; $p = 0.022$).²²

In summary, TED devastates patients’ well-being due to the difficulty of diagnosis, burdensome symptoms, limitations on daily activities caused by visual dysfunction or impairment, and changes in appearance, all of which consequently cause an emotional burden^{42, 66}:

“It makes me feel sad, it’s almost as if that was another life then, because I’m so different now.”

“This is a very difficult disease that causes tremendous damage to one’s health, ability to be independent, and psychologic well-being. As is the case with other autoimmune diseases, it is unpredictable, triggers other, significant health problems, and is always with you.”

Health-related quality of life instruments

Several health-related quality of life (HRQoL) questionnaires have been used to evaluate the humanistic burden of TED, revealing its significant negative impact on patients' QoL.

The Graves' Ophthalmopathy Quality of Life Questionnaire (GO-QOL), is particularly notable for measuring disease-specific aspects of QoL in TED patients. Endorsed by the EUGOGO group, it is used extensively throughout the world, and has become the most validated tool to measure QoL in observational and therapeutic trials of patients with TED.⁷⁷

The GO-QOL questionnaire includes two domains (eight questions each): the impact of double vision and decreased visual acuity on visual functioning, and the psychosocial consequences of altered appearance. The sum of the scores on each subscale and an overall combined score are calculated and transformed to a scale from zero to 100, with 0 indicating worst health state and 100 indicating best health state.⁷⁸⁻⁸⁰

The validity of the GO-QOL was supported by correlations with two generic HRQoL instruments, the Medical Outcomes Study Short-form General Health Survey and the Sickness Impact Profile, and duration and severity of TED.⁷⁸ The GO-QOL is also validated in multiple languages for use in different regions.⁷⁷

Other HRQoL instruments used for TED include the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) and the Dry Eye-related Quality of Life Score (DEQS).

B.1.3.1.6 Economic burden

Due to the rarity of TED and the fact that it can often be mis-or under-diagnosed, there is limited evidence available on the economic burden of TED and no figures directly available for the UK. However, studies from the US and Germany can give a sense of the economic burden. These indicated that TED incurs substantial direct medical costs, primarily from the hospitalisation and surgical costs, and that there is a direct correlation between direct costs and disease severity. These studies also highlight the significant impact of TED on the patients' ability to work, including temporary and permanent work disability and extended sick leave, leading to considerable costs of productivity loss. The direct costs, together with the indirect costs due to work impairment, are associated with disease severity and QoL on daily activities and self-consciousness.⁸¹⁻⁸⁴

Moreover, the higher incidence of TED in females compared to males creates an unequal burden, which can extend to affect women's professional and personal life. TED therefore imposes a significant burden on society, as these individuals are often primary contributors to the workforce as well as caregivers at home.^{58, 60, 85}

B.1.3.2 Relevant clinical practice guidelines

In 2005, NICE conducted an evaluation of the retrobulbar irradiation for TED (NICE Interventional Procedure Guidance 148).⁸⁶ Based on the evidence available at the time, NICE concluded that the procedure seemed to work well enough and be safe enough to justify its use for people who could not have other standard treatments.⁸⁶

The UK Royal College of Physicians (RCP) published clinical practice guidelines for the management of patients with GO in 2015 that included the initial assessment and diagnosis of GO, as well as referral pathways and disease management in primary care and general practice outside of specialist centres.⁸⁷ The RCP advised that low-cost effective interventions, such as eye drops, selenium supplements and smoking cessation advice, can be provided by clinicians in primary care or hospital general medicine for mild TED. Moderate-to severe-disease should be referred to specialised centres such as Tier 2 or Tier 3 specialist endocrine, thyroid and/or ophthalmology clinics.⁸⁷

There is no other published NICE guidance relating to TED and no UK-specific guidelines for the treatment and management of moderate to severe TED.

However, the American Thyroid Association (ATA), European Thyroid Association (ETA) and the EUGOGO have published comprehensive clinical practice guidelines, which describe the management of moderate to severe TED. The ATA/ETA and EUGOGO guidelines are further described *in B.1.3.3.2*.

B.1.3.3 Current pathway of care

B.1.3.3.1 Diagnosis

TED can be difficult to diagnose, leading to therapeutic delays. A UK survey with 278 respondents found that 58% of them received incorrect diagnoses for their eye symptoms initially. Additionally, 45% of respondents reported an interval of more than six months from the onset of initial symptoms to receive diagnosis of TED, and for 26% of respondents, it took longer than 12 months.^{66,42}

Diagnosing TED involves a comprehensive approach as no single clinical finding or laboratory test is definitive.³⁹ Table 6 presents the investigations and tests typically involved in the diagnosis of TED.

Table 6: Diagnosis of TED

Diagnosis approaches
• Medical history review • Physical examination for ophthalmic signs and symptoms, e.g., eyelid retraction along with abnormal thyroid function or regulation, exophthalmos, optic nerve dysfunction, or extraocular muscle enlargement • Radiographic imaging, e.g., ultrasound, CT, MRI, somatostatin receptor scintigraphy, and optical coherence tomography • Laboratory tests: TSH, free T4, or free T3 • Antibody tests: antithyroid peroxidase, TSI, TSAb, and thyroid-binding inhibitory immunoglobulins • Ruling out other diagnoses

Note: TSI levels correlate to TED inflammation and can serve as a marker for disease activity and prognosis
Abbreviation: CT, computed tomography; MRI, magnetic resonance imaging; TED, thyroid eye disease; TSAb, thyrotropin receptor antibodies; TSH, thyroid stimulating hormone; TSI, thyroid stimulating immunoglobulins
Source: Rashad *et al.* (2022), Szelog *et al.* (2022), Weiler (2017), Wang *et al.* (2019).^{24, 25, 39, 48}

According to the EUGOGO guidelines, magnetic resonance imaging (MRI) and computed tomography (CT) scans can offer insights into the extent and distribution of orbital tissue expansion, including muscle thickening and fat volume increase⁴⁷
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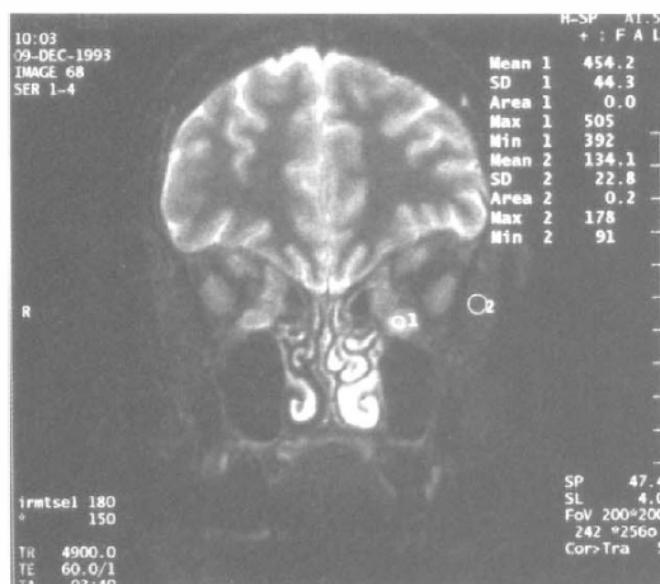
(Figure 5). MRI is recommended for patients with unilateral or significantly asymmetric exophthalmos, suspected optic neuropathy, and euthyroid patients with normal thyroid serology. Certain MRI sequences can be particularly valuable for quantifying disease activity (Figure 6) and predicting responses to anti-inflammatory treatments and overall outcomes in TED. CT is advised before decompression surgery. However, the application of these imaging techniques in daily practice is limited by their cost and availability.⁴⁷

Figure 5: Computerised tomography images showing extraocular muscle enlargement



Computed tomography images demonstrated extraocular muscle enlargement in thyroid eye disease. Computed tomography (CT)-based images in axial (a, b) and coronal (c) planes showcase superior (yellow arrow), medial (red arrow), and inferior (green arrow) rectus muscle enlargement bilaterally. Source: Kulbay et al. (2024).²⁷

Figure 6: Coronal STIR sequence MRI scan



A coronal STIR sequence MRI scan showing an inflamed extraocular muscle with high signal in acute TED. Cursor 1 is around the extraocular muscle and cursor 2 is around the temporalis muscle. The ratio of signal intensity in these two muscles gives the signal intensity ratio or STIR value.

Abbreviation: MRI, magnetic resonance imaging; STIR, short tau inversion recovery; TED, thyroid eye disease Source: Mayer et al. (2001).⁸⁸

B.1.3.3.2 Management of TED

The main treatment goals for patients with active TED are disease inactivation, reduction of soft tissue involvement and proptosis, and the improvement of diplopia and eye motility.⁸⁹ Additional goals include improving visual ability, providing relief from eye symptoms and pain, and enhancing patient's quality of life, as multiple studies suggest that TED can negatively impact vision, quality of life, work productivity, the psychological and physical impact of pain, and mental wellbeing.⁹⁰ ⁹¹ Although several treatment objectives can be identified, including preservation of vision, and improvements in diplopia and patients' quality of life, UK clinicians have advised that standard treatment outcomes or goals are lacking.⁹²

TED can be managed based on disease activity and severity or based on symptomology. The 2022 ATA/ETA consensus statement recommends that clinicians devise a treatment plan based on disease activity, severity, duration, trend across time, the impact of the disease on daily living, patient age and comorbidities, patient preference, and treatment goals.⁹³

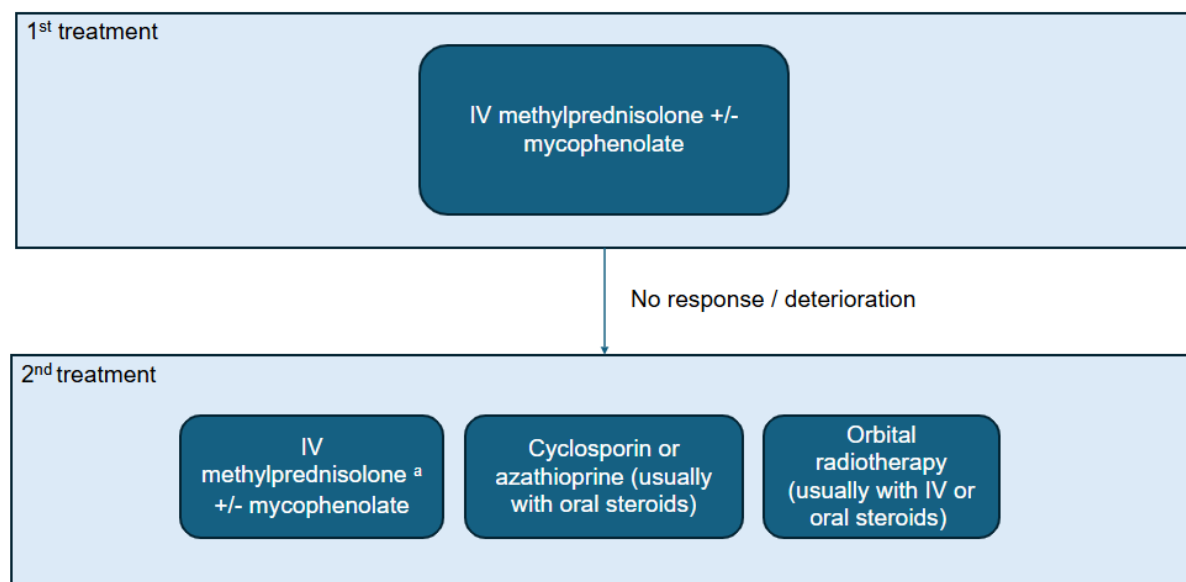
Patients are typically managed with pharmacotherapy during the acute, active phase and surgical intervention in the inactive phase of disease.^{89, 93-95}

Teprotumumab is currently available in the US, and is recommended in the ATA/ETA guidelines as the preferred treatment for people with moderate to severe TED whose treatment goals focus on improving diplopia and proptosis.⁹⁶ It is important to note that, with the exception of teprotumumab, none of the other treatments or interventions described in the current ATA/ETA or EUGOGO guidelines are licensed specifically to treat TED and so they are all used off-label to manage the symptoms of TED, without having any effect on the underlying pathophysiology of the disease. The limitations associated with these options are described in section B.1.3.3.4 below. Management of lifestyle and other known risk factors, in particular stopping smoking and addressing thyroid dysfunction, should also be used as part of established clinical management of the condition. In smokers with TED, for example, the disease is more likely to be severe and less responsive to immunosuppressive therapies than in non-smokers.

B.1.3.3.3 Current care pathway in the NHS for active, moderate-to-severe TED

The current pathway of care for patients with active, moderate-to-severe TED in the NHS is shown in Figure 7.

Figure 7: Current care pathway for moderate-to-severe active TED in the NHS



^aHigher dose of IV methylprednisolone may be given if people do not respond adequately to initial treatment.
Abbreviations: IV, intravenous; TED, thyroid eye disease
Adapted from Bartalena L, *et al.* (2021).⁴⁷

There are currently no pharmacological treatments specifically approved for TED in the UK. Pharmacological management of all active TED patients, irrespective of disease severity, currently consists of off-label treatments which do not target the underlying cause of the disease, with non-meaningful changes in proptosis and diplopia. In addition to pharmacological options, clinical management of active TED includes management of known risk factors, such as treating thyroid dysfunction to ensure a euthyroid state and supporting the patient to stop smoking.

B.1.3.3.4 Treatment of active moderate-to-severe TED

Advice from expert clinicians practising in England indicates that the vast majority follow the 2021 EUGOGO clinical practice guidelines for treating patients with TED.⁴⁷ In accordance with those guidelines, previously untreated UK patients with active, moderate to severe TED almost exclusively receive 12 weeks of IVMP with or without MMF for 24 weeks as an initial treatment.⁹² IVMP is also the preferred

therapy in the ATA/ETA guidelines for the management of moderate to severe TED.⁹⁶

Glucocorticoids such as IVMP have broad anti-inflammatory properties and have been the mainstay treatment option for management of acute, moderate-to-severe TED for more than 50 years, even though they are not specifically licensed for such use.⁹⁷⁻⁹⁹ Glucocorticoids can provide symptomatic relief in TED patients with inflammation, due to their beneficial impact on superficial soft-tissue swelling,^{100, 101} but they have limited impact on diplopia, proptosis and other potentially disfiguring consequences of TED.¹⁴⁵

After treatment with systemic IVMP with or without MMF, there is no single treatment of choice for patients who are in need of a second treatment. According to EUGOGO guidelines if the response to primary treatment is poor and the TED is still active and moderate-to-severe, second-line and subsequent treatment options for consideration include a further course of IV methylprednisolone monotherapy (starting with high single doses of 0.75 g and a maximal cumulative dose of 8 g per cycle), biologic agents (rituximab, tocilizumab), orbital radiotherapy (combined with oral or IV glucocorticoids) and/or systemic immunosuppressants (such as azathioprine and ciclosporin). However, all these options are used off-label and there is no robust clinical evidence for any of these treatments in people with TED.^{102, 103}

The choice of second treatment for previously-treated TED patients in the NHS depends on the individual treating clinician and patient, based on the treatment goals for that patient, patient preferences, and the availability of the intervention given not all options listed in the EUGOGO guidelines are routinely available across the NHS. For example, rituximab and tocilizumab are not routinely available in UK clinical practice. If a UK clinician wants to prescribe either agent, an individual funding request needs to be made before rituximab or tocilizumab can be used. This process is often prohibitive and as such, these agents are rarely used in the management of TED within the NHS. In practice, the availability and choice of second-line treatments is extremely variable across the country. Steroids (most commonly IVMP) remain the cornerstone of 2L treatment and are often used in combination with one of either mycophenolate, azathioprine, ciclosporin or orbital radiotherapy.

Triamcinolone is administered as a local injection. It is only used when systemic corticosteroids are contraindicated due to the significant risk of adverse events⁴⁷ and is not routinely used in UK clinical practice.

Surgery

Surgery is recommended by EUGOGO for the treatment of very severe, sight-threatening TED ([REDACTED].[REDACTED].[REDACTED].[REDACTED].) or chronic TED (which falls outside of the decision problem covered by the present submission). There are complications associated with operating on actively inflamed tissues and the risk of the inflammatory processes continuing post-surgery, thereby reversing any benefit obtained from the initial surgery and necessitating repeated surgical procedures. Secondly, rehabilitative surgery is a highly invasive procedure that is associated with several potential complications including strabismus, diplopia and ischemia among others.

Surgery is not, therefore, a relevant comparator to teprotumumab because it is used at different points in the care pathway.

In summary, the company's understanding is that systemic methylprednisolone (IVMP) with or without MMF is used almost exclusively for people with active, moderate-to-severe TED who have received no prior treatment. It is also used, often at a higher dose, for TED patients who have had an inadequate response to their initial treatment or have experienced deterioration in symptoms or disease progression. For this latter group, ciclosporin, azathioprine or orbital radiotherapy, all usually in combination with steroids, may also sometimes be used.

B.1.3.4 Issues relating to current clinical practice

B.1.3.4.1 Limitations with current treatments

Management of acute TED remains a major challenge with treatment options that are used to manage inflammation and symptoms of TED rather than the underlying pathogenesis of the disease.^{102, 103} Currently there is no approved treatment in the UK; off-label options include glucocorticoids, steroid sparing immunosuppressants (azathioprine, ciclosporin), biological agents (rituximab, tocilizumab) and orbital radiation⁴⁷. These therapies are inconsistently beneficial, not licensed specifically to treat TED, and often associated with major side effects.^{102, 103}

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Glucocorticoids

Glucocorticoids may lead to transient symptomatic relief in TED patients with inflammation, due to their impact on inflammation including superficial soft-tissue swelling.^{100, 101} While inflammation improves over time, proptosis may not return to normal, with a significant percentage of patient cases (ranging from 14% to 41.2%) retaining permanent diplopia and experiencing worsening or sustained visual impairment.^{23, 104, 105} Additionally, they are only appropriate for short term use with extended treatment associated with high rates of adverse reactions.^{93, 102, 106-108} Recurrence of symptoms is likely to occur after tapering of glucocorticoid therapy and will require long-term treatment with its associated risks, such as hepatic, cardiovascular and cerebrovascular complications.^{106, 109-112}

There is currently no robust evidence to demonstrate the impact of glucocorticoids on the hallmarks of TED: proptosis and/or diplopia. Studies on the use of glucocorticoids in TED suggest modest improvements in proptosis and diplopia, however these are not considered to be clinically meaningful.¹¹³ A meta-analysis of the published literature on the efficacy of IV glucocorticoids at the EUGOGO-recommended dose over a 12-week period in patients with acute, moderate-to-severe TED found a modest, but not clinically meaningful effect, on proptosis and diplopia.¹¹²

Immunomodulatory agents

Immunomodulatory agents can also reduce inflammation in active TED but have limited, if any, effect on the long-term sequelae of disease, such as functional disability and facial disfigurement (cited by Douglas 2020 and referenced to Bartalena 2012, Ponto 2009 and Ponto 2011).

Rituximab and tocilizumab

In recent years, off-label rituximab has been prescribed based on a few small, uncontrolled and open-label case studies. However, the evidence regarding its efficacy is still unclear based on conflicting results obtained from three randomized controlled trials (RCTs).¹¹⁴⁻¹¹⁷ One small RCT of 25 participants reported that rituximab offered no additional benefit over placebo in patients with moderate-to

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severe active TED and was associated with a non-negligible side effect profile. Study patients experienced a total of 15 adverse events (4 in the placebo group and 11 in the rituximab group) occurring in 11/25 patients (3 placebo and 8 rituximab). Of those, six events were considered to be moderate or severe (5 in the rituximab group)¹¹⁵

While tocilizumab has been found to improve inflammation (as measured by the CAS) in a randomised, placebo-controlled trial conducted in glucocorticoid-resistant patients, the data showed minimal effect on proptosis and diplopia, especially in the off-treatment period.¹¹⁸ An open label study where glucocorticoid resistant TED patients were treated with tocilizumab until improvement with an undefined treatment duration found improvement in CAS, best corrected visual acuity and intraocular pressure after 1 year of therapy.¹¹⁹

As stated previously, UK clinical experts have advised that neither rituximab nor tocilizumab are routinely used to treat active moderate to severe TED in UK clinical practice, and can usually only be accessed via individual funding requests.

Orbital Radiotherapy

Orbital radiation is sometimes used to treat TED either as monotherapy or in combination with oral glucocorticoids. A 2012 Cochrane review found orbital radiation to be more effective than sham radiotherapy for mild to moderate TED but with no significant changes in quality of life (QoL).¹²⁰

Other studies evaluating the use of orbital radiation in moderate-to-severe TED have found limited efficacy in proptosis, diplopia, eyelid retraction and soft tissue changes.^{114, 115} Regarding the safety of orbital radiation for the management of TED, a literature review conducted in 2021 reported that minor side effects, such as dry eye and cataract, are more common than major ones. However, longer follow-up is necessary to properly monitor for radiation retinopathy or malignancy.¹²¹

B.1.3.4.2 Definition of treatment success and unmet need

Based on section B.1.3.4.2 above, there is significant unmet medical need in TED, and specifically for novel pharmacotherapies with improved efficacy and better tolerability that treat the underlying cause of the disease.^{115, 122-127} Current

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management of TED comprises the use of off-label interventions with a limited evidence base that are not suitable, or available, for all patients. Current treatment paradigms offered in most countries offer symptomatic improvement but fail to target the underlying pathogenic mechanisms, and thus do not significantly alter the long-term disease outcome.¹²⁸

There is an urgent need to update the definition of what constitutes a success in TED treatment and to redefine the treatment paradigm accordingly. The current definition of success is based solely on what has been possible to achieve to date with outdated, generic, unlicensed pharmacological agents and radiation therapy that pre-date the development of biologic and other targeted therapies. While it is true that corticosteroids can successfully reduce disease activity (as measured by the CAS) and orbital inflammation, they are only suitable for short-term use due to their safety profile and have minimal impact on those aspects of disease – principally diplopia and proptosis – that leave TED patients with long-term disability, impaired activities of daily living, and facial disfigurement.

A definition of treatment success based on cessation of inflammation is no longer fit for purpose in an age where biological therapy has the potential to target the underlying causes of disease symptoms and progression, and treat those symptoms not addressed by current unlicensed options, such proptosis, diplopia and other consequences of disease.

Teprotumumab not only reduces the inflammation associated with TED; the inhibition of IGF-IR attenuates the underlying autoimmune pathogenesis of TED, thereby modifying the course of the disease, reducing disability and improving orbital function. Teprotumumab has demonstrated statistically significant reductions in proptosis, diplopia and the inflammatory symptoms of TED (as measured by the clinical activity score [CAS]) in randomised controlled trials, with associated significant improvements in patient-reported quality of life scores. If approved, patients with active, moderate-to-severe TED will finally have a treatment designed for their specific disease, supported by robust clinical trial data in the relevant population.

B.1.3.5 Teprotumumab place in therapy

Teprotumumab is a first-in-class, disease-modifying agent and the first FDA-approved agent for the treatment of patients with TED, regardless of TED activity or duration. According to a consensus statement between the American and European Thyroid Associations, teprotumumab is the preferred treatment option for the improvement of diplopia and reduction of proptosis and “appears to be the more comprehensively effective therapy”.⁹³

As will be shown in Section B.2.6, teprotumumab demonstrates consistent and clinically meaningful improvement in the main manifestations of TED including:

- Proptosis (which reflects the expansion of soft tissues in the orbital space);
- Diplopia (due to the inability to orient the eyes correctly); and
- Acute inflammatory symptoms by reduction of inflammatory signs and symptoms including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness and chemosis

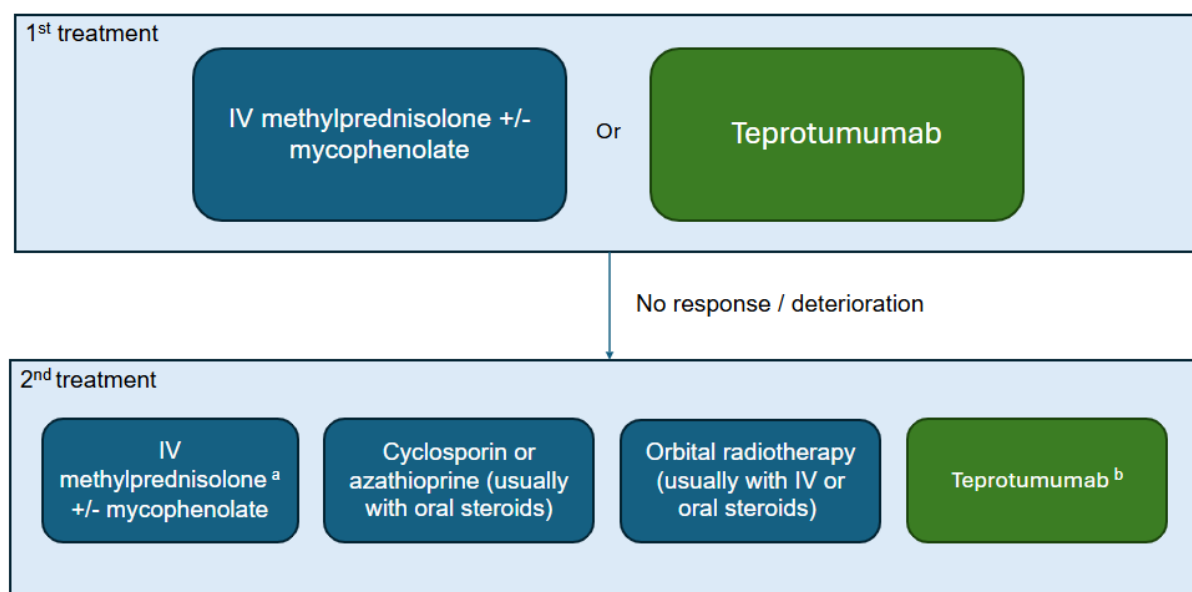
Teprotumumab also leads to meaningful improvements in QoL (improvement in the GO-QoL visual-functioning, appearance and combined scales) in patients with TED.^{49, 80, 113}

Teprotumumab is expected to be licensed in the UK for the treatment of [REDACTED] [REDACTED]. [REDACTED]. Teprotumumab should therefore be considered as an option in the NHS for adult patients with active, moderate-to-severe TED:

- as an alternative to IV glucocorticoids (with or without immunosuppressants); and
- as an alternative to ciclosporin, azathioprine or orbital radiotherapy, for people who have experienced an inadequate response to, or a deterioration in symptoms following an initial response to, IV glucocorticoids +/- MMF.

The anticipated positioning of teprotumumab in the NHS care pathway is shown in Figure 8.

Figure 8: Position of teprotumumab in the care pathway for moderate-to-severe TED



^aHigher dose of IV methylprednisolone may be given if people do not respond adequately to initial treatment;

^bOnly if not previously received.

Abbreviations: IV, intravenous; TED, thyroid eye disease.

Adapted from Bartalena *et al.* (2021).⁴⁷

B.1.4 Equality considerations

As stated in section 1.3.1 above, TED is five times more prevalent in women than men. The typical age of onset/diagnosis is middle age (40-60 years), which means women of working age are disproportionately affected by TED.

The level of disease activity in TED is typically measured by the CAS.⁴⁷ One of the key limitations with the CAS is that any signs of inflammation, such as redness, are more difficult to detect in people who have black or brown skin. Wang *et al.* note that “the clinical activity score (CAS) system was developed in 1999 in Amsterdam and amended by the EUGOGO. Although the original studies did not specify the racial demographics of included patients, a later analysis showed that over 95% of the TED patients referred in the EUGOGO centres were Caucasian”.¹²⁹ They conclude that the data suggests that black patients present with fewer external examination findings suggestive of active TED compared to white patients, but the rates of compressive optic neuropathy and decompression surgery are similar. Therefore, CAS scoring may underappreciate disease activity in black patients.¹²⁹

As the decision problem extends to active TED only, which is often defined clinically according to the CAS, it is important to ensure that any recommendations by NICE do not make it more difficult for people with black or brown skin to access teprotumumab. There is a risk that their CAS assessment alone does not accurately reflect their clinical disease activity level (i.e. they may be assessed as having inactive disease when they have clinically active disease) and, as a result, there is a risk of people of colour being excluded from accessing teprotumumab due to race. Therefore, while the CAS does have clinical utility, it is important to ensure that the definition of active disease allows for alternative, and potentially less subjective measures of disease activity in addition to CAS, such as CT and MRI imaging.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all available evidence on the efficacy and safety of teprotumumab and other treatments for TED, as identified in RCTs and other clinical studies. The SLR aimed to address the following research question: What is the efficacy and safety of teprotumumab and relevant comparators in TED, as identified in RCTs and other clinical studies?

The data sources used to identify the relevant studies included electronic databases and hand-searching of grey literature, including reference lists of included studies and other supplementary sources. The database searches were originally conducted on 9 June 2023 and then updated on 11 September 2024.

The SLR was conducted based on the reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹³⁰ and general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions¹³¹ and key Health Technology Assessment (HTA) bodies, such as NICE, the Canadian Agency for Drugs and Technologies in Health (CADTH),^{132, 133} and the Institute for Quality and Efficiency in Health Care (IQWiG).¹³⁴

B.2.1.1. Search strategy

Full details of the methodology used for the SLR including the search strategy, databases searched, and selection criteria are presented in Appendix D.

B.2.1.2. Study Eligibility

Study eligibility was defined in terms of the population, intervention, comparators, outcomes, and study design (PICOS) criteria. The inclusion/exclusion criteria used to guide SLR study selection are presented in Table 7.

Table 7: PICOS eligibility criteria used in the search strategy

PICOS	Inclusion criteria	Exclusion criteria
Population	• Patients with moderate-to-severe active TED • Patients with chronic or acute TED • Patients with active or inactive TED • Patients with inflammatory or non-inflammatory TED • Patients with CON or DON	Disease other than TED Non-human Healthy volunteers
Interventions	Approved in the US as a treatment for TED • Teprotumumab <u>Recommended in guidelines/off-label use</u> <i>Immunomodulators:</i> • Glucocorticoids (oral or IV, alone or in combination) • Betamethasone • Doxycycline • Methylprednisone <i>Conventional DMARDs:</i> • Mycophenolate • Cyclosporin • Azathioprine <i>Other – surgery/radiotherapy:</i> • Orbital radiotherapy • Orbital surgery (decompression [including 2-wall vs 3-wall vs 4-wall vs fat decompression], strabismus, eyelid surgery [blepharoplasty]) • Orbital surgery with pharmacological interventions <i>Monoclonal antibodies:</i> • Tocilizumab • Rituximab <u>Investigational compounds</u> <i>Monoclonal antibodies:</i> • Batoclimab • Secukinumab • Vunakizumab (SHR-1314) • Infliximab • Adalimumab • VRDN-002 • Efgartigimod • VRDN-001 • VB421 • K1-70 <i>Other – pharmacologic:</i> • Atorvastatin • Bimatoprost	Studies not including at least one of the interventions listed in the inclusion criteria

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	• Sirolimus (Rapamycin) • Selenium <i>Immunomodulators:</i> • Antithymocyte globulin • ATX-GD-59 <i>T-cell co-stimulatory treatments:</i> • Aflibercept • Etanercept <i>Kinase inhibitors:</i> • Linstinib	
Comparator	• Any included intervention • Any non-included intervention	None
Outcomes	<i>Efficacy:</i> • Overall response • Proptosis response • CAS response • Change from baseline in proptosis • Diplopia response • Strabismus • Extraocular motility • Flare • Recurrent disease • Other clinical outcomes <i>Safety:</i> • Treatment-related grade 3 or 4 AEs • Any grade 3 or 4 AEs • SAEs • Other safety outcomes <i>HRQoL and PROs:</i> • Disease-related HRQoL outcomes (GO-QoL, TED-QoL)	No restrictions
Study design	• RCTs, single-arm, non-RCTs • Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	• Non-human, pre-clinical studies • Reviews, Editorials, Notes, Comments, Letters • Case reports/case series
Language restrictions	English language only	Full-text articles not published in English
Timeframe	2013 to present	Published prior to 2013

Abbreviations: AE, adverse events; CAS, clinical activity score; CON, compressive optic neuropathy; DMARDs, disease-modifying antirheumatic drugs; DON, dysthyroid optic neuropathy; GO-QoL, Graves' ophthalmopathy quality of life; HRQoL, health-related quality of life; IV, intravenous; MAIC, matching-adjusted indirect comparison; PK, pharmacokinetic; PRO, patient-reported outcome; RCT, randomized controlled trial; RWE, real-world evidence; SAE, serious adverse event; SLR, systematic literature review; TED, thyroid eye disease; TED-QoL, thyroid eye disease quality of life.

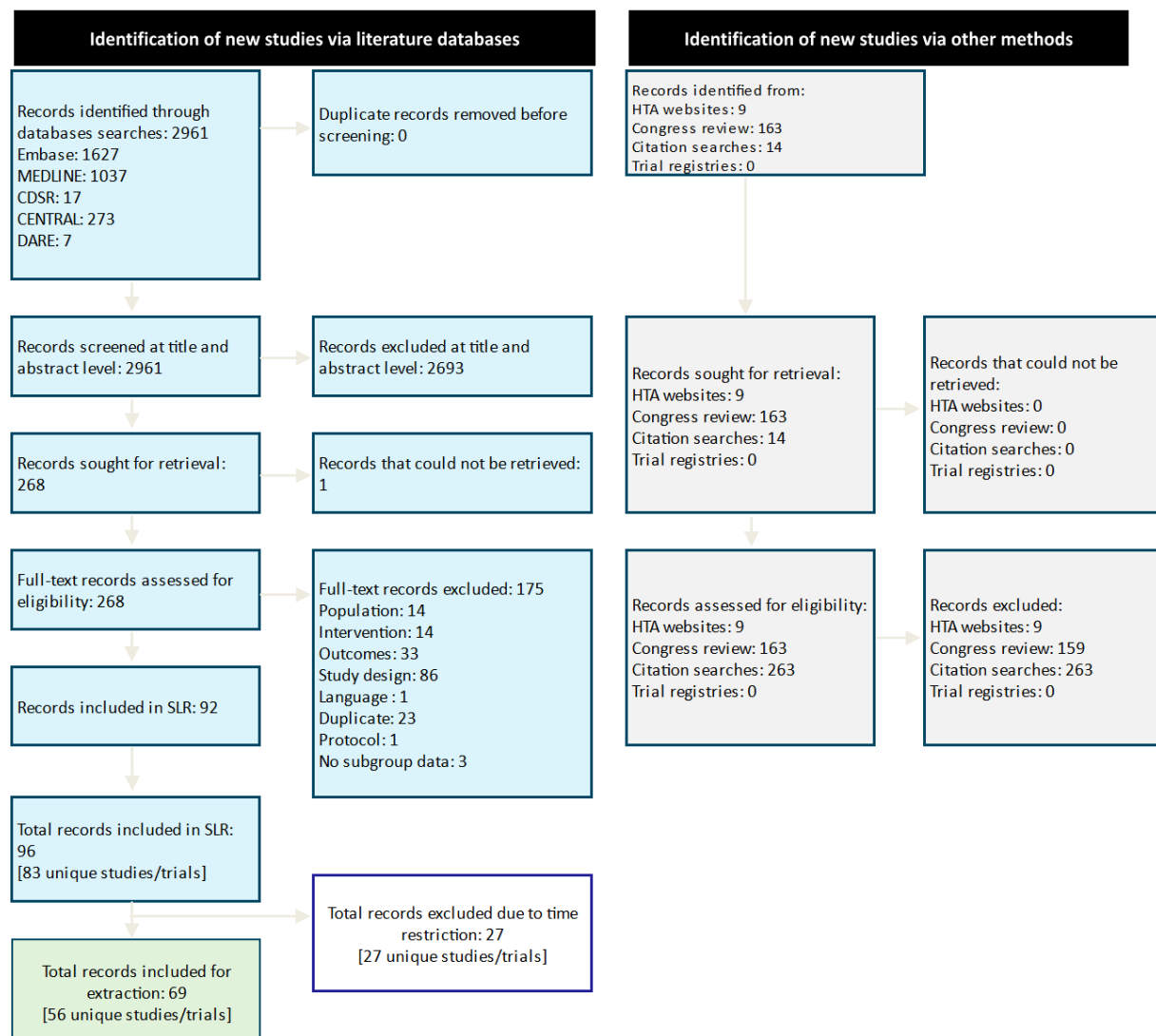
B.2.1.3. PRISMA Flow Diagram

The database searches returned a total of 2961 records (2573 from the original 2023 searches + 388 from the updated 2024 search), which were screened at the title and Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

abstract level. Of these 268 (235 + 33 from the update) were included for full-text screening. After full-text screening, 92 (77 + 15 from the update) reports from database searches met the review inclusion criteria. One hundred and sixty-three (81 + 82 from the update) reports were identified through congress searches, 14 (13 + 1 from update) through bibliographic searches, and 9 (7 + 2 from update) reports through HTA sources. After assessing the records against the PICOS criteria, four records (zero from update) from methods other than database searches were deemed eligible.

In total, 96 (81 + 15) reports from 83 unique studies were included in the SLR. Following the addition of date restrictions to include studies published after 2013, 69 reports from 56 unique studies were included. The literature selection process is shown in Figure 9 and a tabulated summary of the PRISMA results, including reasons for study exclusion, is presented in Table 8.

Figure 9: PRISMA Diagram – Clinical Efficacy SLR



Records with duplicated information were not extracted.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstract of Reviews of Effects; HTA, Health Technology Assessment; MEDLINE, Medical Literature Analysis and Retrieval System Online; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Table 8: PRISMA Summary

Records identified through database searches and selected for title and abstract review	2961
Records excluded	
Total	2693
Population	178
Intervention	97
Outcomes	0
Study design	1380

Duplicate	943
Protocol	95
Reports selected for full-text review	268
Records excluded	
Total	175
Population	14
Intervention	14
Outcomes	33
Study design	86
Language	1
Duplicate	23
Protocol	1
No subgroup data	3
Reports assessed for eligibility from grey literature searches	435
HTA website	9
Congress review	163
Bibliographic search	263
Trial registries	0
Records excluded from grey literature	431
HTA website	9
Congress review	159
Bibliographic search	263
Registry	0
Reports included from database search	92
Reports included from grey literature search	4
Cumulative total reports selected	96
Cumulative total original studies selected	83
<i>Records not extracted</i>	
Records published earlier than 2013	27
Cumulative total reports extracted	69
Cumulative total original studies extracted	56

Abbreviations: HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Full lists of all included and excluded studies are presented in Appendix D1.1.5 and D1.1.6, respectively.

B.2.2 List of relevant clinical effectiveness evidence

Teprotumumab was evaluated in a clinical development programme consisting of two pivotal studies (a phase 2 randomised controlled trial (RCT) [NCT01868997] and the phase 3 OPTIC RCT [NCT03298867]), an open-label extension study from OPTIC (OPTIC-X) for moderate-to-severe acute TED, and a post-FDA phase 4 study in patients with chronic TED. Teprotumumab was also evaluated for the treatment of Japanese patients with moderate-to-severe acute TED in the OPTIC-J study.

The systematic review identified three clinical studies of teprotumumab relevant to the present decision problem: the two pivotal studies (NCT01868997 and NCT03298867), and an open-label extension study from OPTIC (OPTIC-X).

The systematic review also identified a 2023 study that investigated efficacy and safety in patients with TED of long duration and low disease activity, which is not relevant to the present decision problem.

Further details of the identified clinical effectiveness evidence for the technology are provided in Table 9.

Table 9: List of clinical effectiveness evidence

Trial no. (acronym) and primary study ref	Study design	Population	Intervention	Comparator	Supports application for marketing authorisation	Used in the economic model	Is study excluded from further discussion? If yes state rationale	Reported outcomes specified in the decision problem
NCT01868997 Smith, T.J., et al. <i>Teprotumumab for Thyroid-Associated Ophthalmopathy</i> . N Engl J Med, 2017. 376 (18):1748-1761. ⁴⁹	Multicentre, double-blinded, randomised, placebo-controlled	Acute, moderate-to-severe TED	Teprotumumab (N=42)	Placebo (N=45)	Yes	Yes	No (pivotal Phase 2 trial)	Yes: Overall response, change in CAS, adverse events
NCT03298867 OPTIC Douglas, R.S, et al. <i>Teprotumumab for the Treatment of Active Thyroid Eye Disease</i> . N Engl J Med, 2020. 382 (4):341-352. ⁸⁰	Multicentre, double-blinded, randomised, placebo-controlled	Acute, moderate-to-severe TED	Teprotumumab (N=41)	Placebo (N=42)	Yes	Yes	No (pivotal Phase 3 trial)	Yes: Overall response, proptosis, diplopia, adverse events
NCT03461211 OPTIC-X Douglas RS, et al. Teprotumumab Efficacy, Safety, and Durability in Longer-Duration Thyroid Eye Disease and Re-treatment: OPTIC-X Study. <i>Ophthalmology</i> . 2022;129(4):438. ¹³⁵	Open label, extension study	Acute, moderate-to-severe TED, OPTIC trial non-responders and retreated patients	Placebo non-responders (N=37) Teprotumumab non-responders (N=5) Teprotumumab flare (N=9)	N/A	No	No	The OPTIC-X study is not presented in sections B.2.2 – B.2.6 because the results are not used in the economic model. Full details of the study are provided in Appendix M	Yes: Overall response, proptosis, diplopia, adverse events

Abbreviations: CAS, clinical activity score; N/A, not applicable; RCT, randomised controlled trial; TED, thyroid eye disease

Data and outcomes from the two pivotal RCTs (NCT01868997 and NCT03298867) were pooled and used in the economic model and are therefore relevant to this submission as per Section 2.2 above.

The OPTIC-X and OPTIC-J studies provide additional supportive evidence of the efficacy and safety of teprotumumab as a treatment for moderate-to-severe active TED but were not used in the model. OPTIC-X is a non-randomised, open-label extension of the Phase 3 OPTIC study. The pivotal RCTs were preferred for modelling purposes.

Details of the OPTIC-X trial design, methodology, patient characteristics and, where available, results are provided in Appendix M.

OPTIC-J was conducted exclusively in Asian patients. The study has limited generalisability to UK clinical practice because of the different care pathway and Asian population not believed to be representative of the patients likely to be treated in UK clinical practice. As such, OPTIC-J is not discussed further in this submission.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Comparative summary of RCT methodology

The phase 2 trial (NCT01868997) was a multi-centre, randomised, double-blind, placebo-controlled, two arm study to evaluate the efficacy, safety, and tolerability of teprotumumab (investigational name: HZN-001) in patients with acute, moderate-to-severe TED. The study was started in July 2013 and completed in February 2017 with a total of 88 patients enrolled across 15 sites in the US and Europe.^{49, 136}

Eligible patients were randomised in a 1:1 ratio to receive either teprotumumab or placebo. Patients received eight intravenous (IV) infusions (once every three weeks), over six months with an initial dose of 10 mg per kg of body weight, followed by 20 mg per kg for the remaining seven infusions.⁴⁹

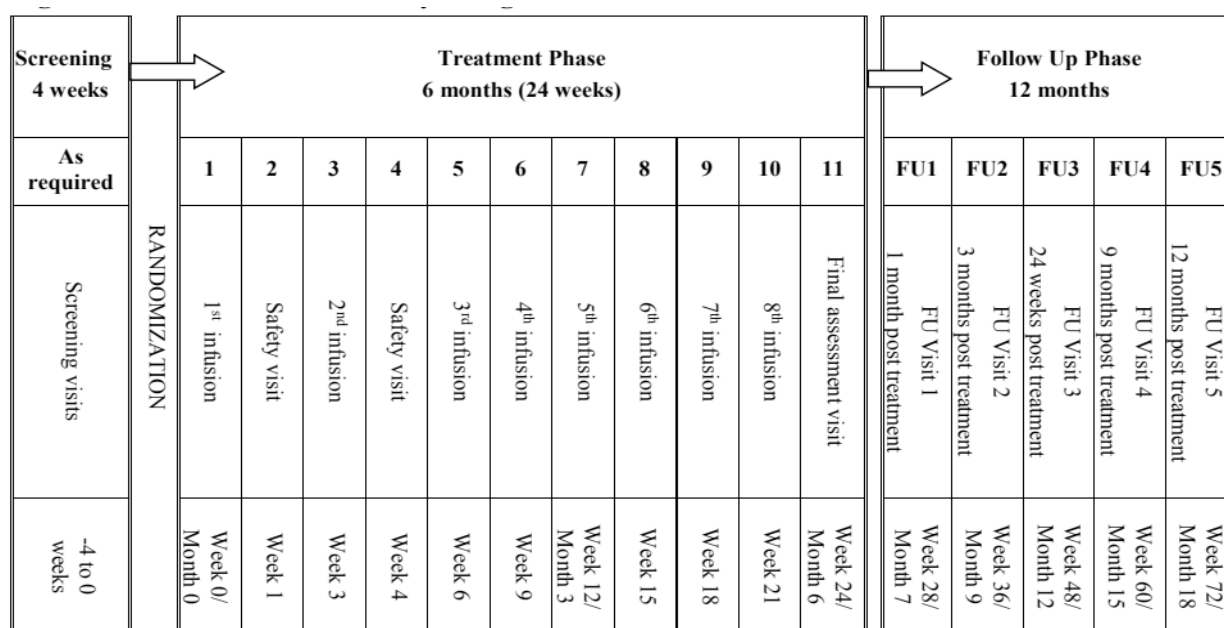
The trial consisted of three phases: a screening phase of 4 weeks ($\pm$ 2 weeks) with no treatment; a double-blinded treatment phase of 24 weeks; and a follow-up phase of 48 weeks with no additional treatment during at least the first 12 weeks.⁴⁹

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Key inclusion criteria included ages from 18 to 75 years, diagnosis of ophthalmopathy within nine months from the onset of symptoms, had a CAS of four or more on a seven-point scale (with a score of ≥ 3 indicating acute thyroid-associated ophthalmopathy) in the more severely affected (study) eye, had not previously received surgical or medical treatment for TED (with the exception of local supportive measures and oral steroids if the cumulative dose was <1000 mg methylprednisolone or equivalent) and did not require immediate surgical ophthalmological intervention.^{49, 137}

A schematic of the trial design is presented at Figure 10.

Figure 10: Schematic of Phase 2 RCT design



Source: Amgen (2018).¹³⁸

The OPTIC trial (NCT03298867) was a phase 3, randomised, double-blind, placebo-controlled, multicentre trial to investigate the efficacy, tolerability, and safety of teprotumumab in the treatment of subjects with moderate-to-severe acute TED⁸⁰.

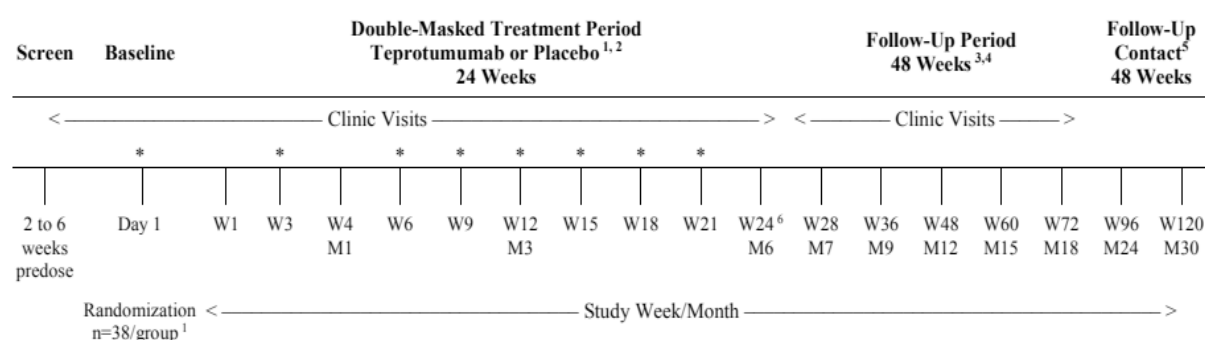
Subjects were screened for the study within 2 to 6 weeks prior to the Baseline (Day 1) Visit. Subjects who met eligibility criteria were randomised on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo. All Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

subjects entered a 24-week double-blind treatment period, during which study drug was infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 (with a final visit at Week 24).

At Week 24, subjects who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter the open-label extension (OLE) study, OPTIC-X. Proptosis responders, as well as non-responders who chose not to enrol in the OLE study, entered a Follow-up Period of up to 48 weeks, during which study drug was not administered.

A schematic of the OPTIC trial design is presented at Figure 11.

Figure 11: Schematic of OPTIC study design



* Infusion of study drug.

Abbreviations: M, Month; q3W, every 3 weeks; TED, thyroid eye disease; W, Week.

1. Subjects were randomised in a 1:1 ratio (stratified by tobacco use status) to receive: a. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or b. Placebo (placebo q3W for all 8 infusions).

2. Visit windows were ± 1 day for Weeks 1 and 4, ± 3 days for Weeks 3, 6, 9, 12, 15, 18 and 21, and ± 7 days for Week 24.

3. Subjects who were proptosis responders or non-responders who do not elect to participate in the open-label extension study entered a Follow-Up Period. Subjects who were responders at Week 24 but relapse during the Follow-Up Period may have enrolled in the open-label extension study if they met the criteria defined in Section 9.3.4 of the Clinical Study Report.

4. Visit windows of ± 7 days.

5. Subjects who completed the Week 72 Visit were contacted via phone or email by research staff to enquire if any treatment for TED had been received since last study contact.

6. Subjects who were proptosis non-responders at Week 24 of the Double-Masked Treatment Period were offered the option to enter an open-label extension study.

Source: Amgen (2019).¹³⁹

A comparative summary of the methodology of the teprotumumab Phase 2 and Phase 3 (OPTIC) RCTs is provided in Table 10 below.

Table 10: Comparative methodology of the Phase 2 and Phase 3 Optic RCTs

Study ID/name	Phase 2	Phase 3 (OPTIC)
Clinicaltrials.gov ID	NCT01868997	NCT03298867
Primary publication	Smith, T.J., et al., <i>Teprotumumab for Thyroid-Associated Ophthalmopathy</i> . N Engl J Med, 2017. 376 (18): p. 1748-1761 ⁴⁹ .	Douglas, R.S., et al., Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med, 2020. 382(4): p. 341-352 ⁸⁰
Study design	Phase 2, multicentre, double-blind, randomised, placebo-controlled trial	Phase 3, multicentre, double-blind, randomised, placebo-controlled trial
Duration	Each trial consisted of 3 phases: • a screening phase of 4 weeks duration (± 2 weeks) • a double-blind treatment phase of 24 weeks • a follow-up phase of 48 weeks	
Location(s)	The trial was conducted at 15 sites, including 11 sites in the United States and 4 sites in Europe	The trial was conducted at 13 sites, including 8 sites in the United States and 5 sites in Europe (Germany, Italy)
Eligibility criteria for participants	Key inclusion criteria • Aged 18-75 years (inclusive) • Clinical diagnosis of Graves' disease associated with TED with a CAS ≥ 4 (on the 7-point version of the scale) for the most severely affected eye • Ophthalmopathy diagnosis fewer than 9 months from onset of TED as determined by patient records • No previous medical or surgical therapy for TED, excluding local supportive measures and oral glucocorticoids (a cumulative dose of ≤ 1 g of methylprednisolone or equivalent, with a 6-week washout period) Key exclusion criteria • Patients with optic neuropathy, severe ocular surface damage • Improvement in CAS of ≥ 2 points between screening and baseline • Treatment with oral or IV steroids or any other immunosuppressive agent for any indication in the	Key inclusion criteria • Aged 18-80 years (inclusive) • Clinical diagnosis of Graves' disease associated with acute TED with a CAS ≥ 4 for the most severely affected eye at Screening and Baseline. • Having ocular symptoms fewer than 9 months before the baseline assessment Key exclusion criteria • Decreasing visual acuity or a visual-field or color vision defect from optic nerve involvement within the previous 6 months • Previous orbital irradiation or surgery for TED • Previous glucocorticoid use (cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of thyroid eye disease) • Previous treatment with rituximab or tocilizumab

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	previous 3 months. Topical steroids for dermatological conditions were not excluded - Any treatment with any investigational agent for any condition in the past 60 days or during the trial. - Previous orbital irradiation or any previous treatment with rituximab	
Treatment group(s)^a	1:1 randomisation to teprotumumab (n=42) or placebo (n=45)	1:1 randomisation to teprotumumab (n=41) or placebo (n=42)
Dosing regimen	Patients received a total of 8 IV infusions: 10 mg per kilogram of body weight for 1 initial infusion, followed by 20 mg per kilogram of body weight for 7 subsequent infusions (1 every 3 weeks for 21 weeks)	
Permitted and disallowed concomitant medication	No prior or concomitant medication or other surgical or medical therapy were permitted for the treatment of TED with the exception of simple analgesics (e.g. acetaminophen, non-steroidal anti-inflammatory therapies). Supportive treatment for adverse events (AEs) was permitted throughout the study at the discretion of the investigator with the exception of oral and systemic corticosteroids. Corticosteroids (IV dexamethasone up to a maximum dose of 20 mg) could only be administered as part of a premedication regimen for patients experiencing infusion associated events. The use of any immunosuppressant i.e. rituximab, tacrolimus, etc. for treatment of any condition was also excluded.	
Primary outcomes (including scoring methods and timings of assessments)	A reduction in overall CAS ≥ 2 points and a reduction in proptosis ≥ 2 mm in the study eye (composite endpoints) in the absence of a corresponding amount of worsening in the non-study eye at week 24	Proptosis response (defined as a reduction in proptosis of ≥ 2 mm from baseline in the study eye without a corresponding increase of ≥ 2 mm in the fellow eye) at week 24
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints included^{49, 79}: - reduction of proptosis: assessed by the Hertel exophthalmometer for each eye - reduction of CAS: consisted of seven components, with each component being scored as present (one) or absent (zero). The score is the sum of components. A change of two points was considered to be clinically relevant - subjective diplopia: based on Gorman Grading of diplopia which categorises patients to four grades. A	- Overall response: defined as a reduction of ≥ 2 points in the CAS plus a reduction in proptosis of ≥ 2 mm without a corresponding increase (of ≥ 2 points or ≥ 2 mm) in the fellow eye - Percentage of subjects with a CAS of 0 or 1 (no or minimal inflammatory symptoms) - Mean change in proptosis - Diplopia response: defined as a reduction in diplopia of ≥ 1 grade from baseline

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	change of 1 grade was considered to be clinically relevant. - the change in GO-QOL score: a change of six points from the range of 0 to 100 points in one or both visual-function and appearance subscales was considered to be clinically important for less invasive treatment - safety: assessed by the incidence of adverse events (AEs), serious adverse events (SAEs), and withdrawals due to AEs, electrocardiograms (ECGs), vital signs, physical and ophthalmic examination, and laboratory parameters (haematology, biochemistry, and urinalysis).	- Mean change in overall score on the GO-QOL. - Safety^b
Other outcomes used in the economic model/specified in the scope	N/A	N/A
Statistical Analysis	- A sample size of 84 was required to have at least 80% power to detect a between-group difference if 42 patients per trial group had data that could be evaluated. - All statistical tests were 2-sided and performed at the 5% significance level. - No interim data analysis was performed. - The analysis of efficacy was performed in all randomised patients who received at least 1 infusion (i.e., ITT population). Safety analyses were conducted in participants who received teprotumumab or placebo - The primary analysis was a logistic regression model with the intervention group as model effect and smoking as a covariate. Patients who did not have week 24 data for any reasons were considered to have treatment failure. - Results of a stratified Cochran–Mantel–Haenszel chi-square test, with smoking status as the stratification factor, enabled confirmation of the logistic analysis results.	- A sample size of 38 participants per trial group was estimated to provide 90% power to detect a 39 percentage-point difference between arms at a two-sided alpha level of 0.05 and allow for a rate of discontinuation of 16% - All efficacy analyses were performed in all patients who underwent randomisation (i.e., ITT population) - Analyses to evaluate the sensitivity of the ITT analyses were performed in all patients who underwent randomisation, received ≥1 infusion, had at least one postbaseline value, and completed the treatment period (i.e., per-protocol population)

	• For assessment of the secondary endpoints, a mixed model of repeated measurements was fit to the individual change from baseline with the use of the PROC MIXED procedure in SAS software. • Each baseline score (including smoking status, intervention group, time, time according to intervention, and time according to baseline interaction) was incorporated into the analysis. • Responses in the non-study eye were assessed with the use of identical analyses • Further details of the statistical analysis and analysis sets are provided in section B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence.	

^a 88 patients underwent randomisation, of these, 87 patients had at least 1 infusion and were considered the ITT population

^b Safety was monitored during the Phase 3 trial especially for the AEs of special interest, including anaphylaxis, infusion related reactions, hyperglycaemia, muscle spasms, diarrhea, and hearing impairment

Abbreviation: CAS, clinical activity score; GO-QOL, Graves' ophthalmopathy-specific quality-of-life questionnaire; ITT, intention-to-treat; IV, intravenous; TED, thyroid eye disease

Source: Smith *et al.* (2017), Douglas *et al.* (2020), Smith *et al.* (2017), Amgen (2019).^{49, 80, 137, 139}

B.2.3.2 Patient Demographics and Baseline Characteristics

B.2.3.2.1 Phase 2 RCT

Table 11 presents the patient characteristics of participants in teprotumumab phase 2 trial for the safety population, which differs from the intention-to-treat (ITT) population because one patient in the placebo group received teprotumumab in error.

The baseline demographic and disease characteristics were mostly well-balanced between treatment arms. Trial participants were stratified by smoking status, a known risk factor for TED. However, there were more smokers in the placebo group than the teprotumumab group, resulting in an imbalance between treatment groups. The potential imbalance in smoking status was adjusted for by including smoking as a covariate.⁴⁹

Table 11. Demographic and Patient Characteristics (Safety Population) – Phase 2

Characteristics	Placebo (n=44)	Teprotumumab (n=43)
Age (years) – means (SD)	54.2 (12.98)	51.6 (10.67)
Female gender – no. of patients (%)	36 (81.8)	28 (65.1)
Time since initiation of treatment for thyroid disease (months) – median (range) ^a	15 (3-189)	8 (1-134)
Duration of eye symptoms or signs (months) – means (SD)	5.2 (2.3)	4.7 (2.1)
Duration of Graves' disease (months) – median (range)	10.8 (1.2-299.0)	10.7 (1.2-228.0)
Race – no. of patients (%)		
White	38 (86.4)	37 (86.0)
Asian	2 (4.5)	1 (2.3)
Black	4 (9.1)	4 (9.3)
Current treatment for thyroid disease – no. of patients (%)		
Antithyroid drug ^b	20 (45)	15 (35)
Levothyroxine	23 (52)	26 (60)
Thyroid extract	3 (7)	1 (2)
Adjustment of medication at trial entry – no. of patients (%)		
Levothyroxine	5 (11)	8 (19)
Antithyroid drug	7 (16)	5 (12)
Smoking status – no. of patients (%)^c		

Characteristics	Placebo (n=44)	Teprotumumab (n=43)
Non-smoker	26 (59)	32 (74)
Smoker	18 (41)	11 (26)
Biochemical status		
TBII (% level of inhibition) – means (SD)	48.7 (25.4)	51.6 (26.9)
TSI (% level of stimulation) – means (SD)	435.1 (105.2)	422.9 (118.1)
Mean thyroid hormone levels (pmol/L) – means (SD)^d		
Free triiodothyronine	4.9 (1.7)	4.8 (1.4)
Free thyroxine	16.3 (3.6)	16.3 (4.8)
Levels of free triiodothyronine and free thyroxine – no. of patients (%)		
Euthyroid at baseline and through intervention phase	13 (30)	20 (46)
Values occasionally outside normal range during intervention phase	25 (57)	18 (42)
Sustained out-of-range values during intervention phase	6 (14)	5 (12)

^a Data shown are for 10 patients in the placebo group and 10 patients in the teprotumumab group.

^b The antithyroid drugs were carbimazole, methimazole, and propylthiouracil

^c Data for smoking status were based on patients who were current smokers at the time of the screening visit. Patients were stratified at randomisation according to smoking status to balance the trial groups with respect to this known risk factor for thyroid-associated ophthalmopathy.

However, there were imbalances in randomisation blocks and discrepancies between patients who were randomly assigned to an intervention as non-smokers at week 0 and those recorded as being smokers in their case-report forms. Data from the case-report forms were considered to be more accurate and were used to define smoking status at baseline.

^d The normal ranges of free triiodothyronine are 2.3 to 4.2 pg/mL (3.5 to 6.5 pmol/L), and of free thyroxine, 0.9 to 1.8 ng/dL (11.6 to 23.2 pmol/L).

Abbreviation: ng/dL, nanograms per deciliter; pg/mL, picograms per millilitre; pmol/L, picomoles per liter; SD, standard deviation; TBII, Thyrotropin-binding inhibitory immunoglobulins; TSI, Thyroid-stimulating immunoglobulins

Source: Smith *et al.* (2017).⁴⁹

B.2.3.2.2 Phase 3 OPTIC

Table 12 provides the characteristics of the ITT population at Baseline. The demographic characteristics at Baseline were generally comparable between the placebo and teprotumumab groups. Mean age was 48.9 years in the placebo group and 51.6 years in the teprotumumab group. Both treatment groups had more females (73.8% placebo and 70.7% teprotumumab) than males and the majority of the subjects were white (88.1% placebo and 85.4% teprotumumab). With respect to geographic distribution, slightly more than half of the subjects in both treatment groups were enrolled at sites in the U.S. (52.4% placebo and 53.7% teprotumumab), with the remainder enrolled at sites in Europe (Germany and Italy). In both the

placebo and teprotumumab groups, more than half of the subjects had never used tobacco (59.5% and 56.1%, respectively).

The time since diagnosis of Graves' disease (median: 0.9 years placebo and 1.0 years teprotumumab) and the time since diagnosis of TED (median: 6.8 months placebo and 6.3 months teprotumumab) were similar between the groups.

Randomisation was stratified by tobacco use status at Baseline, with similar proportions of subjects in the placebo and teprotumumab groups in the user (██████. and ██████████., respectively) and non-user strata (██████████. and ██████████., respectively). Mean values for thyroid panel parameters at Baseline were similar between the treatment groups.¹³⁹

Table 12: Demographic and Patient Characteristics (ITT Population) – OPTIC

Characteristics	Placebo (n=42)	Teprotumumab (n=41)
Age (years) – mean (SD)	48.9 (12.96)	51.6 (12.63)
Female gender – no. of patients (%)	31 (73.8)	29 (70.7)
Duration of TED (months) – mean (SD)	6.4 (2.4)	6.2 (2.3)
Duration of Graves' disease (year) – means (SD)	2.2 (3.2)	3.5 (6.1)
Race – no. of patients (%)^a		
White	37 (88.1)	35 (85.4)
Black	2 (4.8)	4 (9.8)
Asian	1 (2.4)	2 (4.9)
Other	2 (4.8)	0 (0)
Smoking status – no. of patients (%)		
Non-smoker	8 (19)	9 (22)
Smoker	34 (81)	32 (78)
Proptosis measurement (mm) – means (SD)	23.20 (3.21)	22.62 (3.32)
CAS – means (SD) ^b	5.3 (1.0)	5.1 (0.9)
Thyroid hormone levels (pmol/L)^c		
Free triiodothyronine – means (SD)	5.3 (1.7)	5.1 (1.8)
Free thyroxine – means (SD)	16.2 (4.8)	16.5 (5.3)
Thyrotropin level (mIU/liter) – means (SD) ^c	1.42 (2.17)	1.75 (4.16)

^a Race was reported by the patient.

^b The CAS is based on seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component is scored as present or absent (score of 1 or 0, respectively), and the CAS is given as the sum of the scores (range, 0 to 7, with higher scores indicating greater level of inflammation).

^c To convert the values for free triiodothyronine to ng/dL, divide by 15.4. To convert the values for free thyroxine to ng/dL, divide by 12.87. The normal range for free thyroxine is 11.5 to 22.7 pmol/L; for free triiodothyronine, 3.5 to 6.5 pmol/L; and for thyrotropin, 0.55 to 4.78 mIU/L.

Abbreviation: CAS, clinical Activity Score; ng/dL, nanograms/deciliter; mIU/L, milli-international units per liter; pmol/L, picomoles per liter

Source: Douglas *et al.* (2020), Amgen (2019).^{80 139}

No clinically meaningful differences were observed between the treatment groups for medications used prior to entering the study. No subject in either treatment group received IV glucocorticoids prior to study.

The majority of the subjects in the placebo and teprotumumab groups reported prior use of sulphur-containing imidazole derivatives (██████████ and ██████████ respectively) for treatment of Graves' disease and use of thyroid hormones for treatment of hypothyroidism (██████████ and ██████████ respectively). Other prior medications commonly reported in ≥10.0% of all subjects included beta blocking agents (selective), vitamins (multivitamins, plain; vitamin D and analogues), and other ophthalmologic medications.¹³⁹

The majority of the subjects in the placebo and teprotumumab groups were receiving concomitant sulphur-containing imidazole derivatives (██████████ and ██████████, respectively) for treatment of Graves' disease during the double-blind 24-week treatment period. The use of thyroid hormones for treatment of hypothyroidism was reported in ██████████ of placebo subjects and ██████████ of teprotumumab subjects. Other frequently used concomitant medications included vitamin D and analogues, other ophthalmologic medications (typically artificial tears), beta blocking agents (used for treatment of hypertension or symptoms of Graves' disease), and multivitamins.¹³⁹

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the participants eligible to enter the phase 2 and phase 3 OPTIC studies and subject disposition are provided in Appendix D1.2.

B.2.4.1 Phase 2 study

B.2.4.1.1 Analysis timepoints

The Phase 2 study consisted of 3 parts:

- ***A screening phase of 4 weeks*** (± 2 weeks) with no treatment. Subjects attended the clinic once or twice, or as required, during the screening period.
- ***A double-blind treatment phase of 24 weeks***. Subjects attended clinic visits at Week 0 (Baseline visit, 1st infusion), Weeks 1 and 3 (2nd infusion), 4 and 6 (3rd infusion), 9 (4th infusion), 12 (5th infusion), 15 (6th infusion), 18 (7th infusion), 21 (8th infusion), and 24 (final assessment visit). Research staff telephoned subjects focusing on safety and tolerability aspects the day after infusion for the 1st and 2nd infusions, and thereafter as required. Research staff also contacted subjects who experienced an infusion-related event the day after the infusion.
- ***A follow-up phase of 48 weeks*** with no additional treatment during at least the first 12 weeks. Subjects attended clinic visits at Week 28, 36, 48, 60, and 72.

During the screening period, subjects underwent eligibility assessments. Eligible subjects who met study entry criteria were randomly assigned to the double-masked treatment phase in a 1:1 ratio to receive a starting dose of 10 mg/kg of teprotumumab or placebo once every 3 weeks (q3W) intravenously. At Week 3, the dose was escalated to 20 mg/kg IV q3W. Following dose escalation, subjects continued at this dose level for all subsequent infusions. In the case of an intolerable adverse event (AE), subjects were to be withdrawn from the study.

During the 24-week active treatment period, subjects were evaluated at clinic visits every 3 weeks and, if appropriate, by telephone contact by research staff.

Measurements for efficacy, tolerability, safety, biomarkers, and pharmacokinetics were performed according to the assessment schedule.¹⁴⁰

B.2.4.1.2 Populations analysed

Five analysis populations were defined for this study (Table 13). The Enrolled Population included all subjects enrolled in the study. The ITT Population included all subjects who were randomised to treatment and received at least 1 dose of

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medication (either teprotumumab or placebo). The ITT Population was the primary population used for efficacy analyses. The mITT Population included all ITT subjects who had at least 1 postbaseline measurement of primary efficacy. The mITT Population was used to evaluate the sensitivity of the primary efficacy analysis. The PP Population included all mITT subjects who completed the treatment and did not incur any major protocol violation that could challenge the validity of their data. The PP Population was used to evaluate the sensitivity of the primary efficacy analysis and selected secondary analyses. The Safety Population included all subjects who were dosed with any study drug (teprotumumab or placebo). The Safety Population was used for all safety analyses.

A total of 88 subjects were enrolled in the phase 2 study, of which [REDACTED] were included in the Intent-to-Treat (ITT), modified ITT (mITT), and Safety Populations. One subject was randomised but never took study drug and thus was excluded from all analysis populations. [REDACTED] of [REDACTED] subjects were included in the Per Protocol (PP) Population (Table 13). Of the [REDACTED] subjects excluded from the PP Population, [REDACTED] received the wrong treatment for at least 1 infusion and were analysed under the first treatment actually received for the Safety Population. Overall, the most common type of protocol deviation that excluded a subject from the PP population was related to study drug administration (n [REDACTED]), followed by deviation from exclusion criteria (n [REDACTED]).¹⁴⁰

Table 13: Disposition of analysis sets in Phase 2 trial

Analysis set	Placebo N=45 n (%)	Teprotumumab N=42 n (%)	All participants N=87 n (%)
Enrolled	-	-	88
ITT Population	[REDACTED]	[REDACTED]	[REDACTED]
mITT	[REDACTED]	[REDACTED]	[REDACTED]
PP	[REDACTED]	[REDACTED]	[REDACTED]
Safety	[REDACTED]	[REDACTED]	[REDACTED]

Source: Amgen (2018).¹⁴⁰

B.2.4.1.3 Statistical methodology

Descriptive summaries were provided by treatment group. All statistical tests were 2-sided and were performed at the 5% significance level except where otherwise Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

noted. Baseline characteristics and safety tables were presented for the Safety Population unless otherwise specified. Efficacy tables were presented for the ITT Population. Baseline was defined as the last pre-dose measurement unless otherwise specified. Change from baseline was the measurement at each time point minus baseline. Continuous endpoint summaries included the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical endpoint summaries included the frequency and percentage of subjects in each category. In general, the denominator for the percentage calculation was based upon the total number of subjects in the study population for each treatment, unless otherwise specified. All analyses were performed using SAS® Software, Version 9.3.

To control for overall Type 1 error, the primary and secondary endpoints were tested in a hierarchical stepwise fashion, comparing teprotumumab versus placebo. If the primary efficacy analysis achieved significance at the 0.05 alpha level, then the secondary endpoints were evaluated for significance at the same level in the following order 1) GO-QOL - overall score; 2) proptosis; 3) CAS; 4) GO-QOL - visual functioning score; and 5) GO-QOL - appearance score. Testing was to continue in numbered order until the first nonsignificant p-value was encountered, at which time formal statistical testing would cease.¹⁴¹

B.2.4.2 Phase 3 OPTIC trial

B.2.4.2.1 Analysis timepoints

Subjects were screened for the OPTIC study within 2 to 6 weeks prior to the Baseline (Day 1) Visit. Subjects who met the eligibility criteria were randomised on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive 8 infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo. All subjects entered a 24-week double-blind treatment period, during which study drug was infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 (with a final visit at Week 24).

At the end of the double-blind treatment period (Week 24), subjects who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter an open-label extension (OLE) study (OPTIC-X). Proptosis responders, as well as non-responders who chose not to enrol in the OLE study, entered a follow-up period, during which study drug was not administered. Clinic visits were scheduled for Weeks 28, 36, 48, 60 and 72 (Months 7, 9, 12, 15 and 18) during the follow-up period. Subjects who were responders at Week 24 but who met the re-treatment criteria due to a relapse during the follow-up period could also enrol in the OLE study.

Subjects who completed the Week 72 Visit were contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED had been received since last study contact. If yes, the subject was questioned regarding type of treatment and outcome/response. The treatment-free follow-up period was completed with final study contact (Week 120) or earlier if the subject withdrew prematurely.¹³⁹

B.2.4.2.2 Populations analysed

Five analysis populations were used in the OPTIC study (Table 14). The ITT Population was used for all analyses of efficacy endpoints and included all subjects randomised to treatment. The modified Intent-to-Treat (mITT) Population (consisting of all ITT subjects who received at least 1 dose of study drug and had at least 1 post-baseline proptosis measurement) and the Per Protocol (PP) Population (all mITT subjects who completed the 24-week double-blind treatment period and did not incur any major protocol violations that would have challenged the validity of their data) were used to evaluate sensitivity of the primary efficacy analysis.

The Safety Population was used for all analyses of safety endpoints and included all subjects who received at least 1 dose of study drug. The PK Population included all subjects who received at least 1 dose of study drug and had at least 1 quantifiable PK serum concentration measurement.¹³⁹

Table 14: Disposition of analysis sets in OPTIC trial

Analysis set	Placebo N= n (%)	Teprotumumab N= n (%)	All participants N=83 n (%)

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ITT	42	41	83 (100%)
mITT	██████████	██████████	██████████
PP	██████████	██████████	██████████
Safety	██████████	██████████	██████████
PK	██████████	██████████	██████████

Source: Amgen (2019).¹³⁹

The mITT Population excluded ██████████ teprotumumab subject, who was prematurely discontinued from the study after receiving his first dose of study drug due to a TEAE and did not have a post-dose assessment of proptosis. The PP Population included ██████████ placebo and ██████████ teprotumumab subjects. Reasons that led to the exclusion of subjects from the PP Population (subjects could have more than 1 reason for exclusion) included Week 24 assessment conducted outside the visit window (██████████ placebo and ██████████ teprotumumab), did not complete treatment (██████████ placebo and ██████████ teprotumumab), receipt of prohibited medications (██████████ teprotumumab), Baseline and Week 24 Hertel measurements performed by different assessors (██████████ placebo and ██████████ teprotumumab), randomisation >9 months from time of TED symptoms onset (██████████ placebo and ██████████ teprotumumab), and subject underwent restricted surgical procedure (██████████ placebo).¹³⁹

B.2.4.2.3 Statistical methodology

B.2.4.3 Statistical information

A summary of statistical information for the Phase 2 and OPTIC RCTs is provided in Table 15 below:

Table 15: Statistical summary for the Phase 2 and OPTIC trials^{138, 142}

Trial no. (acronym)	Phase 2	OPTIC
Hypothesis objective	The primary objective was to investigate the efficacy, safety, and tolerability of teprotumumab administered every 3 weeks for 6 months, in comparison to placebo, in the treatment of subjects suffering from active TED.	The overall objective of the study was to investigate the efficacy, tolerability and safety of teprotumumab (HZN-001), administered every 3 weeks (q3W) for 24 weeks, in comparison to placebo, in the treatment of subjects with moderate-to-severe active TED. The null hypothesis tested for the primary efficacy endpoint was that teprotumumab and placebo achieved equal proportions of proptosis responders at Week 24. The corresponding alternative hypothesis was that teprotumumab achieved an unequal proportion of proptosis responders at Week 24 compared to placebo. The primary efficacy endpoint was achieved if the null hypothesis was rejected at the 0.05 alpha level in favour of teprotumumab.
Statistical analysis – efficacy analysis	To control for overall Type 1 error, the primary and secondary endpoints were tested in a hierarchical stepwise fashion, comparing teprotumumab versus placebo. If the primary efficacy analysis achieved significance at the 0.05 alpha level, then the secondary endpoints were evaluated for significance at the same level in the following order 1) GO-QOL - overall score; 2) Proptosis; 3) CAS; 4) GO-QOL - visual functioning score; and 5) GO-QOL- appearance score. Testing was to continue in numbered order until the first nonsignificant p-value was encountered, at which time formal statistical testing would cease.	For prespecified primary and secondary outcome measures, teprotumumab was tested against placebo at the 0.05 significance level only if the test statistic was statistically significantly in favour of teprotumumab for the outcome measure preceding it in the hierarchical order. Main analyses were performed on the study eye when appropriate.
Statistical analysis – primary efficacy analysis	The primary result of the primary endpoint was based on the ITT Population using a logistic regression model with treatment group as the model effect and smoking status as a covariate. The same analysis was performed using the mITT Population (if different from the ITT Population) and the PP Population to evaluate sensitivity.	The primary analysis of the proptosis responder endpoint 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 randomisation, tobacco use (non-user, user). Estimates from the 2 strata were combined using Cochran-Mantel-Haenszel 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.

Trial no. (acronym)	Phase 2	OPTIC
		The primary efficacy analysis was repeated for the mITT and PP Populations as sensitivity analyses. 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. 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). Sensitivity analyses were conducted using the primary analysis method to evaluate the impact of missing data. Time to proptosis response was characterised by Kaplan-Meier estimates and the treatment group difference was assessed by the log-rank test stratified by tobacco use status (non-user, user)
Statistical analysis – secondary efficacy analysis	The secondary efficacy endpoints included quality of life scores (GO-QOL), proptosis, and CAS. For each secondary endpoint, a repeated-measures mixed model (MMRM) was fit to the individual change from baseline scores, incorporating the baseline score, smoking status, treatment group, time, time by treatment, and time by baseline score interaction.	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. Secondary efficacy endpoints of change in proptosis and change in GO-QoL transformed overall score were analysed with a 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 unstructured variance covariance matrix was used.
Sample size, power calculation	Planned enrolment for the study was approximately 84 subjects (42 per treatment group). 88 subjects were enrolled. All statistical tests were 2-sided and were performed at the 5% significance level except where otherwise noted.	Planned enrolment for the study was 76 subjects (38 per treatment group). All statistical tests were 2-sided and were performed at the 5% significance level except where otherwise noted.
Data management, patient withdrawals	Subjects who dropped out of the study were encouraged to return at 24 weeks for an evaluation, which was used in the ITT analysis. Dropout subjects who did not return for the Week 24 assessment, or subjects missing the Week 24 evaluation, were considered treatment failures for the primary efficacy analysis.	Subjects missing the Week 24 evaluation were considered treatment failures (non-responders) for the primary analysis. Further, subjects who prematurely discontinued study drug dosing prior to Week 21 during the double-blind treatment period were analysed as treatment failures (non-responders), unless an assessment at Week 24 was available.

Abbreviations: CAS, clinical activity score; Graves' ophthalmopathy quality of life; GO-QOL, ITT, intention to treat; MMRM, mixed model for repeated measures.

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B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment results for the teprotumumab RCTs included in pooled analysis and economic model are described in Table 16.

Table 16: Quality assessment results for RCTs

	Phase 2	Phase 3 OPTIC
Was randomisation carried out appropriately?	Yes. Trial subjects were randomly assigned in the double-blinded intervention phase to either of the two intervention groups in a 1:1 ratio in blocks of two, stratified within each clinical centre according to smoking status using an interactive Web-response system.	Yes. Trial subjects were randomly assigned in a 1:1 ratio to receive IV infusions of either teprotumumab or placebo.
Was the concealment of treatment allocation adequate?	Yes. An interactive Web-response system was used to allocate trial subjects to treatment.	Yes. Randomisation was performed with the use of an interactive Web-response system, administered by Bioclinica eClinical Solutions, a contract research organisation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, the baseline demographic and disease characteristics were similar and mostly well-balanced between treatment arms. Trial participants were stratified by smoking status, a known risk factor for TED. However, there were more smokers in the placebo group than the teprotumumab group, resulting in an imbalance between treatment groups. The potential imbalance in smoking status was adjusted for by including smoking as a covariate.	Yes, the baseline demographic and disease characteristics were similar and mostly well-balanced between treatment arms. Trial participant randomisation was stratified by tobacco use status at Baseline, with similar proportions of subjects in the placebo and teprotumumab groups in the user and non-user strata.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The study subjects and study investigators were blind to treatment allocation. Study pharmacists who were aware of the trial-group assignments prepared the masked/blinded infusion. The on-site principal investigators of the study could identify the participant's intervention only in the case of an emergency.	Yes. The study participants, investigators and trial-site personnel (excluding the formulating pharmacists) were unaware of the trial-group assignments and remained unaware through the follow-up data analysis and completion of the trial-site close-out visit.

	Phase 2	Phase 3 OPTIC
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances in drop-outs.	There were no unexpected imbalances in drop-outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of evaluating the efficacy and safety of teprotumumab and placebo as a treatment for TED.	No. All outcomes were related to the clinical goals of evaluating the efficacy and safety of teprotumumab and placebo as a treatment for TED.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An intention-to-treat (ITT) analysis was included. The ITT population, which included all randomly-assigned participants who received at least one infusion, was used to analyse the primary and secondary efficacy outcomes. The safety population, which included all participants who received either placebo or teprotumumab, was used for all safety analyses. Methods used to account for missing data were appropriate.	An ITT analysis was included. The ITT population, which included all randomly-assigned participants who received at least one infusion, was used to analyse the primary and secondary efficacy outcomes. The safety population, which included all participants who received either placebo or teprotumumab, was used for all safety analyses. Methods used to account for missing data were appropriate.

Abbreviations: ITT, intention to treat; TED, RCT, randomised control trial; thyroid eye disease.

B.2.5.1 Qualitative evidence synthesis

There were five studies identified that reported data for teprotumumab. These were all carried out by one group and progress from single arm, to increasing phases of RCT. The initial single arm study found that teprotumumab reduced proptosis in a series of patients with non-inflammatory TED. A phase 2 RCT (Smith *et al.* 2017) found that in patients with active ophthalmopathy, teprotumumab was more effective than placebo in reducing proptosis and the CAS.

The subsequent phase 3 RCT (OPTIC, Douglas *et al.* 2020) reported that among patients with active TED, teprotumumab resulted in better outcomes with respect to proptosis, CAS, diplopia, and quality of life vs placebo. Another phase 3 RCT (OPTIC-X, Douglas *et al.*, 2022) evaluated safety and efficacy in patients who were non-responsive or who experienced a disease flare. This study showed that patients with TED of longer disease duration responded similarly to those treated earlier in the disease course, suggesting that patients with an insufficient initial response or

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flare may benefit from additional teprotumumab therapy. No new safety risk was identified.

The aim of the phase 4 RCT was to determine the efficacy and safety of teprotumumab in patients with low disease activity and long disease duration. Patients treated with teprotumumab had a significantly greater reduction in proptosis vs the placebo group but, as noted previously, this population falls outside of the expected UK licence indication for teprotumumab and is not relevant to the present decision problem.

A risk of bias assessment was carried out for all 56 studies included in the clinical SLR according to Version 2 of the Cochrane risk-of-bias tool for randomised trials can be found in Appendix D. None of the studies in which teprotumumab was the intervention was found to be at a high risk of bias. Both RCTs were considered to be at low risk of bias in terms of the randomisation process, deviation from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result.

B.2.5.2 Strengths and limitations of the evidence

The clinical SLR had many strengths. Firstly, a robust methodology was followed in accordance with NICE and PRISMA standards. A comprehensive database search strategy capturing relevant publications was utilised in addition to grey literature searches and key congress reviews. Unlike other SLRs in this indication, the searches were not restricted to one intervention or intervention class. Finally, gaps, inconsistencies, and trends in the literature were identified.

Despite these strengths, findings should be interpreted with caution due to limitations. First, timeframe restrictions were applied (i.e., extraction of studies published between 2013 and 2024). Additionally, there was variance in the way key outcomes, such as overall response and CAS response, were defined. Among clinical studies, there were limited head-to-head trials comparing interventions of interest, and statistical or sensitivity analyses were not performed among teprotumumab and other interventions. This limits comparability of intervention effects on outcomes of interest. Reports on TED subpopulations, such as chronic and inflammatory TED, were limited, and definitions of those populations

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inconsistent, presenting a gap in understanding of intervention effects in these subpopulations of interest. Finally, the SLR was limited to English-language publications. While this is generally considered acceptable (most key clinical and RWE studies are published in English-language journals) a risk of bias is possible, as is a risk of possible exclusion of relevant studies.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Phase 2 study (NCT01868997)

The phase 2 trial of teprotumumab demonstrated clinical benefits of teprotumumab in patients with acute, moderate-to-severe thyroid-associated ophthalmopathy by reducing proptosis and the CAS and by improving the patients' QoL during the 24-week treatment phase.⁴⁹

B.2.6.1.1 Primary efficacy outcome

The phase 2 trial demonstrated a 3.5-fold increase in patients responding (i.e., achieving the composite endpoints of ≥ 2 points reduction in CAS and ≥ 2 mm reduction in proptosis) in the teprotumumab arm compared to the placebo arm at Week 24 (69% with teprotumumab vs 20% with placebo [adjusted odds ratio, 8.86; $p < 0.001$]).⁴⁹ The study showed early and consistent efficacy of teprotumumab over placebo, with a greater proportion of patients responding in the teprotumumab group than in the placebo group from Week 6 through the study treatment phase ($p < 0.001$ at each time point).⁴⁹ This clinical benefit was also observed in an extended analysis at week 28 by Kahaly et al. where 31 of 42 (74%) teprotumumab-treated and six of 45 (13%) placebo-treated patients reached response ($p < 0.001$).¹⁴³

The teprotumumab group had a significantly shorter time to the first response than the placebo group with the mean time to first response of 11.2 weeks (standard deviation [SD]: ± 6.6) vs 18.7 weeks (SD: ± 7.6) for teprotumumab vs placebo ($p < 0.001$). In terms of response level, more patients in the teprotumumab group had ≥ 3 points reduction in CAS and ≥ 3 mm reduction in proptosis than the placebo group (50% vs 9% averagely over all visit time points up to Week 24) ($p < 0.001$).⁴⁹

As presented in Table 17, the non-study eye also showed consistent effect in overall responder rate with that seen in the study eye.^{49, 144}

Table 17: Overall Response Rate in Study and Non-study Eye (ITT Population) – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)	Difference (95% CI)^a
Response in study eye – no. of patients (%)			
Week 6	18 (42.9)	2 (4.4)	40.0 (24.2-56.3)
Week 12	23 (54.8)	2 (4.4)	49.0 (32.4-65.6)
Week 18	30 (71.4)	2 (4.4)	65.8 (50.2-81.3)
Week 24	29 (69.1)	9 (20.0)	48.9 (30.2-67.6)
Response in non-study eye – no. of patients (%)			
Week 6	8 (19.1)	2 (4.4)	14.7 (1.3-28.1)
Week 12	13 (31.0)	1 (2.2)	29.6 (14.6-44.6)
Week 18	17 (40.5)	1 (2.2)	38.4 (22.7-54.1)
Week 24	22 (52.4)	6 (13.3)	38.9 (20.6-57.3)

^a Difference and its corresponding 95% CI is based on a weighted average of the difference within each randomization stratum (tobacco user, tobacco non-use) using Cochran–Mantel–Haenszel weights.

Abbreviation: CI, confidence interval; CMH, ITT, intention-to-treat

Source: Smith *et al.* (2017), U.S. FDA (2024).^{49, 144}

B.2.6.1.2 Secondary efficacy outcomes

Table 18 presents the results of secondary efficacy endpoints in the ITT population. Patients who received teprotumumab had reductions in proptosis, the CAS, and subjective diplopia that were clinically meaningful and statistically significant compared to patients who received placebo ($p \leq 0.001$ for all comparisons with placebo).⁴⁹

Table 18: Results of Secondary Efficacy Endpoints (ITT Population) – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)	P-Value
Proptosis (mm) – means (SE)			
Baseline	23.38 (3.16)	23.10 (2.93)	
Change from baseline over all post-baseline time points up to week 24 ^a	-2.46 (0.20)	-0.15 (0.19)	<0.001
Clinical Activity Score – means (SD)^b			
Baseline	5.1 (0.97)	5.2 (0.74)	

Change from baseline over all post-baseline time points up to week 24 ^a	-3.43 (0.18)	-1.85 (0.17)	<0.001
Subjective diplopia^c			
Baseline diplopia according to grade – no. of patients (%)			
No diplopia	4 (10)	14 (31)	
Intermittent	16 (38)	19 (42)	
Inconstant	7 (17)	8 (18)	
Constant	15 (35)	4 (9)	
Odds Ratio (95% CI): 3.78 (1.68-8.54) ^d			0.001
Week 24 diplopia according to grade – no. of patients (%)			
No diplopia	21 (50)	18 (40)	
Intermittent	4 (10)	8 (18)	
Inconstant	9 (21)	7 (16)	
Constant	4 (10)	6 (13)	
Response	26/38 (68)	10/39 (26)	<0.001

^a Secondary endpoints were analysed with the use of a mixed model of repeated measurements with smoking as a covariate. Any apparent discrepancies between the tabulated mixed model of repeated-measurements calculations for change from baseline and data plotted are because tabulated data are an average difference between the trial groups over all post-baseline time points up to Week 24. Values plotted in the are calculations of the mean change from baseline for specific time points.

^b The CAS comprised 7 components. Scores range from 0 to 7, and a change of 2 points is considered clinically relevant

^c Subjective diplopia was assessed on the basis of 4 grades, and a change of 1 grade or more is considered to be clinically relevant. A response in patients with diplopia was defined as a decrease of 1 grade or more. The chi-square test was used to compare data from patients who had a response with data from those who did not at Week 24.

^d The estimated odds ratio shown was calculated with the use of logistic regression for cumulative logits. This imbalance should be viewed in light of the large number of characteristics assessed at baseline. A sensitivity post hoc logistic-regression analysis of the week 24 response, which included adjustment for baseline smoking status, sex, study eye, and diplopia, did not show a substantial difference from the primary analysis (adjusted odds ratio, 8.16; $p < 0.001$).

Abbreviation: CI, confidence interval; ITT, intention-to-treat; SD, standard deviation; SE, standard error

Source: Smith *et al.* (2017).⁴⁹

Reduction in proptosis

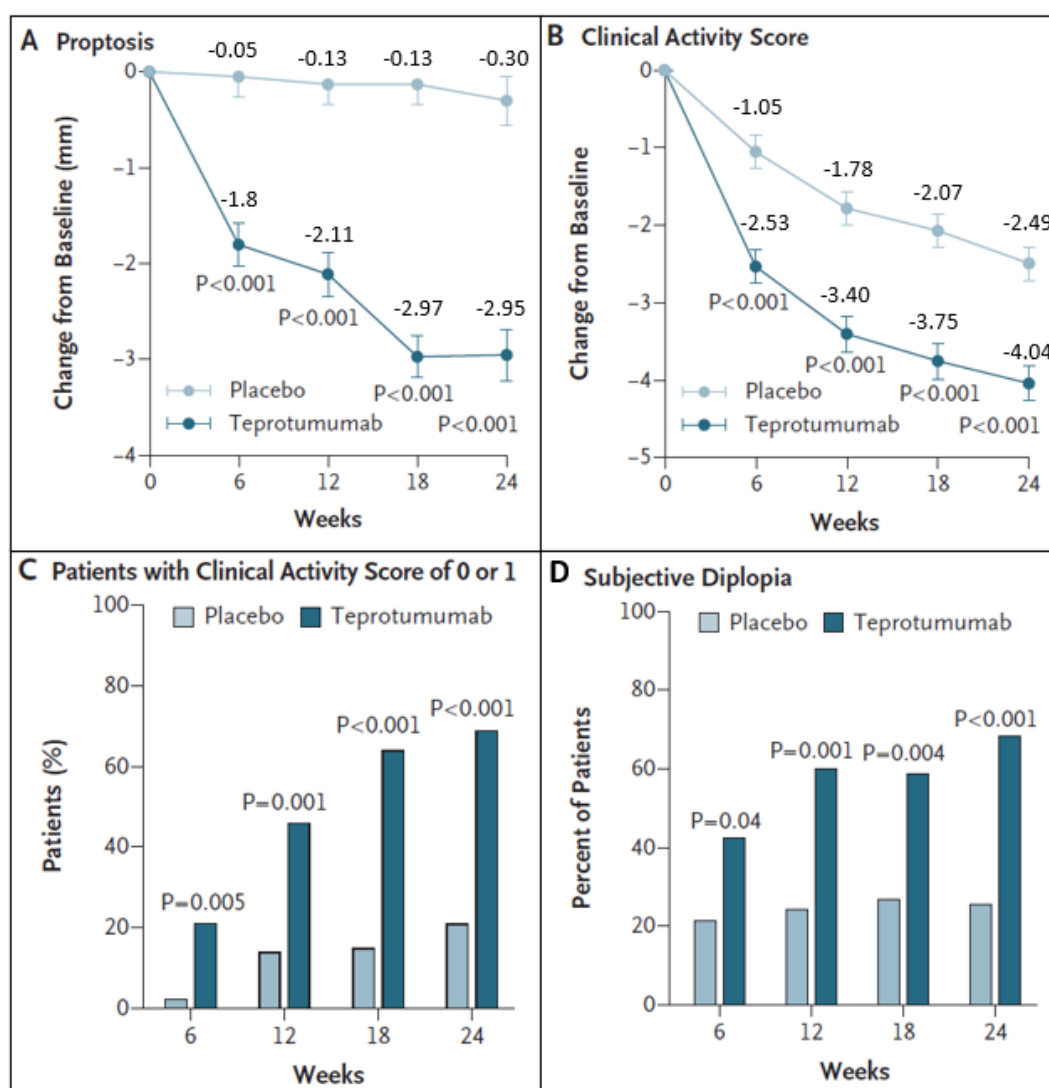
Figure 12A illustrates that, at Weeks 6, 12, 18, and 24, patients treated with teprotumumab experienced a significantly greater reduction in proptosis from baseline compared to those on placebo ($p < 0.001$ for all comparisons).⁴⁹ The mean reduction in proptosis from Baseline to Week 24 was 2.95 mm (standard error [SE]: ± 0.27) in teprotumumab group compared to 0.3 (SE: ± 0.26) (between-group difference: 2.95 mm; 95% CI: 1.92-3.38; $p < 0.001$).^{144, 145}

Early clinical benefit of teprotumumab for improving proptosis was found, with approximately 50% of teprotumumab-treated patients achieving the proptosis Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

response (≥ 2 mm reduction) at Week 6 ($p < 0.001$), while only 9% of patients had response in the placebo group (Figure 13). By Week 24, 71.4% (30/42) of teprotumumab-treated and 20% (9/45) of placebo-treated patients achieved the proptosis response ($p < 0.001$).¹⁴⁵ Table 19 details proptosis response results graded by the reduction in mm. At 24 weeks, 54.8% of teprotumumab-treated patients achieved a high response (≥ 3 mm reduction) compared to 8.9% of placebo-treated; 0% of teprotumumab-treated had no response versus 48.9% of placebo-treated.¹⁴⁵

An extended analysis by Kahaly et al found that, at Week 28, 55% of teprotumumab recipients had a high proptosis response (≥ 3 mm decrease).¹⁴³

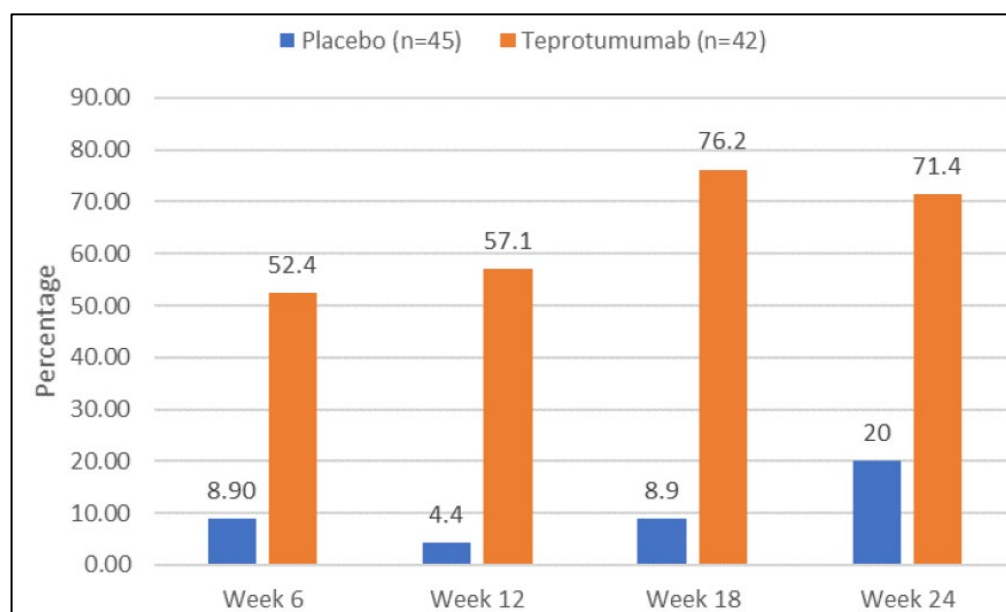
Figure 12: Secondary Efficacy Assessment from Week 0 to Week 24 – Phase 2



Panel A shows the change in proptosis from baseline. Panel B shows the change in the CAS from baseline. Panel C shows the results of the post hoc analysis of the percentage of patients with a CAS of 0 or 1 through week 24. Panel D shows the response with respect to subjective diplopia. In this assessment, patients are categorised according to four grades, and a response in patients with diplopia was defined as a decrease of one grade or more. In Panels A and B, means $\pm$ SE are shown, and p-values were calculated with the use of a mixed model of repeated-measurements analysis involving the ITT population (45 patients in the placebo group and 42 patients in the teprotumumab group). P values shown in Panels C and D were calculated with the use of the chi-square test comparing data from patients who had a response with data from those who did not.

Source: Smith *et al.* (2017).⁴⁹

Figure 13: Proptosis Responders (Percent of Patients with a Decrease ≥ 2 mm from Baseline) – Phase 2



p<0.001 for comparisons at all time-points
Source: U.S. FDA (2024), Douglas *et al.* (2019).^{144, 145}

Table 19: Proptosis Graded Response at Week 24 – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)
Graded response – no. of patients (%)^a		
High response	23 (54.8)	4 (8.9)
≥ 4 mm reduction	17 (40.5)	0 (0)
Response	7 (16.7)	5 (11.1)
Low response	8 (19)	8 (17.8)
No response	0 (0)	22 (48.9)
Missing	4 (9.5)	6 (13.3)

^a A high response indicates a reduction in proptosis of ≥ 3 mm from baseline. A response indicates a reduction in proptosis of 2 to <3 mm from baseline. A low response indicates a reduction in proptosis of 1 to <2 mm from baseline. No response indicates a reduction in proptosis of <1 mm from baseline
Source: Smith *et al.* (2017), Douglas *et al.* (2019).^{49, 145}

Reduction in the CAS

Significant reductions in the CAS were observed at Weeks 6, 12, 18, and 24 in the teprotumumab group compared to the placebo group ($p < 0.001$ for all comparisons), even though the placebo group also showed a progressive decline in CAS (Figure 12).⁴⁹ The teprotumumab group started with a Baseline CAS of 5.1 points (SD: ± 0.97) and achieved a mean reduction of 3.43 points (SD: ± 0.18) vs. a reduction of 1.85 (SD: ± 0.17) in the placebo group, averaged over all post-Baseline time points up to Week 24. This result indicates near-maximal therapeutic effects for some patients treated by teprotumumab. In a post hoc analysis focusing on patients with a CAS of 0 or 1, 69% of those receiving teprotumumab reached a CAS of 0 or 1 at Week 24, compared to 21% in the placebo group (adjusted OR, 8.97; $p < 0.001$) (Figure 12C).⁴⁹

By Week 28, 88% (37/42) of teprotumumab recipients and 60% (27/45) of placebo recipients achieved a ≥ 2 points reduction in CAS ($p = 0.003$).¹⁴³ The reductions in CAS with teprotumumab were comprehensive, not driven by large decreases in specific CAS components. The assessment at Week 28 showed that all individual CAS components were significantly different from placebo ($p \leq 0.04$) except for eyelid erythema ($p = 0.06$).¹⁴³

Subjective diplopia response rates

Subjective diplopia response rates were also higher in the teprotumumab group compared to the placebo group ($p \leq 0.001$ for all placebo comparisons) (Figure 12D).⁴⁹ By Week 24, there was a reduction in patients with constant diplopia (36% vs 10%) and an increase in those without diplopia (10% vs 50%) from baseline in the teprotumumab group.⁴⁹ At Week 24, a significantly higher percentage of patients in the teprotumumab group showed an improvement by ≥ 1 diplopia grade compared to the placebo group (62% vs 22%, $p < 0.001$). This improvement in diplopia grade remained significant at Week 28.¹⁴³

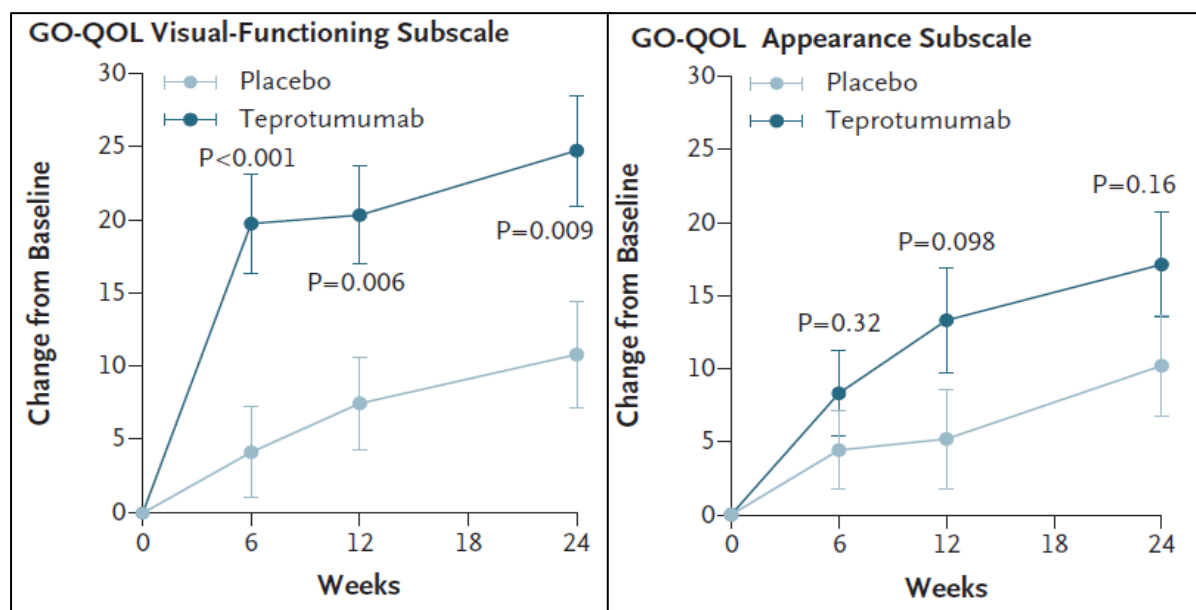
Change in GO-QOL

The phase 2 trial demonstrated that for acute, moderate-to-severe TED, teprotumumab resulted in a significant increase in the GO-QOL visual-functioning score across all time points, ranging from [REDACTED] to [REDACTED] points higher than the placebo group (Figure 14). While a consistent trend toward improvement on the GO-QOL appearance subscale was observed in the teprotumumab group, statistical Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

significance in the difference over the placebo group was not reached. However, when combining the two scales, the mean treatment difference of [REDACTED] (SE: [REDACTED]) between placebo and teprotumumab for the change from baseline in GO-QOL overall score was statistically significant at weeks 24 ($p=0.001$).⁴⁹ [REDACTED]

Figure 14: GO-QOL Scores from Week 0 to Week 24 – Phase 2

Source: Smith *et al.* (2017).⁴⁹



B.2.6.2 Phase 3 OPTIC

B.2.6.2.1 Primary efficacy outcome

The primary endpoint of the OPTIC trial was proptosis response (defined as a reduction in proptosis of ≥ 2 mm from baseline in the study eye without a corresponding increase of ≥ 2 mm in the fellow eye).⁸⁰ Overall, the teprotumumab group consistently demonstrated a higher response rate across all timepoints compared to the placebo group (Figure 15).

At Week 24, the response rate among patients receiving teprotumumab was significantly higher than those receiving placebo. A proptosis response was observed in 83% of patients in the teprotumumab group, comparing with 10% in the placebo group (between-group difference: 73 percentage points; 95% CI: 59-88; $p < 0.001$). The efficacy of teprotumumab was shown in nearly all the patients who

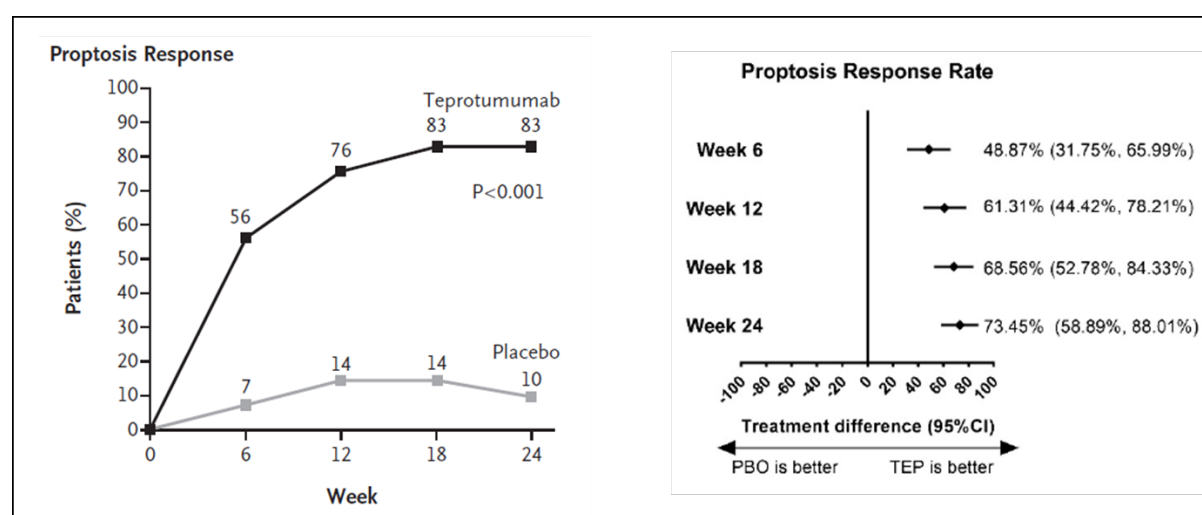
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received the treatment, regardless of the initial severity of proptosis. Notably, over 50% of teprotumumab-treated patients showed a response by Week 6, indicating an early effect of teprotumumab in improving proptosis by at least two mm.⁸⁰

In addition, among the patients in the teprotumumab group, the least squares (LS) mean change in proptosis at week 24 (-3.32 mm) is similar to the best results attained with single-wall orbital decompression surgery.⁸⁰

At Week 72 (48 weeks off-treatment follow-up), [REDACTED] of teprotumumab-treated patients maintained response.¹⁴²

Figure 15: Results of Primary Efficacy Endpoint – OPTIC



The p-value for the between-group differences at week 24 was adjusted for multiplicity.
Abbreviations: CI, confidence interval; PBO, placebo; TEP, teprotumumab
Source: Douglas *et al.* (2020).⁸⁰

B.2.6.2.2 Secondary efficacy outcomes

Overall response

Similar to the results seen in the phase 2 trial, the OPTIC study demonstrated a significantly greater proportion of patients responding to teprotumumab than to placebo. At Week 24, 78% of patients (32 out of 41) achieved an overall response in the teprotumumab group, compared to 7% in the placebo group (3 out of 42). The difference between the groups was 71 percentage points (95% CI: 56-86; $p < 0.001$) (Figure 16A).⁸⁰

The sustained overall responder rate in the teprotumumab group was [REDACTED] of [REDACTED] subjects) at Week 72.¹⁴²

Proportion of patients with a CAS of 0 or 1

The teprotumumab group also showed an increase in patients with a CAS of 0 or 1 throughout the treatment period, significantly surpassing the placebo group at all trial visits. By Week 24, 59% of teprotumumab-treated patients and 21% of placebo-treated patients reported a CAS of 0 or 1 (between-group difference: 36 percentage points; 95% CI: 17-55; $p < 0.001$) (Figure 16B).⁸⁰

At Week 72, [REDACTED]% ([REDACTED] of [REDACTED] subjects) in the teprotumumab group sustained CAS of 0 or 1.¹⁴²

Change in proptosis

The teprotumumab group consistently demonstrated a significantly greater mean change in proptosis from baseline compared to the placebo group at all time points. From Baseline through Week 24, the mean change of proptosis for teprotumumab-treated patients was -2.82 mm (SE: ± 0.19), whereas in the placebo group, the mean change was merely -0.54 mm (SE: ± 0.19) (between-group difference: -2.28 mm; 95% CI: -2.77 – -1.80 ; $p < 0.001$) (Figure 16C).⁸⁰

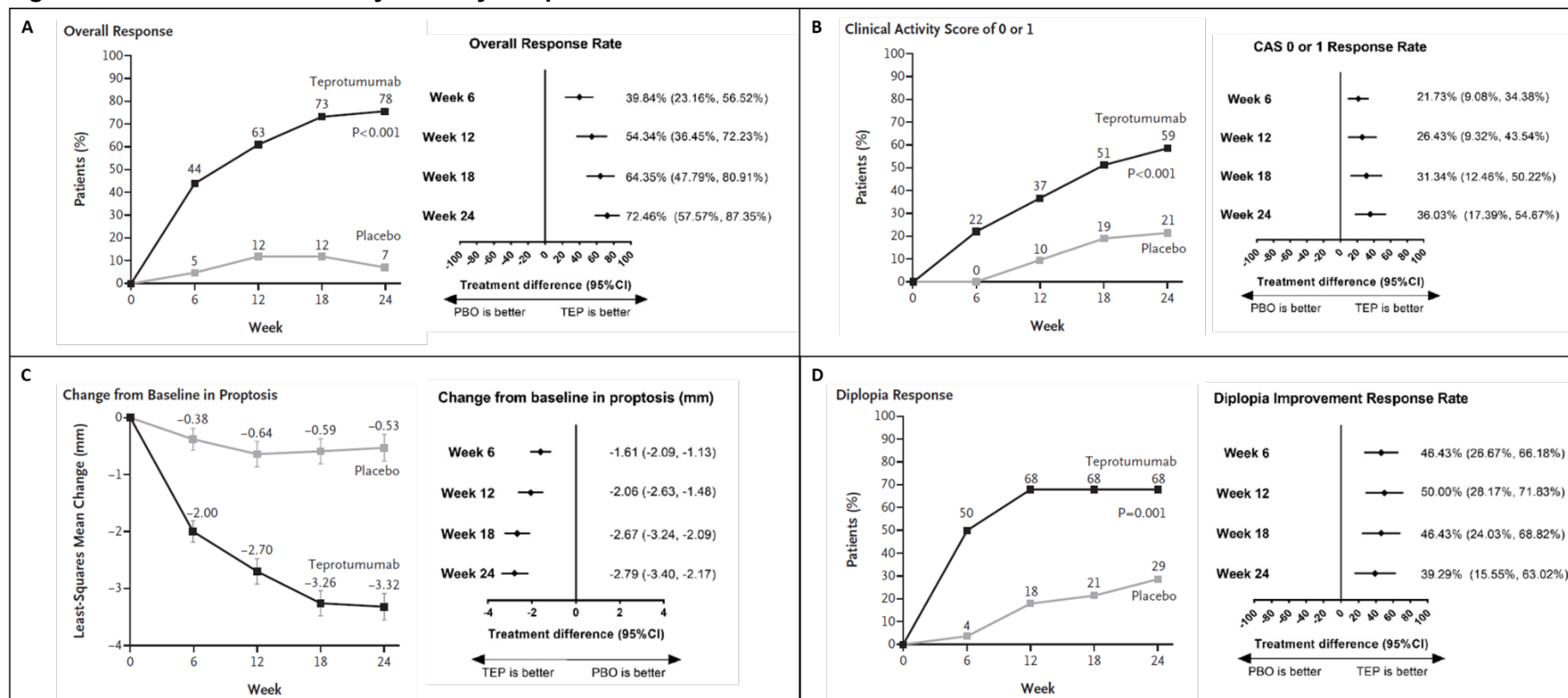
The mean decrease from baseline in proptosis in the study eye at Week 72 was [REDACTED] mm for the teprotumumab group ($n = [REDACTED]$).¹⁴²

Diplopia response

Among the 28 patients having diplopia at Baseline in each group, the teprotumumab group demonstrated a significantly higher diplopia response (reduction of ≥ 1 grade) at the first visit and subsequent visits compared to the placebo group. At Week 24, the response rate was 68% in the teprotumumab group and 29% in the placebo group, with a between-group difference of 39 percentage points (95% CI: 16-63; $p = 0.001$). In addition, a further analysis showed that the improved diplopia response with teprotumumab occurred irrespective of the baseline severity of diplopia (Figure 16D).⁸⁰

The sustained diplopia response rate in the teprotumumab group was [REDACTED]
[REDACTED]% ([REDACTED] subjects) at Week 72. ¹⁴²

Figure 16: Results of Secondary Efficacy Endpoint – OPTIC



The p-values for the between-group differences at week 24 (Panels A, B, and D) were adjusted for multiplicity.

The mean changes in proptosis measurement from baseline to each visit were significantly better in the teprotumumab group

Abbreviations: CI, confidence interval; PBO, placebo; TEP, teprotumumab

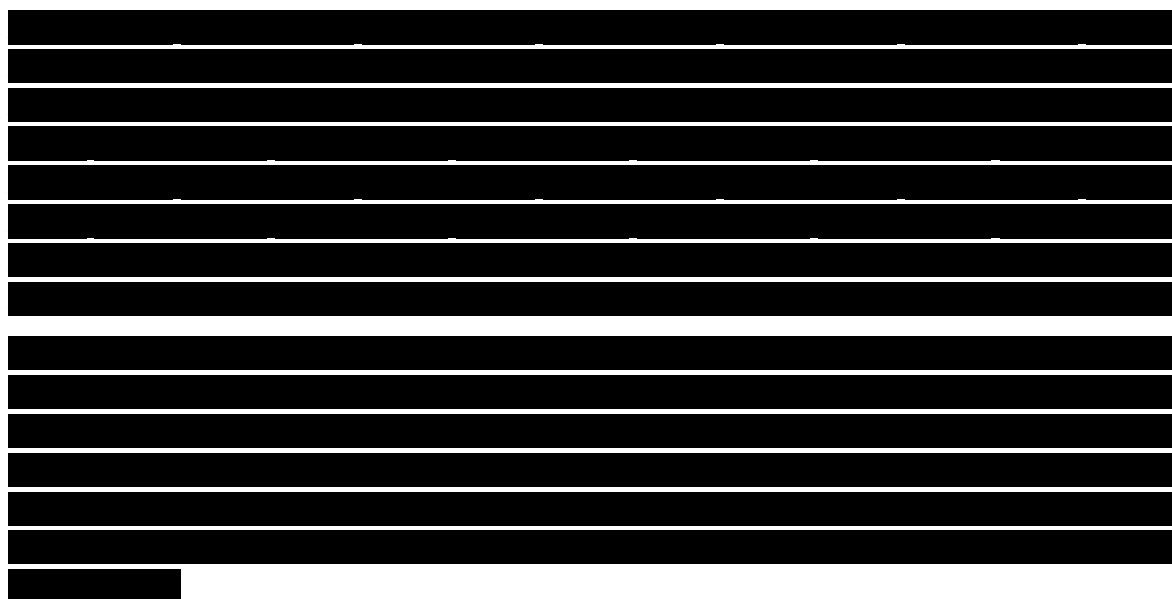
Source: Douglas *et al.* (2020).⁸⁰

Change in GO-QOL

During the trial, patients who received teprotumumab had a better overall score on the GO-QOL compared to those who received placebo. The mean change in GO-QOL overall score was 13.79 points (SE: ± 2.07) with teprotumumab vs. 4.43 points (SE: ± 2.10) with placebo ($p < 0.001$). The difference between the two groups was statistically significant at any visit, except for Week 6 (Figure 17).⁸⁰

Scores on the visual and appearance subscales were also significantly better with teprotumumab than with placebo at Week 24. The LS mean change at Week 24 in the scores on the visual functioning and appearance subscales were 15 points and 19 points (both $p \leq 0.05$), respectively, in the teprotumumab group, and 3 points and less than 1 point, respectively, in the placebo group.¹³⁹

Figure 17: GO-QOL Scores from Week 0 to Week 24 – OPTIC



* $p \leq 0.010$; ** $p \leq 0.05$

Abbreviations: CI, confidence interval; GO-QOL, Graves' ophthalmopathy-specific quality-of-life; PBO, placebo; TEP, teprotumumab

Source: Douglas *et al.* (2020), Amgen (2019).^{80, 139}

A summary of the primary and secondary efficacy outcomes from OPTIC is presented at Table 20.

Table 20: Summary of primary and secondary efficacy outcomes (ITT Population) – OPTIC

	Teprotumumab (n=41)	Placebo (n=42)	Difference (95% CI)	P value
Primary outcome of proptosis response at wk 24				
In the ITT population - % of patients (number/total number)	83 (34/41)	10 (4/42)	73 (59 to 88)	<0.001
In the PP population - % of patients (number/total number)	88 (29/33)	12 (4/34)	76 (61 to 92)	<0.001
Secondary outcomes in the ITT population				
Overall response at wk 24 - % of patients (number/total number)	78 (32/41)	7 (3/42)	71 (56 to 86)	<0.001
Clinical activity score of 0 or 1 at wk 24 - % of patients (number/total number)	59 (24/41)	21 (9/42)	36 (17 to 55)	<0.001
Mean change in proptosis from baseline to wk 24 - mm	-2.82±0.19	-0.54±0.19	-2.28 (-2.77 to -1.80)	<0.001
Diplopia response at wk 24 - % of patients (number/total number with diplopia at baseline)	68 (19/28)	29 (8/28)	39 (16 to 63)	0.001
Mean change in GO-QOL score from baseline at wk 24	13.79±2.07	4.43±2.10	9.36 (4.08 to 14.64)	<0.001

Abbreviation: CI, confidence interval; GO-QOL, Graves' Orbitopathy Quality of Life; ITT, intention-to-treat; mm, millimetre; wk, week
Source: Douglas *et al.* (2020).⁸⁰

B.2.6.2.3 Additional Efficacy Endpoints

The OPTIC study further conducted the orbital imaging before and after the treatment in six patients (assessed both study orbit and non-study orbit from each patient) who received teprotumumab. The results showed that the reduction in proptosis was associated with a reduction in extraocular muscle (EOM) volume, orbital fat volume, or both.^{80, 146}

All examined individual muscles in the study orbit and non-study orbit (n=12 orbits, 48 muscles) demonstrated a significant reduction in muscle volume after treatment. The mean total EOM volume within a single orbit was 4472 (SD: ±1435) mm³ before Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

the treatment and was significantly reduced to 2855 (SD: ± 576) mm³ after the treatment ($p < 0.01$). Average total EOM volume within each orbit was reduced by 33% ($p < 0.02$) at week 24.^{80, 146}

Total orbital fat volume was also reduced in 11 of 12 orbits ($p = 0.04$), with two patients having at least 40% reduction (44% and 40%, respectively).^{80, 146}

EOM motility was not assessed in the key clinical trials of teprotumumab. In an interventional cohort study with 139 TED patients (77 in the decompression group, 51 in the teprotumumab group, and 11 that underwent both procedures) found that the teprotumumab group demonstrated a significantly greater mean improvement in total restriction by 12.0 (SD: 3.4) degrees over decompression (2.6 [SD: 20.9] degrees of improvement in decompression vs. 14.7 [SD: 16.7] in teprotumumab; $p < 0.01$).¹⁴⁷

B.2.6.3 Pooled Analysis from Phase 2 and Phase 3 OPTIC

A pooled analysis examined integrated data and follow-up data from the two studies (phase 2 and phase 3 OPTIC) to assess the consistency of the results across teprotumumab clinical programs for the treatment of acute TED. The pooled analysis is presented in Section B.2.8.

B.2.7 Subgroup analysis

Participants randomised to the Phase 2 and OPTIC RCTs were stratified according to smoking status. The authors of the pooled data analysis, Kahaly *et al.* (2021), also assessed the trial data for the primary and secondary outcomes by pre-specified patient subgroups: tobacco use; age <65 years or older; sex; time to diagnosis; CAS score 4 or 5, or 6 or 7; and thyrotropin binding inhibiting immunoglobulin [TBII] concentration <10 IU/L or ≥ 10 IU/L) versus placebo.¹¹³

A summary of these results is provided in B.2.8 below as part of the pooled analysis presentation.

B.2.8 Meta-analysis

A pooled analysis examined integrated data and follow-up data from the two studies (phase 2 and phase 3 OPTIC) to assess the consistency of the results across

teprotumumab clinical programs for the treatment of acute TED. In both studies, the 24-week treatment period was conducted in randomised, placebo-controlled, double-masked, parallel-group fashion, with same dose regimen.¹¹³ Data through to week 24 were assessed in the integrated ITT population from the two trials. Follow-up data were pooled where possible.¹¹³

Table 21 presents the pre-specified integrated outcomes in the pooled analysis.

Table 21: Prespecified integrated outcomes in the pooled analysis

Endpoints	
Primary endpoint	The proportion of patients with a proptosis response (≥ 2 mm reduction from baseline in the study eye without a corresponding deterioration in the fellow eye) at week 24.
Secondary endpoints	Improvement in subjective diplopia (of ≥ 1 Bahn0Gorman grade) Overall response (reduction in proptosis of ≥ 2 mm and reduction in CAS ≥ 2 points) Disease inactivation (i.e., a CAS of 0 or 1) Mean change from baseline to week 24 in proptosis (mm) Change from baseline to week 24 in GO-QOL total score and GO-QOL visual and appearance subscales Safety
Other endpoints	Proportion of patients with significant abnormal visual exam findings (visual acuity, pupil exam, colour vision assessment, Ishihara colour plates [or equivalent] or related red desaturation, intraocular pressure, and slit lamp exam)

Abbreviation: CAS, clinical activity score; GO-QOL, Graves' ophthalmopathy-specific quality-of-life questionnaire;
Source: Kahaly *et al.* (2021).¹¹³

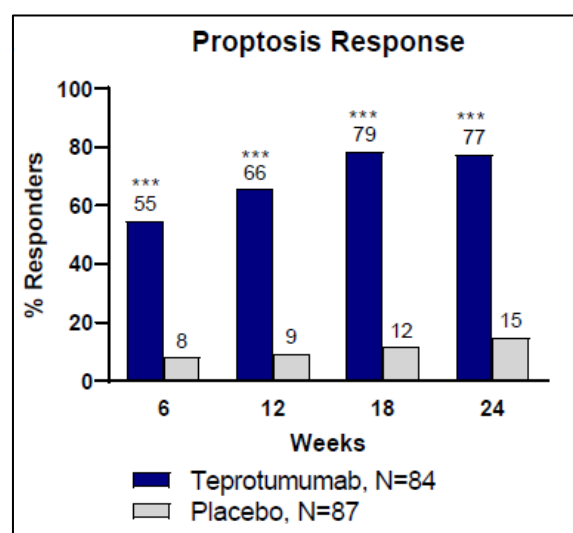
B.2.6.3.1 Primary efficacy outcome

At every visit through to Week 24, the proptosis response rate (≥ 2 mm reduction from baseline) was significantly higher with teprotumumab versus placebo. A higher percentage of patients treated with teprotumumab experienced at least a 2 mm decrease in proptosis by Week 24 compared to those receiving a placebo (77% vs 15%), with stratified treatment difference of 63% (95% CI: 51%-75%; $p < 0.0001$) (Figure 18).¹¹³

Moreover, the improvement in proptosis with teprotumumab over placebo was consistent across various subgroups, including age (under 65 vs 65 and older), gender, smoking status, time since diagnosis of TED (6.2 months or less vs more than 6.2 months), time since diagnosis of Graves' Disease (11.1 months or less vs more than 11.1 months), baseline CAS (5 or less vs 6 or more), and baseline levels

of TBII (10 IU/mL or more vs less than 10 IU/mL). The difference in response rates varied from 47% (95% CI: 21%-73%; $p=0.0015$) among smokers to 83% (95% CI: 60%-100%; $p<0.0001$) in patients aged 65 and older (Figure 18).¹¹³

Figure 18: Proptosis response over 24 weeks – Pooled Analysis



*** $p<0.0001$ for teprotumumab versus placebo

Source: Kahaly *et al.* (2021, supplemental information).¹¹³

Figure 19: Subgroup results of proptosis response – Pooled Analysis

	Placebo (n)	Teprotumumab (n)		Treatment difference (95% CI)	p value
Female	67	58		62 (48 to 76)	<0.0001
Male	20	26		69 (48 to 89)	<0.0001
Age (years)					
<65	74	71		60 (47 to 73)	<0.0001
≥65	13	13		83 (60 to 100)	<0.0001
Tobacco non-user	61	64		68 (56 to 81)	<0.0001
Tobacco user	26	20		47 (21 to 73)	0.0015
Time to diagnosis of thyroid eye disease ≤6.2 m	41	45		56 (39 to 74)	<0.0001
Time to diagnosis of thyroid eye disease >6.2 m	46	39		70 (53 to 86)	<0.0001
Time to diagnosis of Graves' disease ≤11.1 m	46	40		58 (40 to 77)	<0.0001
Time to diagnosis of Graves' disease >11.1 m	41	44		67 (52 to 83)	<0.0001
Baseline CAS ≤5	54	57		64 (50 to 79)	<0.0001
Baseline CAS ≥6	33	27		58 (35 to 80)	<0.0001
Baseline TBII ≥10 IU/L†	20	20		90 (76 to 100)	<0.0001
Baseline TBII <10 IU/L†	22	21		58 (35 to 81)	<0.0001
Overall	87	84		63 (51 to 75)	<0.0001

† Performed in phase 3 OPTIC study only

Abbreviations: CAS, Clinical Activity Score; CI, confidence interval; TBII, Thyrotropin-binding inhibitory immunoglobulins

Source: Kahaly *et al.* (2021).¹¹³

B.2.6.3.2 Secondary and other efficacy outcomes

Diplopia response

At all visits, the integrated diplopia response rate (improved diplopia by ≥ 1 grades) was significantly higher with teprotumumab versus placebo. The diplopia response

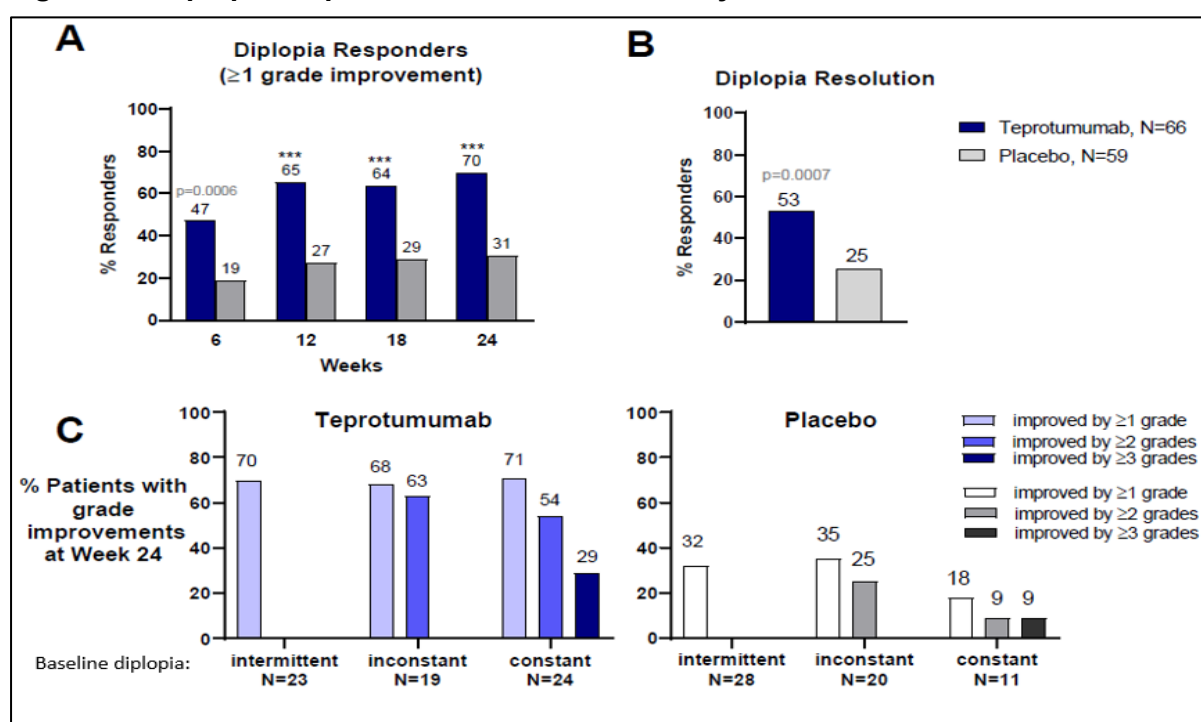
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rate was 70% (46 out of 66) with teprotumumab versus 31% (18 out of 59) with placebo at Week 24 (treatment difference: 39%, 95% CI: 23%-55%; $p<0.0001$) (Figure 20A).¹¹³

A greater proportion of patients had diplopia resolution in the teprotumumab group (53% [35 out of 66]) compared to the placebo group (25% [15 out of 59]) (treatment difference: 28%, 95% CI: 12%-44%; $p=0.0007$) at Week 24 (Figure 20B).¹¹³

Among patients who experienced diplopia at baseline, 71% (17 of 24) in the teprotumumab group showed an improvement of one or more grades in diplopia compared to 18% (2 of 11) in the placebo group by Week 24. The difference in improvement between the treatments was 47% (95% CI: 13%-80%, $p=0.0061$). All responses based on baseline grades of diplopia and number of grade improvements favoured teprotumumab over placebo (Figure 20C).¹¹³

Figure 20: Diplopia response results – Pooled Analysis



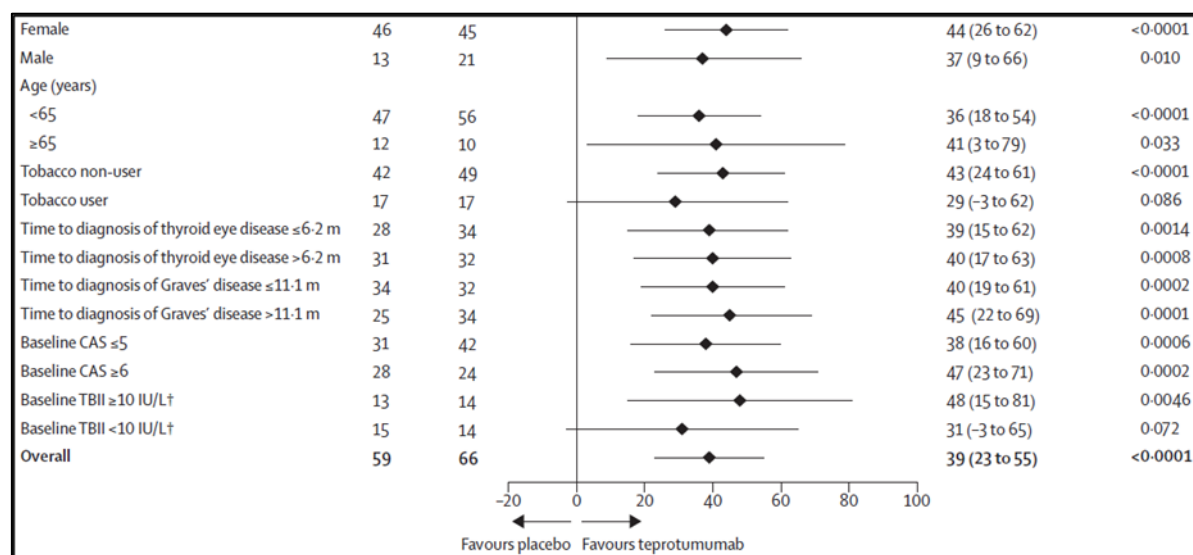
Panel A: percentage of patients with diplopia response (≥ 1 grade improvement from baseline). Panel B: percentage of patients having resolution of diplopia at week 24. Panel C: Grade 1 (intermittent), 2 (inconstant) and 3 (constant) diplopia at baseline who had ≥ 1 , ≥ 2 and ≥ 3 grades improvement

*** $p<0.0001$

Source: Kahaly *et al.* (2021).¹¹³

In each subgroup, diplopia treatment difference was greater with teprotumumab except in tobacco users (29% difference, 95% CI: -3%-62%; p=0.086) and those with TBII <10 IU/L at baseline (31% difference, 95% CI: -3%-65%; p=0.072)(Figure 21).

Figure 21: Subgroup Results of Diplopia Response – Pooled Analysis



† Done in phase 3 OPTIC study only

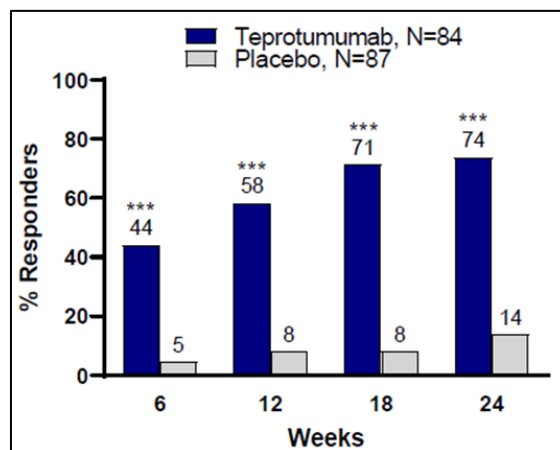
Abbreviations: CAS, Clinical Activity Score; CI, confidence interval; TBII, Thyrotropin-binding inhibitory immunoglobulins

Source: Kahaly *et al.* (2021).¹¹³

Overall response

The integrated overall response rate (≥2mm proptosis reduction and ≥2 CAS reduction) was 74% in the teprotumumab group compared to 14% in the placebo group at week 24, with a stratified treatment difference of 60% (95% CI: 48-72; p<0.001). Improved overall responses with teprotumumab versus placebo were observed at every visit through to Week 24 (Figure 22).

Figure 22: Results of Overall Response – Pooled Analysis



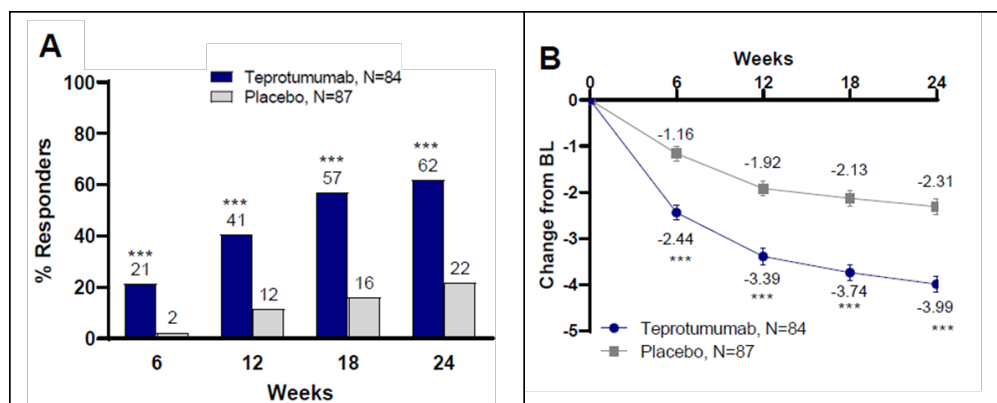
*** p<0.0001
Source: Kahaly *et al.* (2021).¹¹³

Disease inactivation (CAS of 0 or 1)

The proportion of achieving CAS of 0 or 1 was 62% in the teprotumumab group compared to 22% in the placebo group, with a stratified treatment difference of 39.85% (95% CI: 27-53; p<0.001) ¹¹³(Figure 23A).

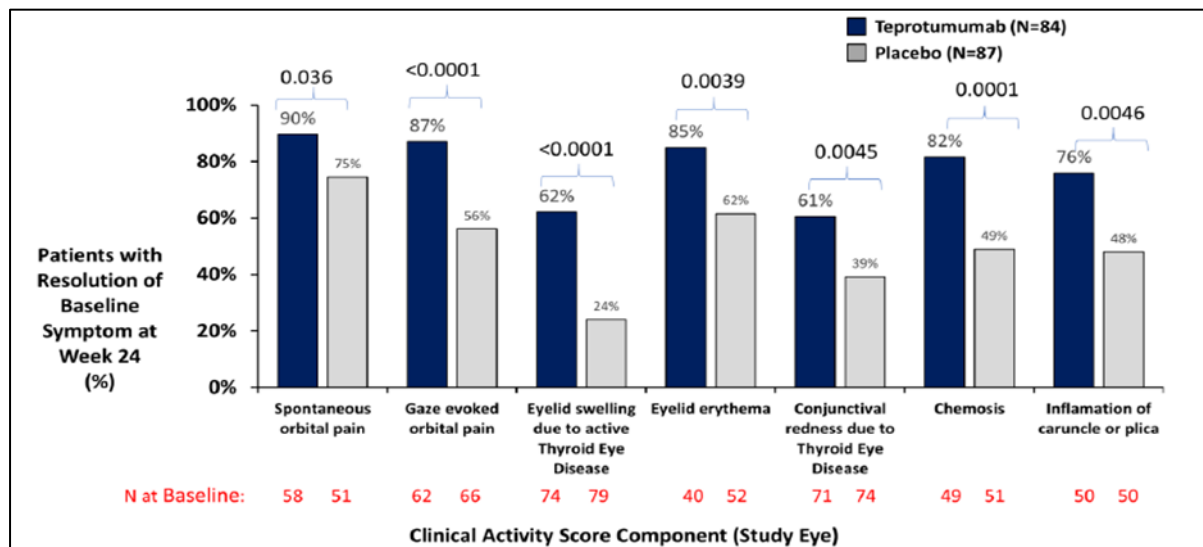
The change in CAS over time was significantly greater with teprotumumab at all timepoints (Figure 23B). At Week 24, each CAS component was resolved in a greater percentage in the teprotumumab group compared to the placebo group (Figure 24).¹¹³

Figure 23: Results of CAS Response and Improvement – Pooled Analysis



*** p<0.0001
Abbreviations: BL, baseline; CAS, Clinical Activity Score
Source: Kahaly *et al.* (2021).¹¹³

Figure 24: Percentage with Resolution of Each CAS Symptom at Week 24 – Pooled Analysis

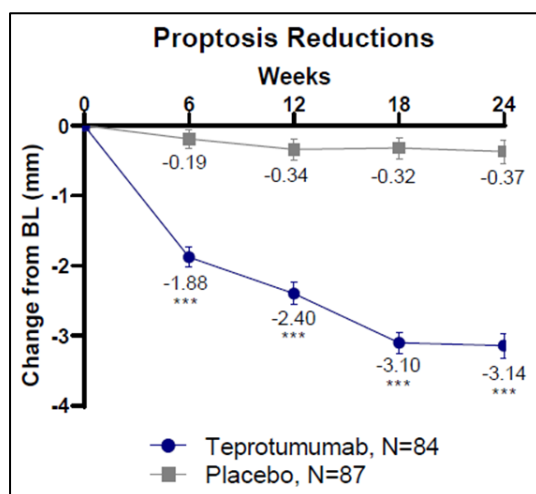


Abbreviations: Clinical Activity Score
Source: Kahaly *et al.* (2021).¹¹³

Change in proptosis

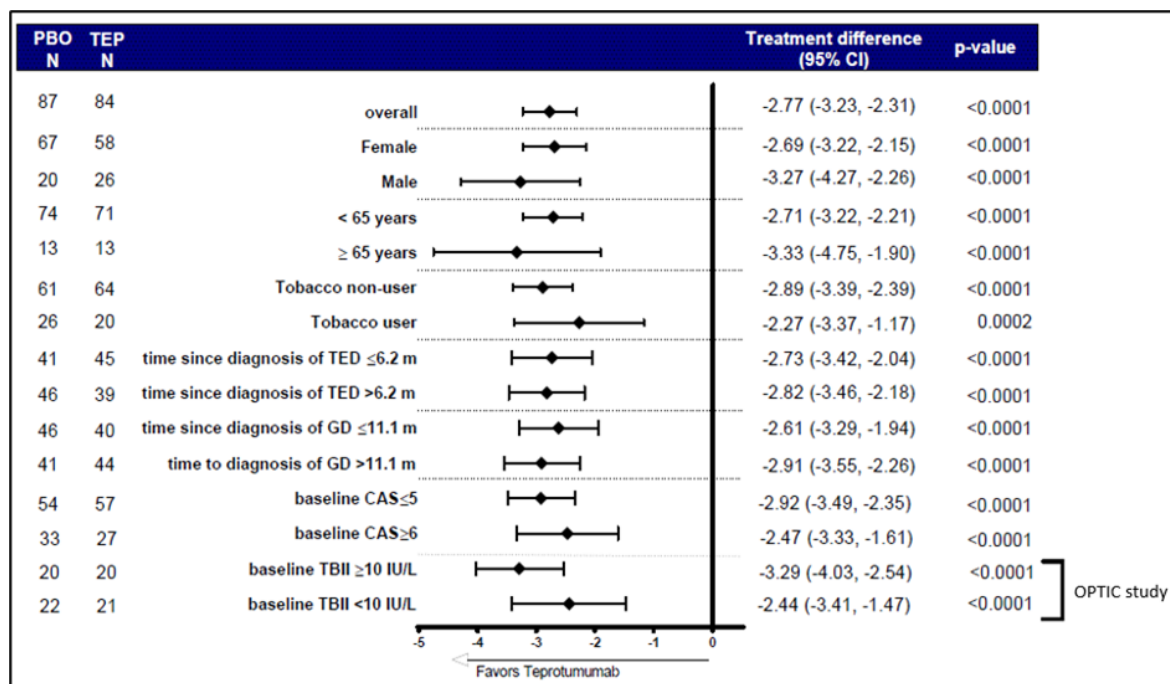
The pooled analysis reported a 3.14 mm proptosis reduction in the teprotumumab group and 0.37 mm reduction in the placebo group (treatment difference: 2.77 mm, 95% CI: 2.31-3.23; $p < 0.0001$), from baseline to week 24 (Figure 25). A larger mean reduction in proptosis was observed in the teprotumumab group than in the placebo group across all subgroups (Figure 26).¹¹³

Figure 25: Results of Proptosis Reductions – Pooled Analysis



Source: Kahaly *et al.* (2021).¹¹³

Figure 26: Subgroup results of proptosis reduction – Pooled Analysis



Abbreviations: CAS, Clinical Activity Score; CI, confidence interval; GD, Graves' Disease; PBO, placebo; TBII, Thyrotropin-binding inhibitory immunoglobulins; TEP, teprotumumab
Source: Kahaly *et al.* (2021).¹¹³

Abnormal visual exam findings

During the 24-week treatment periods, nine (10%) of 87 patients receiving placebo changed from normal or clinically insignificant ophthalmic exam findings at baseline to abnormal clinically significant finding (e.g., marked loss of visual acuity) at any time post-baseline versus 0 of 84 patients with teprotumumab.¹¹³

Change in GO-QOL

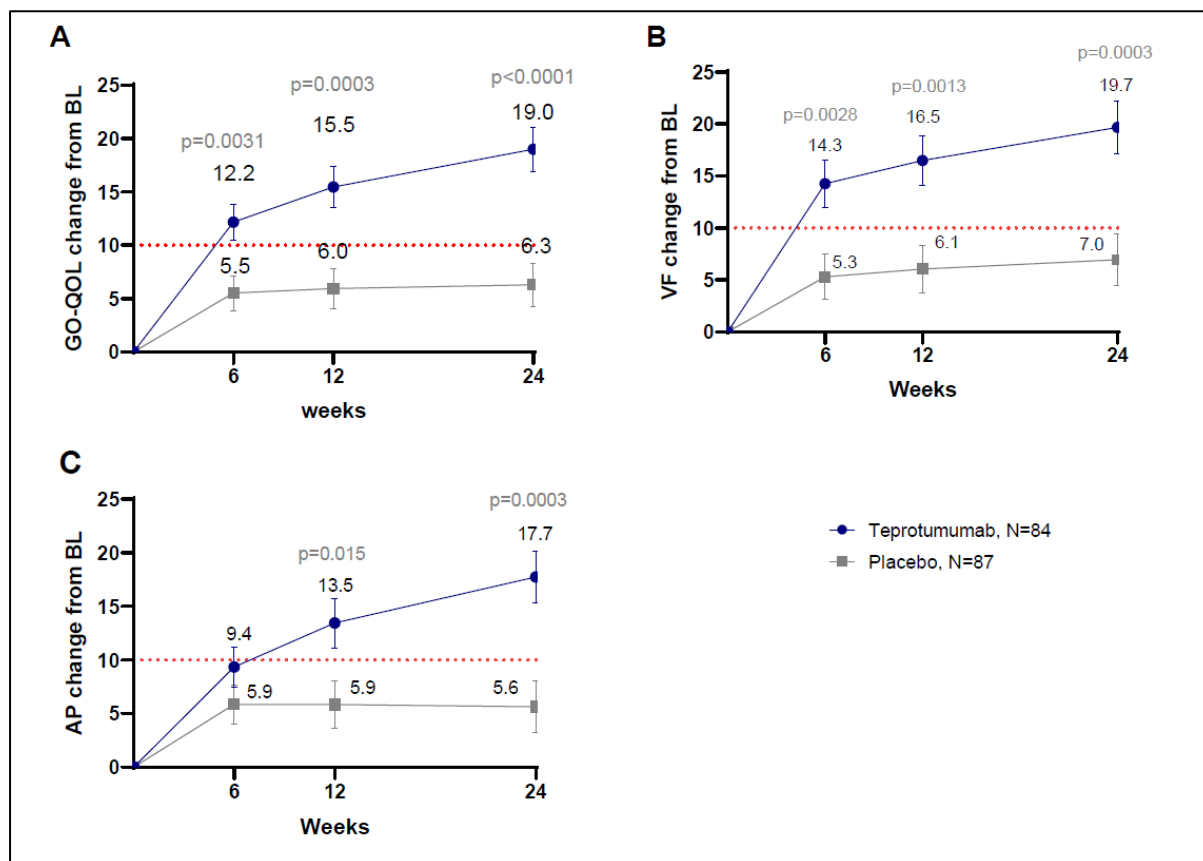
Patients receiving teprotumumab had a greater improvement in GO-QOL at Week 24 than those receiving placebo in the mean total, visual functioning, and appearance subscales.

Total GO-QOL score improved by a LS mean of 19.0 points (SE: ±2.1) in the teprotumumab group and by 6.3 points (SE: ±2.0) in the placebo group ($p < 0.0001$) from a baseline mean of 61.3 and 60.1, respectively. The improvement at Week 24 in the visual functioning and appearance subscales were 19.7 points (SE: ±2.6) and 17.7 points (SE: ±2.4), respectively, in the teprotumumab group, and 7.0 points (SE:

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± 2.5) and 5.6 points (SE: ± 2.4), respectively, in the placebo group (both $p=0.0003$) (Figure 27).¹¹³

Figure 27: Improvement in GO-QOL – Pooled Analysis



Panel A: GO-QOL Total score. Panel B: GO-QOL Visual Functioning subscale. Panel C: GO-QOL Appearance subscale
Abbreviations: AP, appearance; GO-QOL, Graves' ophthalmopathy-specific quality-of-life; VF, Visual Functioning
Source: Kahaly *et al.* (2021).¹¹³

Follow-up data

The pooled analysis conducted off-treatment follow-up analyses at 7 and 51 weeks after the final dose in the two trials.¹¹³

There was no evidence of acute disease rebound (increase in proportion of patients no longer meeting proptosis, diplopia, or ophthalmic composite outcome responses) at Week 28 (7 weeks off-treatment). Proptosis, diplopia and ophthalmic composite outcome (improvement in ≥ 1 eye from baseline without deterioration in either eye in ≥ 2 of the following: absence of eyelid swelling; CAS ≥ 2 ; proptosis ≥ 2 mm; lid aperture ≥ 2 mm; diplopia disappearance or grade change; or improvement of eight

degrees of globe motility) responses occurred in 62/71 (87%), 38/58 (66% of patients with baseline diplopia) and 66/72 (92%) of teprotumumab-treated patients.¹¹³

In the patients with available long-term follow-up data (51 weeks after last dose), 38/57 (67%), 33/48 (69% of patients with baseline diplopia), and 48/58 (83%) were proptosis, diplopia, and composite outcome responders, respectively.¹¹³

Conclusions

The integrated outcomes from the pooled data analysis of the phase 2 study and the phase 3 OPTIC study reported significantly better clinical results with teprotumumab compared to placebo on proptosis response rate (77% vs 15%; $p < 0.0001$), diplopia response rate (70% vs 31%; $p < 0.0001$), overall response rate (74% vs 60%; $p < 0.001$), and disease inactivation (i.e., achieved CAS of 0 or 1) (62% vs 22%; $p < 0.001$) at Week 24.¹¹³

The improvement in proptosis with teprotumumab over placebo was consistent across various subgroups, including age, gender, smoking status, time since diagnosis of TED, time since diagnosis of Graves' Disease, baseline CAS, and baseline levels of TBII patients.¹¹³

Proptosis, diplopia and ophthalmic composite outcome response in teprotumumab-treated patients were 62/71 (87%), 38/58 (66%), 66/72 (92%) at week 28 (7 weeks off-treatment) and 38/57 (67%), 33/48 (69%), 48/58 (83%) at week 72 (51 weeks off-treatment).¹¹³

B.2.9 Indirect and mixed treatment comparisons

Both RCTs (phase 2, and OPTIC) undertook a comparison of teprotumumab vs. placebo. As described in B.1.3 above, current standard of care for moderate to severe TED in the active phase is a cumulative dosage of 4.5 to 5.0 g of intravenous methylprednisolone (IVMP) administered over 12 weeks, with or without mycophenolate. In the absence of any clinical studies directly comparing the efficacy of the most recommended dose of IVMP with teprotumumab or placebo, the company conducted a de novo indirect treatment comparison (ITC) using matching-adjusted indirect comparison (MAIC) methodology to estimate relative treatment

effects between the three interventions. Full details of the methodology for the indirect comparison are provided in Appendix D.

The company also reports here a MAIC comparing teprotumumab with placebo and with IVMP that was previously conducted and published by Douglas *et al.* (2022).¹⁴⁸

B.2.9.1 De novo ITC

B.2.9.1.1 Overview

For the de novo ITC, an unanchored matching-adjusted indirect comparison (MAIC) was conducted to estimate the treatment effect of teprotumumab relative to IVMP and teprotumumab relative to IVMP + MMF in patients with acute moderate-to-severe TED. Matching-adjusted methodology was chosen as the clinical trials identified in the feasibility assessment were not connected by a common comparator. A literature review was conducted to identify existing published literature assessing the most commonly recommended dose of IVMP among patients with moderate to severe active TED. Details of the methods for the clinical literature review and for the ITC are provided in Appendix D. The results are presented below.

The primary MAIC analysis set consisted of pooled IPD from the Phase 2 and OPTIC trials for teprotumumab, together with reported data from eight identified studies for IVMP. As both diplopia and proptosis response are needed to derive the transition probabilities in the economic analyses, two outcomes for the ITC were reported: mean difference in change from baseline proptosis score (mm), reflective of the continuous nature of the endpoint, and odds ratio (OR) for diplopia response (defined as reduction in diplopia of ≥ 1 grade), reflective of the binary nature of the endpoint. The outcomes were considered at week 12 for IVMP and week 24 for teprotumumab, to align with the end of their standard treatment periods.

Treatment effect modifiers and prognostic variables were identified both from a previous ITC comparing teprotumumab with IVMP (Douglas *et al.*, 2022¹⁴⁸) and an Amgen clinical expert, and then were further validated with three external key opinion leaders. Covariate selection for base-case and scenario analyses was based on the order of importance determined by clinical opinion and on the availability of data from the IVMP studies. Based on the availability of data, the ranking of

importance of baseline characteristics, and the ESS considerations, the covariates that were considered in the base-case MAIC analyses were:

- proportion of smokers [mean, %]
- baseline diplopia [mean, %]
- baseline proptosis [mean, mm]
- RIT [mean, %].

For the IVMP+MMF comparison, only three of the most important factors identified by clinical experts could be included in the MAIC, based on availability of baseline characteristics reported in the IVMP+ MMF study and the ESS threshold of >30. These were:

- proportion of smokers [mean, %]
- baseline diplopia [mean, %]
- baseline proptosis [mean, mm]

For each outcome for teprotumumab versus IVMP and teprotumumab vs IVMP +MMF, a number of scenarios were conducted. Sensitivity analyses were also performed to assess the impact of covariate selection and outliers.

A summary of the sensitivity and scenario analyses is presented in Table 22.

Table 22: MAIC base-case and scenario analyses

		Studies	Covariates	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Teprotumumab versus IVMP	Base-case	Only RCTs	• Smoking • Baseline diplopia • Baseline proptosis • RIT	• Smoking • Baseline diplopia • Baseline proptosis	• Smoking • Baseline diplopia	Excluding patients with outlier weights
	Scenario 1	Europe and North America (RCTs and non-RCTs)	• Smoking • Baseline diplopia • Baseline proptosis • RIT	-	-	
	Scenario 2	RCTs and RWEs	• Smoking • Baseline diplopia • Baseline proptosis • RIT	-	-	
	Scenario 3	OPTIC only	• Smoking • Baseline diplopia • Baseline proptosis • RIT	-	-	
Teprotumumab versus IVMP + MMF	Base-case	Only RCTs	• Smoking • Baseline diplopia • Baseline proptosis	• Smoking • Baseline diplopia	Excluding patients with outlier weights	
	Scenario 1	OPTIC only	• Smoking • Baseline diplopia • Baseline proptosis	-	-	

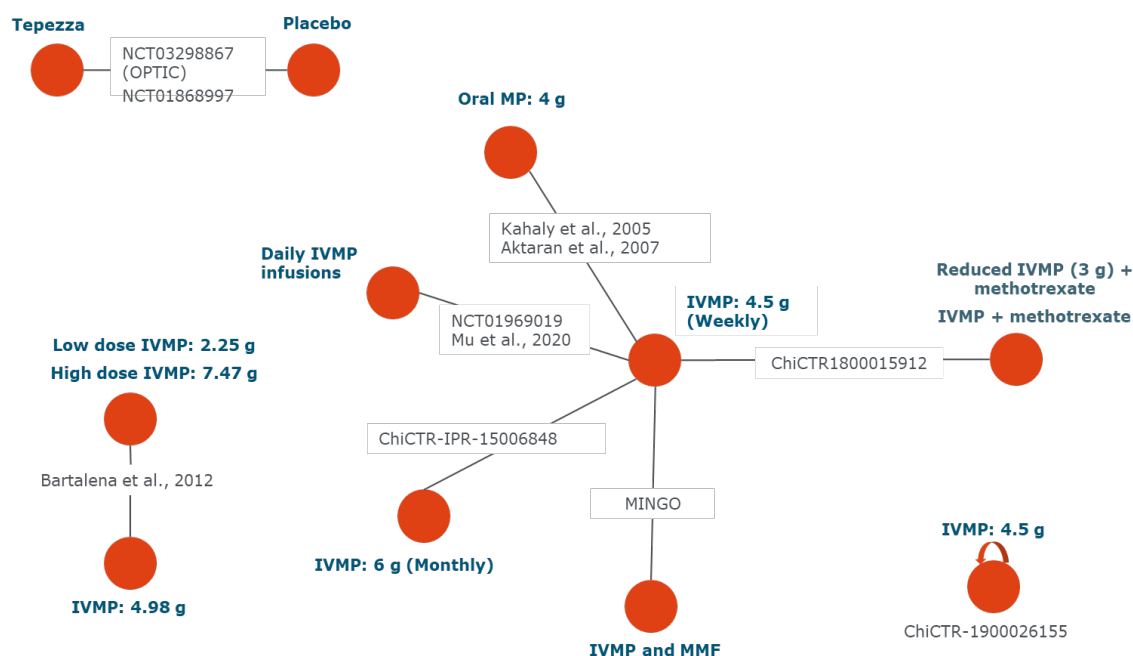
Abbreviations: IVMP, Intravenous methylprednisolone; MAIC, Matching-adjusted indirect comparison; MMF, mycophenolate mofetil; RCT, Randomised controlled trial; RIT, radioiodine therapy; RWE, real world evidence

B.2.9.1.2 Results

Network of evidence

The full network of evidence for ITCs comparing IVMP, IVMP + MMF and teprotumumab, based on the studies identified in the original clinical SLR (June 2023 searches) after applying the PICOS exclusion criteria, is presented in Figure 28. Additional studies were added to include relevant studies published before 2013 (the date limitation of the clinical SLR). Mu *et al.* (2020) was identified in a previous MAIC by Douglas *et al.*, (2022),¹⁴⁵ and was included for consideration as it met all the PICOS criteria for the MAIC.

Figure 28: Set of clinical trials evidence based on the included studies after feasibility assessment



Abbreviations: g, Grams; IVMP, Intravenous methylprednisolone; kg, Kilograms; mg, Milligrams; MMF, Mycophenolate mofetil; MP, Methylprednisolone

Descriptive Data

Studies forming the evidence base for the base-case MAICs are presented in Table 23.

Table 23: Summary of baseline characteristics across the evidence base

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
IVMP													
He <i>et al.</i> , (2017). ²⁶ (ChiCTR-IPR-15006848)	Phase NR, RCT	18	41.20	44.44	22.20	NR	17.20	Absent: 6 (33.30) Intermittent: 2 (11.10) Inconstant: 6 (33.30) Constant: 5 (22.20)	NR	33.30	NR	NR	NR
Kahaly <i>et al.</i> , (2018). ³³ ((MINGO) EUDRAC T2008-002123-93)	Phase NR, RCT	81 (73 at week 12)	50.60	20.99	51.00	8.50 months	NR	52 (64.00)	0.52 mIU/L	20.00	NR	NR	NR
Zhu <i>et al.</i> , (2014). ²⁸	Phase 4, RCT	39	45.30	38.46	13.51	NR	21.66	Absent: 11 (28.21) Intermittent: 6 (15.38) Inconstant: 15 (38.56)	0.41 μ IU/L	10.26	NR	NR	FT3: 4.42 pmol/L FT4: 13.43 pmol/L

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline n (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
								Constant : 7 (17.95)					
Shen <i>et al.</i> , (2022) ²⁹	Phase NR, RCT	30	46.50	30.00	0.00	NR	22.30	Absent: 9 (30.00) Intermittent: 3 (10.00) Inconstant: 7 (23.30) Constant : 11 (36.70)	NR	20.00	NR	3.30	FT3: 4.70 (4.10-5.30) FT4: 12.60 (10.60-13.80)
Mu <i>et al.</i> (2020). ¹⁴⁹	Phase NR, RCT	46	35.20	60.87	34.80	12.64 months	17.25	16 (34.80)	0.26	NR	NR	NR	FT3: 12.39 pmol/L FT4: 31.08 pmol/L
Aktaran <i>et al.</i> , (2007). ²²	Phase NR, RCT	25	44.30	44.00	40.00	NR	22.20	Constant : 2(18.00) Inconstant:4 (36.00) Intermittent:5 (45.00)	1.90 (1.30) μ U/mL	NR	NR	NR	FT3:2.70 $\pm$ 1.90 ng/dL FT4:1.50 $\pm$ 0.30 ng/dL

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
Bartalena <i>et al.</i> (2012). ²¹	Phase NR, RCT	54	50.00	42.59	54.00	12.40 months	22.20	Constant : 9 (17.00) Intermittent: 20 (37.00) Absent: 11 (20.00) Absent: 14 (26.00)	1.10 mIU/L	9.00	NR	NR	NR
Kahaly <i>et al.</i> (2005). ²³	Phase NR, RCT	35	52.00	28.57	60.00	4 months	NR	Constant : 23 (66.00) Intermittent: 3 (9.00) Absent: 0 (0)	NR	NR	NR	NR	NR
IVMP + MMF													
Kahaly <i>et al.</i> (2018). ⁹	Phase NR, RCT	83	52.10	27.00	53.00	9 months	21.09	Constant : 13 (16.00) Intermittent: 23 (28.50) Absent: 19 (23.50)	0.72 mIU/L	18	NR	NR	FT3: NR FT4: NR

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
Teprotumumab													
Smith <i>et al.</i> (2017). ¹ (NCT01868997)	Phase 2, RCT	41	51.60	35.00	26.00	NR	23.40	Absent: 4 (10.00) Intermittent: 16 (38.00) Inconstant: 7 (17.00) Constant: 15 (35.00)	NR	NR*	NR	NR	FT3: 4.80 (1.40) pmol/L FT4: 16.30 (4.80) pmol/L
Douglas <i>et al.</i> (2020). ² (NCT03298867 (OPTIC))	Phase 3, RCT	42	51.60	29.00	9.00	6.20 months	22.62	68.29 (NR)	1.75 mIU/L	NR*	NR	NR	FT3: 5.10 pmol FT4: 6.46 pmol/L

*Reported in clinical trial clinical study report. Abbreviations: dL, Deciliters; FT3, Free triiodothyronine; FT4, Free thyroxine; IVMP, Intravenous methylprednisolone; L, Litres; mg, Milligrammes; mIU, Milli-international units; mm, Millimetres; MMF, Mycophenolate mofetil; MP, Methylprednisolone; mU, Milli-units; μ U, Micro-units; n, Number; NR, Not reported; pmol, Picomoles per litre; RIT, Radioiodine therapy; SD, Standard deviation; TED, Thyroid eye disease; TRAb, Thyrotropin receptor antibody; TSH, Thyroid stimulating hormone; TSI, Thyroid-stimulating immunoglobulin

B.2.9.1.3 Outcome Data

The numbers of patients in both the teprotumumab, IVMP and IVMP + MMF populations for the base-case and scenario analyses are listed below in Table 24.

Table 24: Number of patients per outcome in each scenario before matching

	Teprotumumab (n)	IVMP (n)	IVMP + MMF (n)
Base-case			
Change from baseline proptosis	██████████	██████████	██████████
Diplopia response rate	██████████	██████████	N/A
Scenario 1 (North American and Europe)			
Change from baseline proptosis	██████████	██████████	N/A
Diplopia response rate	██████████	██████████	N/A
Scenario 2 (RCTs and RWE)			
Change from baseline proptosis	██████████	██████████	N/A
Diplopia response rate	██████████	██████████	N/A
Scenario 3 (OPTIC only)			
Change from baseline proptosis	██████████	██████████	██████████
Diplopia response rate	██████████	██████████	N/A

Abbreviations: IVMP, Intravenous methylprednisolone; MMF, Mycophenolate mofetil; n, number; N/A, Not applicable; RCT, Randomised controlled trial; RWE, Real world evidence

Indirect treatment comparison base-case: Teprotumumab versus IVMP (CFB proptosis outcome)

In the base-case analysis, seven IVMP RCT studies (Bartalena *et al.*, 2012,²¹ Aktaran *et al.*, 2007,²² He *et al.*, 2017,¹⁹ Mu *et al.*, 2020,¹⁴⁹ Zhu *et al.*, 2014,²⁸ Shen *et al.*, 2022,²⁹ and Kahaly *et al.*, 2018³³) and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867 were included. The studies were matched on four covariates: smoking, baseline diplopia, baseline proptosis and RIT. The distribution of the weights for the base-case is presented in Figure 29; rescaled weights ranged from ██████████ to ██████████, with the median

skewed towards [REDACTED]. One patient was assigned a much larger weight of [REDACTED] compared to other weights. A considerable number of individuals were assigned a weight of less than 1 ([REDACTED]) indicating that they contributed little to the overall treatment effect, resulting in a drop in the ESS from [REDACTED] to [REDACTED].

Figure 29: Histogram of rescaled weights - base-case (teprotumumab versus IVMP)



Results presented in Table 25 show teprotumumab is associated with a statistically significantly greater mean difference change from baseline in proptosis compared to IVMP (mean difference in CFB: [REDACTED] mm [95% CI [REDACTED]]).

Table 25: Base-case MAIC results for mean change from baseline proptosis (teprotumumab versus IVMP)

	ESS	Mean change from baseline proptosis difference (teprotumumab vs IVMP) (SE)	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis, RIT)				
Adjusted results	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Unadjusted results	N/A	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: CI, Confidence interval; ESS, Effective sample size; IVMP, Intravenous methylprednisolone; mm, millimetres; N/A, Not applicable; RCT, Randomised controlled trial; RIT, Radioiodine therapy; SE, Standard error
Source: Amgen (2024).¹⁵⁰

Indirect treatment comparison base-case: Teprotumumab versus IVMP + MMF (CFB proptosis outcome):

In the base-case analysis, one IVMP + MMF RCT study³³ and the pooled IPD from the two teprotumumab trials NCT01868997¹ and NCT03298867 were included. The studies were matched on three covariates: smoking, baseline diplopia, and baseline proptosis. The distribution of the weights for the base-case is presented in Figure 30; rescaled weights ranged from [REDACTED] to [REDACTED], with the median skewed towards [REDACTED]. One patient was assigned a much larger weight of [REDACTED] compared to other weights. A considerable number of individuals were assigned a weight of less than 1 ([REDACTED]) indicating that they contributed little to the overall treatment effect, resulting in a drop in the ESS from [REDACTED] to [REDACTED].

Figure 30: Histogram of rescaled weights - base-case (teprotumumab versus IVMP + MMF)



Results presented in Table 26 show teprotumumab is associated with a statistically significantly greater mean difference change from baseline in proptosis compared to IVMP + MMF (mean difference in CFB: [REDACTED] [95% CI: [REDACTED]]).

Table 26: Base-case MAIC results for mean change from baseline proptosis (teprotumumab versus IVMP + MMF)

	ESS	Mean change from baseline proptosis difference (teprotumumab vs IVMP + MMF) (SE)	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis)				
Adjusted results	██████	██████████	██████	██████
Unadjusted results	N/A	██████████	██████	██████

Abbreviations: CI, Confidence interval; ESS, Effective sample size; IVMP, Intravenous methylprednisolone; mm, millimetres; MMF, mycophenolate mofetil; N/A, Not applicable; RCT, Randomised controlled trial; SE, Standard error

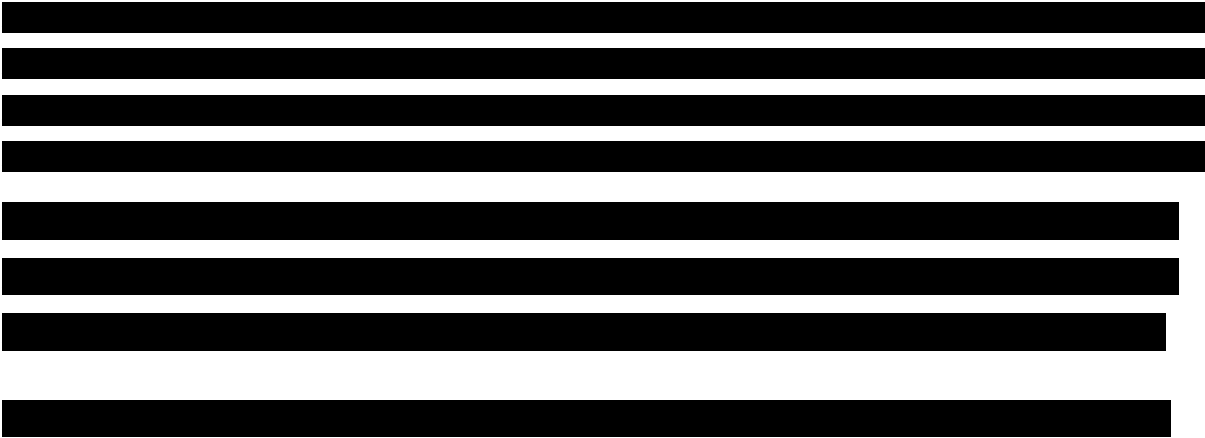
Source: Amgen (2024).¹⁵⁰

Indirect treatment comparison base-case: Teprotumumab versus IVMP (diplopia response rate outcome)

The four IVMP studies (He, Zhu, Shen, Kahaly 2005)^{23, 26,28,29} included for the diplopia response rate outcome were compared with the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867 and were matched on smoking, baseline diplopia, baseline proptosis and RIT.

The distribution of rescaled weights is presented in Figure 31; rescaled weights ranged from ████████ to ████████, with the median skewed towards ██████. Three patients had noticeably larger weights indicating a greater influence on the overall treatment effect. Application of these weights to the dataset caused the ESS to decrease from ████████ to ████████.

Figure 31: Histograms of rescaled weights for the diplopia response rate MAIC - base-case (teprotumumab versus IVMP)



A summary of the analysis is presented in Table 27. Results indicate that the odds of diplopia response for patients treated with teprotumumab are over three times higher than those treated with IVMP. Results were statistically significant as the 95% CIs do not cross 1. (OR: [redacted] [95% CI: [redacted]]).

Table 27: Base-case diplopia response rate MAIC results – adjusted results (teprotumumab versus IVMP)

	ESS	OR	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted results	N/A	[redacted]	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; ESS, Effective sample size; mm, millimetres; N/A, not applicable; OR, odds ratio; RCT, Randomised controlled trial; RIT, Radioiodine therapy; SE, Standard error
Source: Amgen (2024).¹⁵⁰

B.2.9.2 Douglas et al., (2022) MAIC

Douglas, et al. published a meta-analysis and MAIC comparing teprotumumab, IVMP and placebo in 2022.¹⁴⁵

Data sources for the MAIC included patient-level data for teprotumumab or placebo from the phase 2 (NCT01868997) and phase 3 OPTIC trials and published aggregate-level data for IVMP (4.5-5 g over 12 weeks). Given the similar inclusion and exclusion criteria for the two teprotumumab trials, data were pooled to obtain

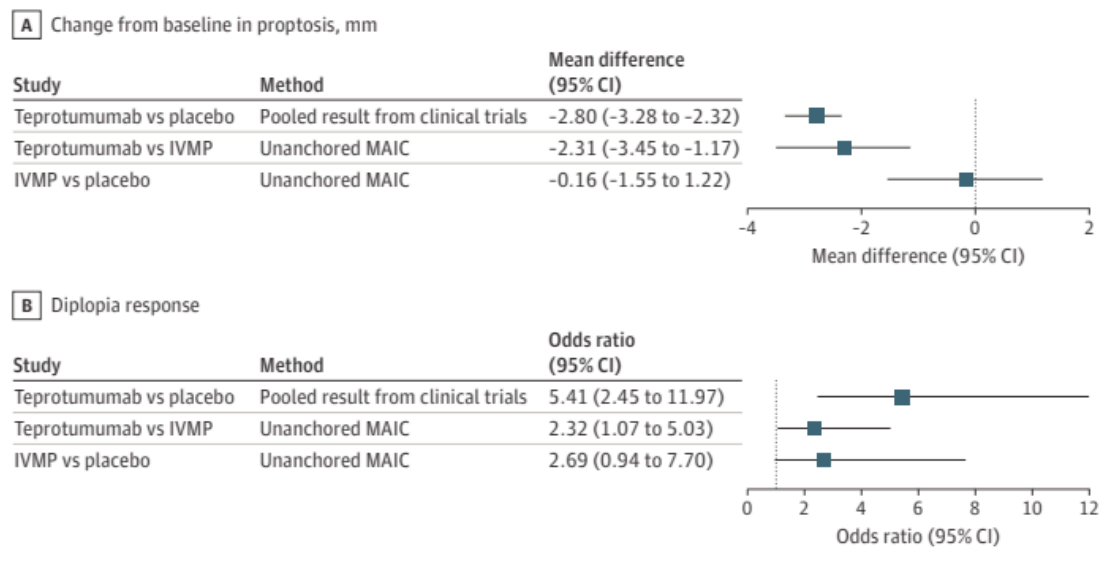
treatment arms with 84 randomised patients and 87 randomised patients for teprotumumab and placebo, respectively.^{148, 151} Outcomes of interest were change from baseline in proptosis and diplopia response (in patients with diplopia).

Overall, 12 studies were included in the analysis: 11 studies reported change from baseline in proptosis and 4 studies reported the proportion of patients with diplopia response. No IVMP studies were placebo-controlled, 7 were RCTs, and the rest were observational. The teprotumumab studies were placebo-controlled, double-masked, multicentre studies conducted in Europe and the US. Two of the IVMP studies were multicentre and the rest were single centre; 5 were conducted in Europe, 1 in Turkey, and 6 in China. Patient inclusion criteria and baseline characteristics were similar across studies, and all studies included patients 18 years or older with moderate to severe active TED (i.e., patients with similar levels of inflammation and with a clinical activity score ≥ 3). Some differences were noted for the proportion of smokers across the studies, which ranged from 22% to 76%. For the proptosis and diplopia analyses, 419 and 125 patients receiving IVMP were included, respectively.¹⁴⁵

B.2.9.2.1. Change from baseline in proptosis

The Douglas et al. MAICs showed that teprotumumab was associated with a statistically significantly greater change from baseline in proptosis compared with IVMP (MD, -2.31 mm; 95% CI, -3.45 to -1.17 mm; effective sample size: 56 (Figure 32A)). The difference in proptosis change from baseline in the IVMP group compared with the placebo group was not statistically significant (MD, -0.16 mm; 95% CI, -1.55 to 1.22; effective sample size: 37 [Figure 32A]). Results for the unadjusted and scenario analyses were aligned with these primary analyses.¹⁴⁵

Figure 32: Unanchored Matching-Adjusted Indirect Comparisons and Pooled Results from Clinical trials for Change From Baseline in Proptosis (A) and Diplopia Response (B)



Randomisation controls for known/unknown confounders vs. matching-adjusted indirect comparison controls for subset of known confounders.

Abbreviations: CI, confidence interval; IVMP, intravenous methylprednisolone; MAIC, matching-adjusted indirect comparison

Source: Douglas *et al.* (2022), Douglas *et al.* (2022).^{148, 151}

B.2.9.2.2. Diplopia response

After adjusting for baseline characteristics, results from the MAICs showed that IVMP was associated with numerically increased odds of diplopia response compared with placebo (OR, 2.69; 95% CI, 0.94- 7.70; effective sample size: 24 [Figure 32B]). Furthermore, the teprotumumab diplopia response was greater when compared with IVMP (OR, 2.32; 95% CI, 1.07-5.03; effective sample size: 44 [Figure 32B]).^{148, 151}

Results for the unadjusted and scenario analyses were largely aligned with the primary analyses; however, some changes in statistical significance were noted for the comparisons between IVMP and placebo, potentially because of the small effective sample size.

B.2.9.3 Discussion

The primary objective of the *de novo* ITC was to compare the relative clinical effectiveness of teprotumumab versus IVMP and teprotumumab versus IVMP + MMF for treating moderate-to-severe (acute) TED. This was achieved through following a structured process for ITCs as described in the NICE DSU. Two SLRs were conducted to identify the relevant clinical and real-world data. The identified clinical studies from the SLRs were assessed in the FA, leading to a final selection of studies for analysis. Meta-analyses and MAICs were then performed to estimate the relative clinical effectiveness of teprotumumab versus IVMP and teprotumumab versus IVMP + MMF. The analyses focused on two outcomes: mean change from baseline proptosis and diplopia response rate, with results considered at Week 12 for IVMP and Week 24 for teprotumumab and IVMP + MMF.

The base-case analysis for IVMP, in which four covariates were considered (smoking, baseline proptosis, baseline diplopia, and RIT) showed that teprotumumab was associated with a statistically significantly greater mean change from baseline in proptosis compared to IVMP (mean difference in CFB: [REDACTED] mm [95% CI: [REDACTED]]). Teprotumumab also demonstrated statistically significant increased odds of diplopia response compared to IVMP (OR: [REDACTED] [95% CI: [REDACTED]]). The base-case analysis for IVMP+ MMF (in which three covariates were considered (smoking, baseline proptosis, and baseline diplopia) showed that teprotumumab was associated with a statistically significantly greater mean change from baseline in proptosis compared to IVMP + MMF (mean difference in CFB: [REDACTED] mm [95% CI: - [REDACTED]]).

The potential impact of including and excluding different PFs and TEMs were explored in two sensitivity analyses.

Results showed that teprotumumab was associated with a statistically significantly greater mean change from baseline in proptosis compared to IVMP (mean difference in CFB of [REDACTED] mm [95%CI [REDACTED]] in sensitivity analysis 1 and [REDACTED] mm [95%CI [REDACTED]] in sensitivity analysis 2) and IVMP + MMF (mean difference in CFB of [REDACTED] [95% CI [REDACTED]] in sensitivity analysis 1 and [REDACTED] mm [95%CI [REDACTED]] in sensitivity analysis 2). Additionally, results showed statistically significant increased odds of diplopia response rate compared to IVMP of Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

■■■■ [95%CI ■■■■] in sensitivity analysis 1 and ■■■■ [95%CI ■■■■] in sensitivity analysis 2. These results support the base-case results and confirm that the mix of PFs and TEMs do not make a significant difference to the base-case results. This confirms that excluding important covariates would result in limited residual confounding bias.

Three scenario analyses were conducted for further exploration of teprotumumab versus IVMP. In the first scenario, which considered only studies that took place in Europe and North America, teprotumumab was associated with a statistically significant greater mean change from baseline in proptosis compared to IVMP (mean difference in CFB: ■■■■ mm [95% CI: ■■■■]). Teprotumumab also demonstrated significant increased odds of diplopia response rate (OR ■■■■ [95% CI: ■■■■]). The second scenario included both RCTs and RWE studies and showed teprotumumab to be more effective at reducing proptosis (mean difference in CFB: ■■■■ mm [95% CI: ■■■■]) and achieving diplopia response rate (OR ■■■■ [95% CI: ■■■■]). However, RWE studies are associated with caveats such as lack of randomisation and selection bias. As a result, despite the larger sample size, this analysis was not considered robust. The last scenario analysis included IPD only from the phase 3 OPTIC trial. In this exploratory analysis, teprotumumab was associated with a statistically significantly greater mean change from baseline in proptosis compared to IVMP (mean difference in CFB: ■■■■ mm [95% CI: ■■■■]). Teprotumumab also demonstrated statistically significant increased odds of diplopia response compared to IVMP (OR ■■■■ [95% CI: ■■■■]). The results from scenario analyses were largely consistent with the base-case results.

One scenario analysis was conducted for further exploration of teprotumumab versus to IVMP + MMF. The scenario analysis included IPD only from the phase 3 OPTIC trial. In this exploratory analysis, teprotumumab was associated with a statistically significantly greater mean change from baseline in proptosis compared to IVMP + MMF (mean difference in CFB: ■■■■ mm 95% CI ■■■■). The result from scenario analysis was consistent with the base-case results.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

Although standard methods were used for assessing ITCs and adjusted for clinically relevant characteristics, comparing results across different studies introduces a Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

source of bias. First, an unanchored MAIC was conducted for the de novo ITC because there was no common comparator arm between the teprotumumab and IVMP studies. Douglas et al. noted the same limitation in their own ITC.¹⁴⁸ The de novo ITC conducted by the company included only RCT evidence, whereas the Douglas et al. MAICs included non-RCT studies, including studies reporting median change from baseline in proptosis.

B.2.9.5 Conclusions

In the absence of head-to-head trials of IVMP vs teprotumumab, these MAICs provide an estimate of the comparative efficacy of the two treatments.

In the de novo MAIC, teprotumumab was associated with a statistically significant change from baseline in proptosis and a 3-times increased odds of diplopia response compared to IVMP.

In the MAIC published by Douglas et al., teprotumumab was associated with larger improvements in proptosis and diplopia than IVMP. Compared with IVMP, teprotumumab was associated with greater, and clinically meaningful, improvement in proptosis, with a 2 times greater odds of diplopia response.¹⁴⁸

B.2.10 Adverse reactions

Safety evidence for teprotumumab in the population of interest for this submission is provided by the Phase 2 and OPTIC studies and the OLE phase, OPTIC-X. Key safety outcomes for the Phase 2 and OPTIC studies, together with the pooled analysis are presented in Sections B.2.10.1.1, B.2.10.1.2 and B.2.10.1.3 below, respectively. Safety outcomes for the OPTIC-X study are presented in Appendix F.

The clinical trial evidence showed that teprotumumab is generally well-tolerated, with a maximum discontinuation rate of 11% across the phase 2, OPTIC and phase 4 studies. The rate of any TEAE in the teprotumumab group compared to the placebo group was 74-85% vs 69-80% across phase 2, OPTIC and phase 4 studies. The most common AEs associated with the administration of teprotumumab were muscle spasms, alopecia, nausea, diarrhoea, dry skin, dysgeusia and hearing impairment. Most observed adverse events were of mild or moderate severity.

Serious AEs were uncommon with teprotumumab in all pivotal studies (2.4-12% with teprotumumab vs 2-5% with placebo). No deaths or anaphylactic reactions occurred during the trials. Overall, the reported AEs were generally of limited duration and able to be managed without leading to discontinuation of the trial drug. No clinically meaningful differences in the TEAE profile were observed between the acute and chronic TED clinical trial populations. There were no instances of antidrug antibodies (ADAs) or drug neutralising antibodies (NAbs) of clinical relevance.

B.2.10.1 Studies reported in section B.2.2

B.2.10.1.1 Phase 2

Table 28 outlines AEs reported in over 5% of patients in the teprotumumab group, and that were greater in number in the teprotumumab group than in the placebo group, and SAEs. Overall, teprotumumab was well tolerated for patients with acute, moderate-to-severe TED.

Table 28. Adverse Events and Serious Adverse Events (Safety Population, ≥5% of patients) – Phase 2

	Teprotumumab (n=43)^a	Placebo (n=44)
AE during intervention – no. of patients (%)^b		
Nausea	8 (18.6)	4 (9.1)
Muscle spasms	8 (18.6)	2 (4.5)
Diarrhea	6 (14.0)	2 (4.5)
Hyperglycaemia	5 (11.6)	2 (4.5)
Alopecia	3 (7.0)	2 (4.5)
Dry skin	3 (7.0)	0
Dysgeusia	3 (7.0)	0
Headache	3 (7.0)	2 (4.5)
Paresthesia	3 (7.0)	0
Hearing impairment	3 (7.0)	0
Weight loss	3 (7.0)	0
Any AE during intervention	32 (74.4)	32 (72.7)
SAE – no. of patients (%)^c		
Optic neuropathy ^d	0	1 (2.3)
Diarrhoea	1 (2.3)	0
Inflammatory bowel disease	1 (2.3)	0
Escherichia sepsis ^e	1 (2.3)	0
Hashimoto's encephalopathy	1 (2.3)	0
Urinary retention	1 (2.3)	0
Any SAE	5 (11.6)	1 (2.3)

^a One patient in the placebo group received a single dose of teprotumumab in error at week 15. That patient is included here in the teprotumumab group.

^b AEs of any cause were defined as those that occurred between the administration of the first dose and 30 days after the administration of the final dose. Listed AEs that emerged during the intervention phase are those that occurred in more than 5% of patients in the teprotumumab group and that occurred in greater numbers in the teprotumumab group than in the placebo group. Patients may have had more than one AE.

^c Listed are all SAEs reported in the trial, including any AE involving hospitalization. In the teprotumumab group, four patients discontinued the intervention because of the following SAEs: diarrhea that occurred after six infusions, inflammatory bowel disease after seven, Escherichia coli sepsis after three, and Hashimoto's encephalopathy after six.

^d A total of three patients in the placebo group withdrew from the trial because of worsening eye symptoms or a lack of response. One case of dysthyroid optic neuropathy designated by an investigator as a SAE occurred 3 days after the week 24 evaluation.

^e This patient was the only one whose intervention was unmasked during the course of the trial.

Abbreviation: AE, adverse event; SAE: serious adverse event

Source: Smith *et al.* (2017), Amgen (2024).^{49 141}

The rate of any AE during intervention was similar between the teprotumumab group and the placebo group. The majority of AEs were mild, requiring no treatment and resolving as patients continued intervention. Nausea and muscle spasms were the most common AEs among teprotumumab group. Hyperglycaemia was the only AE related to teprotumumab. In non-diabetic patients, it was consistently grade 1, intermittent, and had similar rates in both groups. Some diabetic patients receiving teprotumumab experienced grade 2 or 3 hyperglycaemia, which was effectively managed after adjusting diabetes medication. Glycaemic control after the 6-month treatment phase was similar to that at baseline levels in all patients who received teprotumumab⁴⁹.

No deaths occurred during the trial, and six patients in each group discontinued intervention. SAEs were observed in 12% (5 of 43) of teprotumumab patients and 2% (1 of 45) of placebo patients. Diarrhoea and mental confusion in patients who received teprotumumab were deemed "possibly" treatment related SAEs, while other SAEs were considered unrelated.⁴⁹

B.2.10.1.2 OPTIC

Table 29 outlines AEs observed in at least 5% of patients in either trial group within 21 days after the final dose. Most AEs during this period were of grade 1 or 2, with muscle spasms, alopecia, nausea, and fatigue being the most common in the teprotumumab group. Potential infusion reactions were reported by six patients in the teprotumumab group and four in the placebo group experienced.⁸⁰

AEs of special interest, including potential infusion-related reactions, hyperglycaemia, muscle spasms, diarrhoea, and hearing impairment, that occurred within 21 days after the final dose were of grade 1 or 2, and with the exception of a single teprotumumab infusion-related reaction, none led to discontinuation of the trial drug. Hyperglycaemia was reported in two patients (<5%) in the teprotumumab group, both mild cases. Hearing impairment was reported in five teprotumumab patients (two hypoacusis, one deafness, one autophony, and one mild patulous eustachian tube), and all events were resolved. No auditory issues occurred in the placebo group. In the teprotumumab group, five patients (four women) experienced a body-weight loss of at least 5.0 kg during the trial, with intentional weight loss of 19

kg in one case. No AEs associated with decreased body weight were reported through 21 days after the final dose.⁸⁰

No deaths occurred. SAEs were reported in two patients in the teprotumumab group, including pneumothorax (likely unrelated to the trial drug) and an infusion reaction leading to trial withdrawal. In the placebo group, one patient reported a SAE (visual-field defect requiring decompression surgery) and was withdrawn. No antidrug antibodies were detected in teprotumumab-receiving patients.⁸⁰

Table 29: Adverse Events and Serious Adverse Events (ITT Population, ≥5% of patients)^a – OPTIC

	Teprotumumab (n=41)	Placebo (n=42)
AE during intervention – no. of patients (%)		
Muscle spasms	13 (31.7)	4 (9.5)
Alopecia	8 (19.5)	5 (11.9)
Nausea	6 (14.6)	4 (9.5)
Fatigue	5 (12.2)	1 (2.4)
Diarrhoea	4 (9.8)	5 (11.9)
Headache	4 (9.8)	4 (9.5)
Dry skin	4 (9.8)	0
Dysgeusia	4 (9.8)	0
Stomatitis	3 (7.3)	1 (2.4)
Amenorrhoea	3 (7.3)	0
Dizziness	3 (7.3)	0
Cough	2 (4.9)	3 (7.1)
Upper abdominal pain	2 (4.9)	3 (7.1)
Influenza	1 (2.4)	3 (7.1)
Any adverse events	35 (85.4)	29 (69.0)
SAE during intervention – no. of patients (%)		
Infusion reaction	1 (2.4)	0
Pneumothorax	1 (2.4)	0
Visual-field defect	0	1 (2.4)
Any SAE	2 (4.9)	1 (2.4)

^a Shown are the AEs that occurred in 5% or more of patients in either study group within 21 days after the final dose of the trial drug or placebo.

Abbreviation: AE, adverse event; ITT, intention-to-treat, SAE: serious adverse event

Source: Douglas *et al.* (2020), U.S. Amgen (2019).^{80, 139}

B.2.10.1.3 Pooled Analysis from Phase 2 and Phase 3 OPTIC

During the 24-week treatment period, most AEs were mild to moderate (grade 1 or 2) in intensity with placebo (98% [59 of 60]) and teprotumumab (94% [63 of 67]).

Serious adverse events were observed in 8% (seven of 84) patients in the teprotumumab group, including diarrhoea, infusion reaction, Hashimoto's encephalopathy, Escherichia sepsis, urinary retention, pneumothorax, and inflammatory bowel disease. Among these, three events reported in the integrated analysis of diarrhoea, infusion reaction, and Hashimoto's encephalopathy (coincident with confusion), were deemed related (or possibly related) to teprotumumab and led to study discontinuation. No deaths were reported.¹¹³

Table 30 outlines AEs observed in at least 5% of patients in either integrated trial group

Table 30: Adverse Events and Serious Adverse Events (≥5% of patients) – Pooled Analysis

	Teprotumumab (n=84)	Teprotumumab related ^a (n=84)	Placebo (n=86)
Summary of adverse events in double-masked study period – no. of patients (%)			
AEs	67 (80)	47 (56)	60 (70)
SAEs	7 (8)	3 (4) ^b	1 (1)
Deaths	0	0	0
AE occurring in ≥5% of patients in the double-masked study period – no. of patients (%)			
Muscle spasms	21 (25)	16 (19)	6 (7)
Nausea	14 (17)	8 (10)	8 (9)
Alopecia	11 (13)	8 (10)	7 (8)
Diarrhea	10 (12)	7 (8)	7 (8)
Fatigue	10 (12)	3 (4)	6 (7)
Hyperglycemia	8 (10)	7 (8)	1 (1)
Hearing impairment	8 (10)	4 (5)	0
Dysgeusia	7 (8)	4 (5)	0
Headache	7 (8)	5 (6)	6 (7)
Dry skin	7 (8)	4 (5)	0
Rash	5 (6)	3 (4)	5 (5)

^a Probably or possibly related to teprotumumab as assessed by investigator.

^b The SAEs reported by investigator as teprotumumab-related or possibly related: infusion-related reaction, diarrhea, and Hashimoto's encephalopathy

Abbreviation: AE, adverse event; ITT, intention-to-treat, SAE: serious adverse event

Source: Kahaly *et al.* (2021).¹¹³

B.2.10.1.4 Cumulative Safety Experience

The periodic benefit-risk evaluation report (PBRER) for teprotumumab assessed all new available safety information received within the period of 21st January 2024 to 20th July 2024 by the US marketing authorisation holder.¹⁵²

As of the report date of 16th September 2024, a total of 725 subjects have been exposed to teprotumumab in Amgen-sponsored clinical trials. The post-authorisation patient exposure was estimated to be 1,297 patient years during the reporting period and 10,565 patient years cumulatively from 21st January 2020 (the approved date for marketing of teprotumumab in the US) to 20th July 2024.¹⁵²

Hearing impairment is a significant identified risk associated with teprotumumab. The US prescribing information has added hearing impairment, including hearing loss, to the 'Warnings and Precautions' section. During the reporting interval from 21st January 2024 to 20th July 2024, and cumulatively through July 20, 2024, there were 943 cases with 1,261 events of hearing impairment reported from post-marketing sources. Tinnitus and hypoacusis were the most frequently reported conditions, accounting for 504 events (39.97%) and 392 events (31.09%), respectively. Out of the 1,261 events, 976 (77.4%) were classified as non-serious, while 285 (22.6%) were classified as serious.¹⁵²

In a prospective TED case series, 22 of 27 patients (81.5%) reported otologic changes. Of these, 11 patients reported hearing loss and 45.5% (5 of 11) of patients with subjective hearing loss experienced resolution.¹⁵³ Notably, a retrospective study found that 20% of TED patients who were not treated with teprotumumab also had diagnosis of hearing loss, indicating that some TED patients may have hearing changes before exposure to teprotumumab and highlighting the need for baseline audiometric testing.¹⁵⁴ A prospective study conducted baseline audiometric testing and showed that, after treatment with teprotumumab, 1 of 32 TED patients with normal baseline audiograms had new onset hearing loss at 6-month follow-up and 4

of 20 TED patients who had baseline hearing dysfunction had worsening of their hearing.¹⁵⁵

Based on pre- and post-authorisation experience, the safety concerns presented in Table 31 were considered to be important identified risks, important potential risks, and missing information at the beginning of the reporting period.¹⁵²

Table 31: Summary of Safety Concerns at the Beginning of the Periodic Benefit-Risk Evaluation Reporting Period

Risk category	Safety concern
Important identified risks	Infusion reactions (hypersensitivity) Hyperglycaemia Exacerbation of Inflammatory Bowel Disease Hearing Impairment
Important potential risks	New Onset of Inflammatory Bowel Disease
Missing information	None

Source: Amgen (2023).¹⁵²

Based on pre- and post-authorisation experience, the safety concerns considered to be the most important identified risks were infusion reactions (555 cases reported with 732 events), hyperglycaemia (533 cases reported with 611 events), exacerbation of inflammatory bowel disease (16 cases reported with 16 events), and hearing impairment (943 cases reported with 1261 events).

Based on the information presented in this latest PBRER, the report authors concluded there was no significant change in the risk profile of teprotumumab. Therefore, the risk-benefit profile remains favourable for the US approved indication.¹⁵²

B.2.10.3 Safety conclusions

The clinical evidence showed that teprotumumab was safe and well-tolerated in patients with TED. The rate of any AEs in the teprotumumab group compared to the placebo group was 74 - 85% versus 69 - 73% across Phase 2 and OPTIC. The rate of any TEAE in the teprotumumab group and in the placebo group was comparable in Phase 4 studies for chronic TED. The most common AEs in the teprotumumab group were muscle spasms, alopecia, nausea, diarrhoea, dry skin, dysgeusia and

hearing impairment. SAEs were uncommon with teprotumumab in all pivotal studies (2.4 - 12% with teprotumumab vs. 2 - 5% with placebo). No deaths or anaphylactic reactions occurred during the trials. Overall, the reported AEs were generally of limited duration and able to be managed without leading to discontinuation of the trial drug.

B.2.11 Ongoing studies

There are no completed or ongoing studies for teprotumumab that are expected to provide additional evidence relevant to the decision problem during the next 12 months.

B.2.12 Interpretation of clinical effectiveness and safety evidence

The efficacy and safety of teprotumumab in active, moderate-to-severe TED have been consistently demonstrated in two multicentre, randomised, double-blind, placebo-controlled studies (Phase 2 and Phase 3 OPTIC studies, section 2.2) and in the open-label extension study (OPTIC-X, Appendix M). The collective results from these studies provide strong evidence of teprotumumab's clinical benefits in patients with active disease, showing rapid improvements in proptosis, CAS and overall response (proptosis plus CAS) compared to placebo, as well as clinically meaningful improvements in patient QoL.

Teprotumumab's mechanism of action, involving IGF-1R inhibition, significantly reduces muscle and fat tissue remodelling, correlating with reductions in proptosis and diplopia.¹⁴⁶ A pooled analysis of the phase 2 and OPTIC studies showed that 77% of patients treated with eight doses of teprotumumab experienced at least a 2 mm reduction in proptosis at week 24, compared to only 15% in the placebo group¹¹³ and an overall response rate of 74% in the teprotumumab group vs 14% in the placebo group ($p < 0.001$). Moreover, the level of proptosis reduction was comparable to that achieved through orbital decompression, suggesting teprotumumab can prevent the need for orbital decompression surgeries.¹⁴⁵ Additionally, a study found a statistically significant difference between the bony decompression rates in the teprotumumab and control groups (20% vs 85%, $p < 0.0001$) in practice patterns for the treatment of TED.¹⁵⁶ In terms of diplopia improvement, 70% of patients in the teprotumumab group showed an improvement

of ≥ 1 grades, compared to 31% in the placebo group. Furthermore, 61.9% achieved a CAS of 0 or 1 in the teprotumumab group versus 21.8% in the placebo group at week 24. The differences in improving response rates on diplopia, proptosis and CAS between placebo and teprotumumab were statistically significant.¹¹³

The trials also revealed teprotumumab's effects on the non-study eye. In the phase 2 study, 52.4% of patients in the teprotumumab group achieved overall response (≥ 2 points reduction in CAS plus ≥ 2 mm reduction in proptosis) in non-study eyes, compared to only 13.3% in the placebo group (sections 2.2.1).

The OPTIC-X extension trial evaluated teprotumumab in patients from the OPTIC study who were non-responsive or experienced a disease flare. This trial demonstrated teprotumumab's effectiveness, with nearly 80% of initial non-responders or those experiencing a disease flare following initial response showing improved proptosis by at least two mm upon re-treatment.

Regarding patients' HRQoL, teprotumumab improved visual function, appearance, and overall HRQoL. In acute, moderate-to-severe TED patients, the GO-QoL overall scores and scores on the visual and appearance subscales were significantly better with teprotumumab than with placebo at week 24. The pooled analysis of phase 2 and OPTIC trials reported mean changes of 19.01 vs 6.3, 19.7 vs 7.0, and 17.7 vs 5.6 in GO-QoL overall scores, visual functioning subscale, and appearance subscale in the teprotumumab vs placebo group, respectively, at week 24. These differences were statistically significant.¹¹³

In indirect comparisons using MAIC methodology, teprotumumab was associated with a statistically significantly greater mean difference change from baseline in proptosis compared to both IVMP (mean difference in CFB: [REDACTED] mm [95% CI: [REDACTED]]) and IVMP + MMF (mean difference in CFB: [REDACTED] mm [95% CI: [REDACTED]]). The odds of diplopia response for patients treated with teprotumumab were more than three times higher than for those treated with IVMP, which was a statistically significant result (OR: [REDACTED] [95% CI: [REDACTED]])

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Teprotumumab was well-tolerated across clinical trials (section 2.6.1), with a consistent safety profile as per the cumulative safety report (section 2.6.2). In clinical Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

trials, the most frequently reported AEs associated with teprotumumab were muscle spasms, alopecia, nausea, diarrhoea, dry skin, dysgeusia, and temporary hearing loss. These AEs were mild or moderate in severity, mostly transient or temporary, and generally well tolerated.

Strengths and limitations of the clinical evidence

Based on clinical study data, the evidence base supporting the safe and effective use of teprotumumab includes the following strengths^{49, 145, 157}:

- Teprotumumab's efficacy in active, moderate-to-severe TED was evaluated in two pivotal studies: the phase 2 trial and phase 3 OPTIC studies. These studies, designed as randomised, double-blind, placebo-controlled, parallel-group trials, represent the gold standard in evaluating causal relationships, as randomisation mitigates much of the bias inherent in other study designs. This design also allows for attributing outcome differences directly to the intervention. Overall, the clinical studies were of high quality, with clear definitions for each variable.
- In the phase 2 and OPTIC studies, patients were stratified at randomisation based on smoking status, a known risk factor for TED, to ensure balanced trial groups.
- The phase 2 and OPTIC studies were pooled for the purposes of analysis and used to inform the economic model.
- Teprotumumab's benefits were based on clinically meaningful primary and secondary endpoints:
 - Proptosis reduction by 2mm or more is expected to reduce diplopia and improve corneal epithelial health by allowing the lids to fully cover the cornea
 - CAS of 0 or 1 is widely accepted as indicative of absence of disease activity.⁴⁷
 - A change of at least six points in the GO-QOL questionnaire is considered clinically significant for non-invasive therapy.⁷⁹
- In general, demographic and baseline characteristics were comparable among the treatment groups.
- Analysis of age and gender subgroups did not show differences in response to teprotumumab. Reduction in proptosis was similar between smokers and non-

smokers in the phase 2 and OPTIC studies, although this post-hoc analysis was limited by the small number of smokers in the teprotumumab group.

- Reported AEs were generally of limited duration and manageable without interrupting therapy. The safety profile of teprotumumab in patients with ophthalmopathy is encouraging and consistent with previous oncology studies and other anti-IGF-IR antibody studies.

Limitations of the evidence base for the safe and effective use of teprotumumab for TED include^{49, 145, 157}:

- The phase 2 trial used in the economic model included patients treated in the UK, but the phase 3 OPTIC trial did not. However, both trials did include patients treated in a European setting.
- The trials enrolled only patients with recently onset acute disease (CAS of four or more), not assessing teprotumumab's potential in patients with milder, less active, or stable disease. The EUGOGO guidelines suggest treating at CAS ≥ 3 (i.e. the participants in OPTIC had higher degrees of disease activity at baseline than might be expected in UK clinical practice). However, it is expected that the outcomes observed in the pivotal trials will be generalisable to TED patients with a CAS of 3 or more, which is the point at which UK clinicians would typically want to initiate treatment.
- In the phase 2 trial, the lack of orbital imaging leaves uncertainty about which orbital tissues were primarily affected by the therapy. The orbital imaging before and after the teprotumumab treatment was conducted in the phase 3 OPTIC study.
- CAS alone may not be reliable indicator of disease activity in patients with darker skin.

Only subjects with an underlying diagnosis of GO were enrolled into the OPTIC trial. However, the trial outcomes are expected to be generalisable to all TED patients with active disease, whether they have underlying GO or other forms of autoimmune thyroid disease.

- A formal indirect treatment comparison has been carried out by the submitting company between teprotumumab and the most commonly-used treatment option for active TED, IVMP and IVMP + MMF. As per the decision problem, azathioprine, ciclosporin and orbital radiotherapy (all usually in combination with oral or IV steroids) may also be used to treat moderate to severe active TED in the NHS, however these alternative comparators are used much less frequently, and almost exclusively as a second or subsequent line option for people with an inadequate response to IVMP and IVMP + MMF. The evidence base for these alternative comparators is lacking, especially at later lines of treatment, given they are used off label, and as such it was not possible to do a formal comparison. However, it may be assumed, conservatively, that teprotumumab is at least as effective vs. azathioprine, ciclosporin and orbital radiotherapy at second and later lines, as it is versus IVMP and IVMP + MMF at first line, and the outcomes observed in the clinical studies and in the MAIC versus IVMP and IVMP + MMF are generalisable to other comparators at second line for the following reasons:

1. These other agents are expected to be less effective than the current standard of care, IVMP and IVMP + MMF, at treating TED at second or subsequent lines of therapy. Robust evidence for their use is limited, however there is published literature to indicate a lack of additional benefit over and above that conferred by steroids:
 - In the UK CIRTED RCT and CIRTED extended study, the authors concluded that there was no added benefit to adding orbital radiotherapy or immunosuppression (azathioprine) to the standard TED treatment of systemic corticosteroids.¹⁵⁸
 - In a study comparing prednisone and ciclosporin, the authors found that among the 9 patients who initially received prednisone, the addition of ciclosporin resulted in improvement in 5 patients (56 percent), and concluded that single-drug therapy with prednisone was more effective than ciclosporin in patients with severe disease.¹⁵⁹

2. TED patients who have not responded, or who are refractory, to IVMP +/- MMF, are expected to be harder to treat using other existing therapies given they only target inflammation and symptoms of TED, rather than the underlying pathogenesis of the disease;^{160, 161} and
3. As a result of its targeted mechanism of action, the clinical efficacy outcomes for teprotumumab-treated patients observed in the phase 2 and phase 3 clinical trials and OLE are expected to be similar whether or not the patient has received prior treatment for their TED or not; that is, the clinical benefits of teprotumumab are assumed irrespective of line of therapy and so the benefits observed at 1L would be expected to be similar at 2L. There is recent real-world data to support this assumption:
 - Toro-Tobon et al. evaluated the clinical outcomes and safety of teprotumumab and tocilizumab in patients with steroid-resistant TED. The authors concluded that teprotumumab improved inflammation in patients with moderate-to-severe TED who had failed previous steroid therapy and showed similar improvement in proptosis and diplopia to the teprotumumab controls.¹⁶²
 - Tamhankar and colleagues concluded that teprotumumab is an effective treatment in patients with DON in whom previous treatment with steroids, surgery or orbital radiotherapy was unsuccessful.¹⁶³

As such, it may be conservatively assumed that the clinical trial outcomes for teprotumumab observed in the previously-untreated active TED population and the results of the MAIC can be generalised to second [and subsequent] treatment settings. Given that all other treatment options are expected to show lower efficacy than IVMP and IVMP + MMF irrespective of line of therapy, teprotumumab may conservatively be expected to be no less effective or cost-effective as a second or subsequent treatment as it is vs. IVMP and IVMP + MMF in the untreated population.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Two systematic literature reviews were conducted to identify 1) economic evidence and 2) healthcare resource use (HCRU) evidence associated with moderate-to-severe active thyroid eye disease (TED). The original database searches were conducted in May 2023 and later updated in October 2024, which included cost-effectiveness, -utility, -benefit, -minimisation studies, and budget-impact analysis studies. Systematic reviews, meta-analyses, pooled analyses, and match-adjusted indirect comparisons (MAICs) were also included for cross-checking purposes. Searches were limited to English-language publications without geographical restrictions within the last 10 years. Manual searches of conference abstracts were performed for three conferences, published between 2020 and 2024.

Thirteen unique studies were included in the economic/HCRU SLRs, of which seven were retrospective studies, two were randomized controlled trials (RCT), four were cross-sectional in design, and one study, Holt *et al.* (2022) examined QALYs in moderate-to-severe TED.¹⁶⁴ Full details of the economic SLR are given in Appendix G.

No cost-effectiveness, cost-utility, or cost-benefit studies were identified in the economic SLR for teprotumumab in moderate-to-severe TED patients. One study, Holt *et al.* (2022), was identified in the economic SLR, which examined QALYs in moderate-to-severe TED.¹⁶⁴

B.3.2 Economic analysis

In the absence of any published cost-effectiveness analyses of teprotumumab for the treatment of moderate-to-severe active TED, a *de novo* cost-effectiveness model (CEM) was developed in line with NICE's reference case.¹⁶⁵ Details of the CEM methodology, structure, and data population are given in the following sections.

B.3.2.1 Patient population

The patient population in the CEM reflects the indication under appraisal, of moderate-to-severe active TED. This population is aligned with the inclusion criteria of both the Phase 2 clinical trial and the Phase 3 OPTIC clinical trial,^{166,142} with the Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

model base-case populated using pooled clinical data to maximise the sample size. The decision to pool the clinical trial data was made due to the small number of patients, and the small-time window (2-3 years) of active disease for these patients on presentation before more permanent physiology occurs. Baseline characteristics are presented in Table 32, and detailed further in Section 2.3.2.

Table 32: Patient characteristics

Characteristic	Pooled Phase 2 and Phase 3 OPTIC ^{142, 166}
N.	171
Mean age (years), (SD)	51.58 (12.34)
Male (%)	27.03
Mean weight (kg), (SD)	78.07 (19.08)

Abbreviations: kg, kilogram; N, number; SD, standard deviation.

Source: Amgen (2020), Amgen (2017).^{142, 166}

B.3.2.2 Model structure

A cohort-based, six health state, Markov model was developed in Microsoft Excel® to estimate the costs and QALYs associated with moderate-to-severe active TED patients treated with teprotumumab or comparator treatment(s), with the assessment run over a modelled lifetime time horizon, as per the NICE reference case (Figure 33).¹⁶⁵

Patients enter the active disease model in one of six distinct health states to represent the range of clinical presentations in TED. These modelled health states are defined by the combination of TED symptomatic proptosis and diplopia scores, and are consistent with the teprotumumab clinical trial endpoints (Section 2.6). The choice and robustness of the health state definitions were validated for their relevance to the clinical management and impact of TED by a selected group of UK clinical experts.¹⁴¹

The six active TED disease health states are based on the following symptom presentation pairings:

- Small proptosis, no diplopia.
- Large proptosis, no diplopia.
- Small proptosis, intermittent/inconstant diplopia.
- Large proptosis, intermittent/inconstant diplopia.
- Small proptosis, constant diplopia.

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- Large proptosis, constant diplopia.

The definitions used to characterise proptosis are aligned with the American Thyroid Association severity classification.¹⁶⁷ ‘No proptosis’ was not considered as a health state in the model as the model describes patients with moderate-to-severe TED (proptosis would be expected to be present by definition, unlike diplopia which may or may not be present). Proptosis is described by the change from the upper limit of normal for a non-TED patient of the same race and sex, with the upper limits of normal for proptosis by race and sex are given in Table 33.¹⁶⁷

The definitions for classifying proptosis severity are:

- Small proptosis: <3 mm above the upper limit of normal for a non-TED patient of the same race and sex.
- Large proptosis: ≥3 mm above the upper limit of normal for a non-TED patient of the same race and sex.

Table 33: Upper limit of normal proptosis by race and sex

Race	Sex	
	Female (mm)	Male (mm)
African American	23	24
White	19	21
Asian	16	17 (Thai) 18.6 (Chinese)

Abbreviations: mm, millimetre.

Source: Ross *et al.* (2016).¹⁶⁷

The definition used to characterise diplopia are aligned with the Clinical Measures of Severity assessment.¹⁶⁸ For the CEM, the intermittent and inconstant scores were combined to a single state, to minimise the number of health states represented in the CEM, and to address uncertainty in generating the transition probabilities from the relatively small patient sample size. Furthermore, this approach aligned with the utility data available from the study Smith *et al.* 2023, which noted that the decrease in disutility for lower diplopia states, such as intermittent and inconstant, was minimal.¹⁶⁹

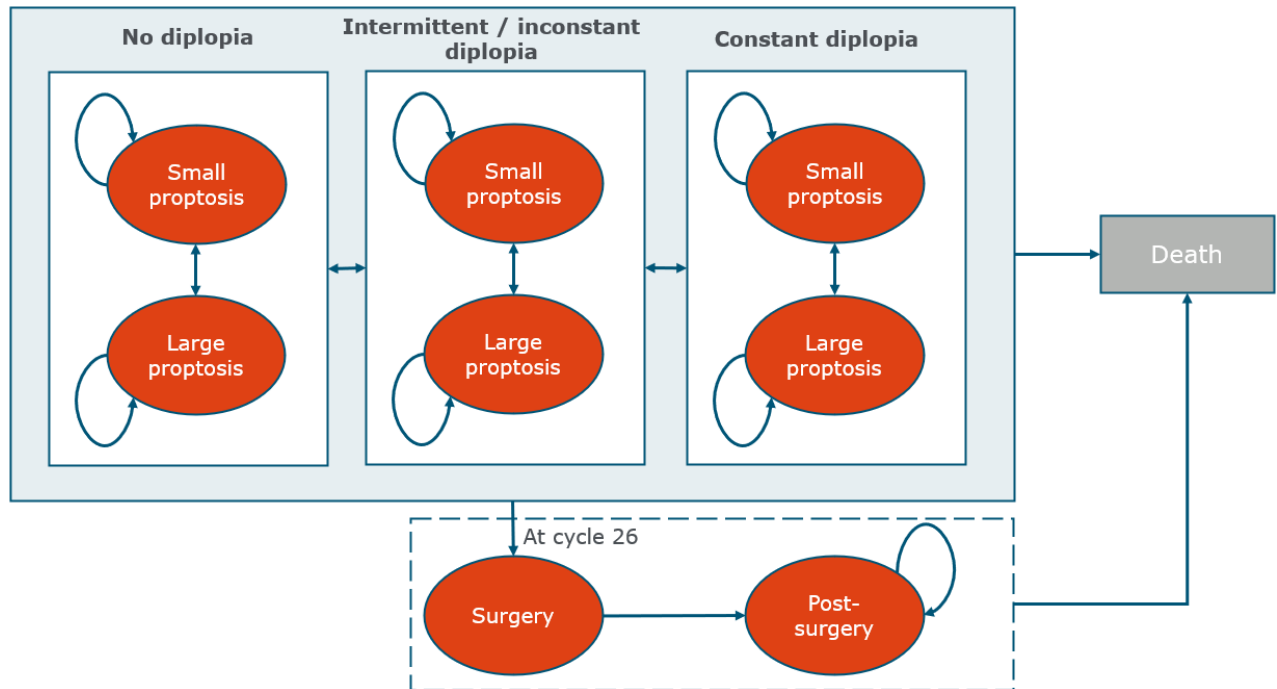
The definitions for classifying diplopia severity are:

- No diplopia: Clinical Measures of Severity assessment score of 0.

- Intermittent/inconstant diplopia: Clinical Measures of Severity assessment score of 1 (intermittent) or 2 (inconstant).
- Constant diplopia: Clinical Measures of Severity assessment score of 3.

The definitions for proptosis and diplopia are then combined to give the six defined health states of the CEM.

Figure 33: Model schematic*



*Only a proportion of patients enter the surgery health state at cycle 26, informed by UK clinicians.¹⁴¹ Patients who do not transition to the surgery health state remain in their respective health states for the remainder of the model time horizon.

The starting distribution in the active disease model base-case is informed by the pooled baseline distribution of patients in Phase 2 and Phase 3 OPTIC trials (Table 34).^{142, 166} Patients can then transition to any of the active disease modelled health states, or remain in their current state, at each model cycle (based on a 6-week cycle length). Death is included as an absorbing state that patients may enter at any time.

Table 34: Baseline distribution of patients entering the model^{142, 166}

Small proptosis, no diplopia	Large proptosis, no diplopia	Small proptosis, intermittent/inconstant diplopia	Large proptosis, intermittent/inconstant diplopia	Small proptosis, constant diplopia	Large proptosis, constant diplopia

Source: Amgen (2020), Ross *et al.* (2016).^{142, 166}

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Two additional health states, based on Surgery and Post-surgery, are included in the model to reflect a proportion of patients who will go on to receive treatment as part of their TED treatment pathway.

A proportion of patients transition to the Surgery health state at three years (26 cycles, 6-week cycle length), and remain in this health state for 3.5 years (30 cycles), before transitioning to a Post-surgery health state where they remain for the remaining duration of the modelled lifetime. The duration of the Surgery health state accounts for patients who may receive multiple surgeries, with a long waiting time between surgeries.

The Surgery and Post-surgery transition time points, and the proportion of patients transitioning to the Surgery health state from each of the active disease health states Table 35), are informed and validated by UK clinicians due to a lack of data in the literature.¹⁴¹ Uncertainty in the Surgery transition time point and the duration of the Surgery health state are explored further in the scenario analysis.

Patients who do not transition to the Surgery and Post-surgery health states (the majority of patients with TED) remain in the six-health health state disease model for the lifetime horizon, or until a death event, given proptosis and diplopia are symptoms relevant to both the active and chronic TED. The CEM does not formally model the transition from active to chronic TED.

Table 35: Proportion of patients transitioning to surgery state in the active model (at model cycle 26 / 3 years)

	Small proptosis , no diplopia	Large proptosis , no diplopia	Small proptosis, intermittent t/ inconstant diplopia	Large proptosis, intermittent t/ inconstant diplopia	Small proptosis , constant diplopia	Large proptosis , constant diplopia
Proportion of patients (%)						

Source: Amgen (2024).¹⁴¹

Patients in the Surgery health state can receive one of four types of surgeries: orbital decompression, strabismus, eyelid blepharoplasty (upper lid), and blepharoplasty

(lower lid). The choice of surgeries were informed by the EUGOGO 2021 guidelines and validated by UK clinicians.^{141, 170}

Surgery procedure and complication costs are applied as a one-off cost in the model, described in Section 1.6.1.3.

B.3.2.2.1 Time horizon

As TED is a chronic disease, composing of an active and an extended chronic stage, a lifetime horizon (up to a patient age of 100 years) was considered appropriate to capture the future costs and outcomes associated with treating moderate-to-severe TED patients. This is consistent with the NICE reference case, states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.¹⁶⁵

B.3.2.2.2 Cycle length

The CEM uses a cycle length of six weeks, aligned with patient efficacy assessment time points in both the Phase 2 and Phase 3 OPTIC clinical trials^{142, 166} and dosing regimens for teprotumumab and comparators. Half-cycle correction is applied in the model base-case.

B.3.2.2.3 Discounting

A discount rate of 3.5% per annum was applied in CEM base-case to life years (LYs), QALYs, and costs, in line with the National Institute for Health and Care Excellence (NICE) reference case.¹⁶⁵ An alternative discount rate applied of 1.5% was explored in the scenario analysis.

B.3.2.2.4 Perspective

The analysis was conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, in line with the NICE reference case.¹⁶⁵

B.3.2.3 Features of the economic analysis

Key features of the economic analysis are presented in Table 36.

Table 36: Features of the economic analysis

Factor	Chosen values	Justification
Patient population	Adults with moderate-to-severe active TED.	Reflective of the indication under appraisal.
Model structure	Markov model	1. Aligned with the outcomes of the Phase 3 OPTIC clinical trial. 2. A partitioned survival model was believed not to accurately capture the dynamics of the disease pathway. 3. Insufficient patient data did not allow for a robust patient level simulation modelling.
Time horizon	Lifetime	In line with NICE reference case. ¹⁶⁵
Discounting	3.5% per annum	In line with NICE reference case. ¹⁶⁵
Perspective	NHS and PSS	In line with NICE reference case. ¹⁶⁵
Source of clinical efficacy and safety	Pooled Phase 2 and Phase 3 OPTIC clinical trial.	Maximised the sample size of clinical data due to rare nature of TED.
Source of utilities	US qualitative study ¹⁶⁹	Validated by UK clinicians ¹⁴¹ , multiple regression analysis demonstrated alignment with GO-QoL scores from the Phase 3 OPTIC clinical trial.
Source of costs	NHS, PSS costs, and relevant literature where appropriate.	In line with NICE reference case. ¹⁶⁵
Treatment waning effect?	Not included	Treatment effect is captured within the transition matrices (as patients move fluidly across the health states). Patients with TED are not expected to experience significant changes to their levels of proptosis and diplopia after treatment cessation.

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal social services; TED, thyroid eye disease.

B.3.2.4 Intervention technology and comparators

Intervention

The intervention considered in this analysis is teprotumumab, at a dose of 10 mg/kg patient body weight for the first infusion, and 20 mg/kg once every 3 weeks thereafter for an additional seven infusions.¹⁴² The mean patient weight of 78.07 kg from the pooled from the Phase 2¹⁶⁶ and Phase 3 OPTIC¹⁴² clinical trials was used to calculate the total dosage per administration.

Comparators

Teprotumumab is a first-in-class medication, with the currently available comparators only targeting symptom management and not the underlying disease. The main comparators selected in the CEM are intravenous methylprednisolone (IVMP), and IVMP combined with mycophenolate mofetil (MMF); both of which are used off-label. These comparators are consistent with the main first-line treatment options detailed in the EUGOGO 2021 clinical practice guidelines, typically adhered to by UK clinicians¹⁴¹, given no published UK guidelines for TED.¹⁷⁰ Please see Section B.1.3 for discussion of other comparators listed within the decision problem.

The dosing regimen administered for IVMP was based on the EUGOGO 2021 clinical practice guidelines.¹⁷⁰ Patients are recommended to receive 500 mg weekly for the first six weeks, followed by 250 mg weekly for the next six weeks.¹⁷⁰ For IVMP + MMF, the dosing regimen of IVMP is the same as IVMP monotherapy, with the addition of a 1,000 mg MMF oral tablet taken daily for 24 weeks.¹⁷⁰

B.3.3 Clinical parameters and variables

The clinical parameters included in the economic analysis include:

1. Transition probabilities between the six active disease health states, and to the surgery health state.
2. Discontinuation and compliance.

Adverse events are considered in terms of their impact on costs and health-related quality of life in Section B.4.4.4.

B.3.3.1 Transition probabilities between health states

Transition probabilities are used to capture the patient's movement between the defined proptosis and diplopia end points, described in Section B.1.3.2. Transition probabilities are applied at each 6-week model cycle, and are dependent on the treatment the patient receives.

The IVMP and IVMP + MMF transition probability calculations were developed in collaboration an external expert, who validated the method and performed a quality check of the calculations to ensure accuracy.

Teprotumumab

The teprotumumab transition probabilities were calculated for each 6-week cycle, up to 24 weeks, and informed by the pooled patient data from the Phase 2 and Phase 3 OPTIC clinical trials.^{142, 166} The full list of transition probability tables are described in Appendix J. The decision to pool patient data was made to increase the robustness of the transition probability estimates by increasing the available sample size, given the similarity of the trials in terms of patient eligibility and study design.

To derive the transition probability matrices, subjects were categorized at 6-weekly intervals, based on their subjective diplopia and proptosis scores. To calculate the transition probabilities per 6-week cycle, the number of patients within each health state at the start of each cycle was first determined. Following patient movement by the end of the cycle allowed for the transition percentages per health state per cycle to be calculated. For example, of the ten patients who were categorised as small proptosis, no diplopia at baseline (week 0) treated with teprotumumab, eight remained in the health state by week 6, resulting in a transition probability of 80% for patients to remain in the active health state. This calculation was performed for all active disease health states for the first four cycles for patients treated with teprotumumab.

IVMP and IVMP + MMF

Transition probabilities for IVMP and IVMP + MMF up to week 24 were informed by two separate *de novo* unanchored matching-adjusted indirect comparisons (MAICs). An MAIC approach was necessarily undertaken due to a lack of head-to-head Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

comparative evidence to teprotumumab. Full details of the MAIC methods and calculation to derive transition probabilities are given in Appendix D, a summary of the methods is given below.

De novo MAIC for IVMP (versus teprotumumab)

Eight identified studies were included in the IVMP MAIC, reporting on both proptosis and diplopia outcomes. Outcome and cohort data from these studies were compared to the pooled patient data for teprotumumab. Treatment effect modifiers and prognostic variables included in the MAIC were identified from a previous ITC comparing teprotumumab with IVMP,¹⁷¹ and validated by UK clinicians.¹⁴¹ Covariate selection was based on the order of importance determined by clinical opinion and on the availability of data from the IVMP studies, with covariates added in order of importance. Included covariates used in the base-case and scenario analysis are detailed in Table 37. The base-case results showed that teprotumumab is more effective at reducing proptosis versus IVMP (mean difference in change from baseline [CFB]: ██████████ mm [95% CI: ██████████]) and the result is statistically significant (CIs do not contain 0). Additionally, the odds of diplopia response in patients treated with teprotumumab is over three times higher than those treated with IVMP and is statistically significant (OR: ██████████ [95% CI: ██████████ ██████████]; CIs do not cross 1). Similar results were also observed for the two scenarios included in the model, with all results being statistically significant in favour of teprotumumab.

Table 37: De-novo ITC results (teprotumumab versus IVMP)

Covariates		Proptosis				Diplopia			
		ESS	MD (mm)	LCI	UCI	ESS	OR	LCI	UCI
Base-case	Smoking, baseline diplopia, baseline proptosis, RIT	██████████	██████████	██████████	██████████	██████████	██████████	██████████	██████████
Scenario 1	Smoking, baseline diplopia	██████████	██████████	██████████	██████████	██████████	██████████	██████████	██████████
Scenario 2	Smoking, baseline diplopia,	██████████	██████████	██████████	██████████	██████████	██████████	██████████	██████████

	baseline proptosis								

Abbreviations: CFB, change from baseline; ESS, effective sample size; ITC, indirect treatment comparison; IVMP, involves intravenous methylprednisolone; LCI, lower confidence interval; MD, mean difference; OR, odds ratio; RIT, radioiodine therapy; UCI, upper confidence interval.

Source: Amgen (2024).¹⁵⁰

The model assumes the IVMP transition probabilities for equal or worsening diplopia to be the same as teprotumumab, a conservative assumption in the absence of data, as the MAIC only reported on improving diplopia grade (and not for equal or worsening).

Given proptosis and diplopia were separate reported outcomes in the MAIC, separate IVMP proptosis and diplopia transition probability matrices were derived, and then combined by multiplying the proptosis and diplopia transition probabilities together. Given the MAIC had different endpoints for IVMP and teprotumumab due to the differing treatment lengths (week 12 and week 24, respectively), the IVMP transition probability matrices for weeks 1 – 6 and weeks 6 – 12 were adjusted to match the teprotumumab transition probabilities for weeks 1 – 12 and weeks 12 – 24, respectively.

De novo MAIC for IVMP + MMF (versus teprotumumab)

One study was included in the IVMP + MMF MAIC, and only reported proptosis outcomes.¹⁷² Similar to IVMP, the IVMP + MMF outcomes were compared to the pooled patient data for teprotumumab. Covariate selection was based on the order of importance determined by clinical opinion and on the availability of data from the IVMP + MMF study. Included covariates used in the base-case are detailed in Table 38. The base-case ITC results demonstrated that teprotumumab was associated with a statistically significantly greater mean CFB in proptosis compared to IVMP + MMF (mean difference in CFB:  mm [95% CI: ]).

Table 38: De-novo ITC results (teprotumumab versus IVMP + MMF)

Covariates		Proptosis			
		ESS	MD (mm)	LCI	UCI
Base-case	Smoking, baseline diplopia, baseline proptosis				

Abbreviations: ESS, effective sample size; LCI, lower confidence interval; mm, millimeters; MMF, mycophenolate mofetil; UCI, upper confidence interval.

Source: Amgen (2024).¹⁵⁰

The combined transition probabilities for IVMP + MMF were calculated from the proptosis transition matrix in the IVMP + MMF MAIC, and the diplopia transition matrix calculated from IVMP MAIC in the absence of data for IVMP + MMF. Given the IVMP + MMF MAIC endpoints were the same for both IVMP + MMF and teprotumumab, no adjustment to align timepoints with teprotumumab was made.

Alternative transition probabilities for IVMP and IVMP + MMF, explored in the scenario analysis, informed a separate published MAIC.¹⁷¹ Douglas *et al.* (2022) included 12 studies, looking at both RCT and non-RCT studies, with teprotumumab demonstrating an increase in proptosis response and diplopia compared to IVMP. Additionally, Douglas *et al.* (2022) chose to use the median and not the mean proptosis CFB, and matched on a different set of covariates (mean age, proportion of women and proportion of tobacco users) in their analysis.¹⁷¹ Therefore, is limited compared to the MAIC used in the CEM base-case.

B.3.3.2 Transition probabilities beyond 24 weeks

Patients remain in the health state they were in at 24 weeks for the remainder of the model duration, for all treatments, with the exception of the proportion of patients who move to the Surgery (and ultimately the Post Surgery) health state at cycle 26. Health states were stabilised in this way to offset the considerable inherent uncertainty in the data after this point. Although 72-week follow-up data for the OPTIC Phase 3 clinical trial is available, only a small number of patients completed this longer follow-up. Therefore, calculating robust long-term teprotumumab transition probabilities would not be possible without introducing considerable uncertainty, given some health states would be informed by individual patients or have zero occupancy. Furthermore, no published follow-up data were available for IVMP or IVMP + MMF beyond week 24.

B.3.3.3 Discontinuation, compliance, and flare

B.3.3.3.1 Treatment discontinuation

The model includes a treatment discontinuation rate to capture the number of patients who stop treatment in each cycle. Discontinuation was informed by all-cause discontinuation values, including discontinuation due to level of therapeutic benefit, adverse events and other causes. Patients who discontinue treatment no longer
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accrue primary treatment costs, adverse event costs, or resource use costs, and remain in the health state they were in when they discontinue treatment. This approach was taken for simplification as discontinued patients were included in efficacy estimates that inform the transition probabilities. Discontinued patients are still eligible for surgery in the cycle where surgery is applied.

The discontinuation probability for teprotumumab was calculated from the all-cause discontinuation of patients in the pooled Phase 2 and Phase 3 OPTIC trials.^{142, 166} The all-cause discontinuation probability for IVMP and IVMP + MMF were sourced from Kahaly *et al.* 2018,¹⁷² which was chosen given the large sample size (n=164) and dosing alignment to the assumption in the CEM. Discontinuation rates for all treatments were converted to a 6-week probability to align with the CEM cycle length. Due to limited data availability, the discontinuation probability is constant regardless of the cycle.

The probabilities of discontinuing in any given cycle are presented Table 39.

Table 39: Probability of discontinuing treatment in any given cycle

Treatment	Per cycle probability of discontinuation	Source
Teprotumumab	██████%	Pooled Phase 2 and Phase 3 OPTIC trials ^{142, 166}
IVMP	1.34%	Kahaly <i>et al.</i> (2018) ¹⁷²
IVMP + MMF	1.29%	Kahaly <i>et al.</i> (2018) ¹⁷²

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

Source: Amgen (2020), Amgen (2017), Kahaly *et al.* (2018).^{142, 166, 172}

B.3.3.3.2 Treatment compliance

Compliance is included in the CEM to account for missed doses for all treatments. Compliance for teprotumumab (██████) was calculated from the pooled Phase 2 and Phase 3 OPTIC trials, as the total number of doses received by all patients out of the total number of doses that would be received if all patients had completed the full treatment course.^{142, 166} To avoid double counting with discontinuation, missed doses were only considered for patients during the time they were on treatment (e.g. if a patient discontinued after receiving six doses, but they received all six doses up until this point, they would not be considered to have missed any doses).

Compliance for IVMP and IVMP + MMF was assumed to be equal to teprotumumab, due to lack of published data for either IVMP or IVMP + MMF.

The patient compliance is applied to the number of patients in each health state per cycle to calculate the treatment cost per cycle, with the same compliance percentage applied irrespective of health state and cycle number.

B.3.3.3.3 Disease flare

There is no strong evidence to suggest patients teprotumumab have a difference in flare rate compared to either IVMP or IVMP + MMF. Furthermore, wider evidence around the clinical implications of flare, and treatment of flare, is lacking. Therefore, disease flares are not captured within the model to reduce the level of uncertainty and complexity within the economic analysis.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

The Graves' orbitopathy quality of life (GO-QoL) questionnaire, recommended by the EUGOGO guidelines,¹⁷⁰ was used to assess health-related quality of life (HRQoL) in the Phase 3 OPTIC clinical trial. This follows NICE's guidelines on using alternative methods to generate health state utility values when the EuroQol 5 Dimension (EQ-5D) questionnaire is not suitable.¹⁷³ With the NICE DSU acknowledging that EQ-5D is probably not appropriate for assessing specific forms of visual impairment.¹⁷⁴ The limitations of the EQ-5D to accurately assess eye conditions and visual impairment are well known, and considered to be inferior to disease-specific alternatives in conditions such as Grave's disease,¹⁷⁵ age-related macular degeneration and diabetic retinopathy,¹⁷⁶ chronic ophthalmological disease,¹⁷⁷ and patients with various levels of low vision. EQ-5D was therefore not collected in the Phase 3 OPTIC clinical trial.¹⁷⁸

B.3.4.2 Mapping

Mapping to EQ-5D would not overcome the fundamental limitations of EQ-5D in accuracy and sensitivity in eye conditions, and there is currently no mapping algorithm available to transform the outcomes from the GO-QoL to EQ-5D.¹⁶⁵ Therefore, alternative sources of utilities were explored.

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B.3.4.3 Health-related quality of life studies

In the absence of a mapping algorithm to convert the OPTIC clinical trial patient reported data (GO-QoL) to EQ-5D, an initial targeted literature review was conducted to explore alternative sources of utility values. Beauchamp *et al.* (2005) reported utility values by different grades of diplopia in patients with strabismus, but did not report whether the patients had active TED.¹⁷⁹ Gerding *et al.* (1997) and Choi *et al.* (2012), were also identified, but were excluded as neither were deemed suitable; the former reporting limited data on TED patients in a study conducted over 25 years ago, and the latter only reporting on a Korean population.^{180, 181}

Due to the limited available literature and no EQ-5D available, a new utility study was conducted specific to active moderate-to-severe TED¹⁶⁹; following NICE's hierarchy of preferred HRQoL methods.¹⁶⁵ The TED health state vignettes used in the TTO approach were developed from patient interviews, two placebo-controlled clinical trials,¹⁸²⁻¹⁸⁴ validated by clinicians, and align with the six-health state Markov model in this appraisal. The utility values from Smith *et al.* (2023) were further validated by UK clinicians, who agreed they were reflective of the quality of life seen for moderate-to-severe active TED patients in the UK.¹⁴¹ Multiple regression analysis was performed to validate the health state utility values derived from the TTO study with GO-QoL scores.¹⁸⁵ An updated HRQoL SLR was also performed in October 2024 (Appendix H), however this only found the Smith *et al.* (2023) study as a source for utility values.

The health state utility values from Smith *et al.* (2023), used in the base-case, are presented in Table 40. Utility values associated with the Surgery and Post-surgery health states are averages of the four lowest utility values and the four highest utility values, respectively.¹⁶⁹ This assumption was made in the absence of published alternatives, given patients post-surgery are likely to have a greater quality of life compared with patients currently undergoing surgery.

Table 40: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
Small Proptosis, No Diplopia	0.60	0.54-0.67	Smith <i>et al.</i> , 2023 ¹⁶⁹

Large Proptosis, No Diplopia	0.46	0.40-0.52	Smith <i>et al.</i> , 2023 ¹⁶⁹
Small Proptosis, Intermittent/Intermittent Diplopia	0.52	0.45-0.58	Smith <i>et al.</i> , 2023 ¹⁶⁹
Large Proptosis, Intermittent/Intermittent Diplopia	0.43	0.36-0.49	Smith <i>et al.</i> , 2023 ¹⁶⁹
Small Proptosis, Constant Diplopia	0.34	0.29-0.40	Smith <i>et al.</i> , 2023 ¹⁶⁹
Large Proptosis, Constant Diplopia	0.30	0.24-0.36	Smith <i>et al.</i> , 2023 ¹⁶⁹
Surgery	0.38	-	Assumed to be the average of four highest utility values
Post-surgery	0.50	-	Assumed to be the average of four lowest utility values

Source: Smith *et al.* (2023)¹⁶⁹

B.3.4.4 Adverse events

The model base-case includes adverse events that were $\geq$ Grade 3, and occurred in $\geq 5\%$ of patients. The CEM assumes Grade 1 and 2 adverse events can be managed by the patient at home and, therefore, have minimal impact in terms of cost to the NHS.

Adverse events for teprotumumab were informed by the Phase 2 and Phase 3 OPTIC clinical trials (Table 41).^{142, 166} The most common adverse events reported for teprotumumab were muscle spasms, nausea, and alopecia. No adverse events for teprotumumab were included in the base-case as they did not meet inclusion criteria ($\geq$ Grade 3; $\geq 5\%$ of patients).

Adverse events for IVMP were informed by the relevant literature (Table 42), with the adverse event probabilities for IVMP + MMF assumed equal to IVMP, given the lack of published data available for this comparator. Salvi *et al.* (2015), used to inform IVMP and IVMP + MMF adverse event incidence, was chosen in the base-case as it was the only identified studies that reported $\geq$ Grade 3 adverse events that occurred in $\geq 5\%$ of patients.¹⁸⁶ Three additional studies were identified, which reported any Grade adverse events that occurred in 5% (not specified by $\geq$ Grade 3).¹⁸⁷⁻¹⁸⁹

Adverse events reported in these three studies are explored in the scenario analysis,

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as three separate scenarios, in addition to a scenario where adverse events are not included.

For each included study, the duration over which each reported adverse event probability was measured differed. Therefore, the adverse event probability was transformed to a probability over a 6-week period, to align with the model cycle length.

Equation 1 first converts the probability (p) into a rate (r) over the study report time period (t), the denominator is divided by six to scale the rate to a six-weekly rate.¹⁹⁰ Equation 2 then converts the rate back into a probability.

Equation 1:

$$r = \frac{-[\ln(1-p)]}{t/6}$$

Equation 2:

$$p = 1 - e^{-rt}$$

Table 41: Adverse event probabilities per cycle used in the model for teprotumumab and BSC

Treatment	Adverse event	Phase 2 and Phase 3 OPTIC ^{142, 166}					
		All AEs >5%		Per cycle: All AEs >5%		Mode base-case: Only Grade ≥3 AEs in ≥5%	
Teprotumumab	Muscle spasms						
	Alopecia						
	Nausea						
	Sleepiness/fatigue						
	Diarrhoea						
	Dry skin						
	Dysgeusia						
	Headache						
	Amenorrhoea						
	Dizziness						
	Stomatitis						
	Abdominal pain						
	Cough						
	Influenza						
	Cushingoid habitus						
	Weight gain						
	Hypertension						
	Depression						
	Myalgias						
	Glucose intolerance						
	Gastritis						
	Urinary tract infection						
	Palpitation						
	Hyperglycaemia						

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	10-fold increase of aminotransferases				
	5-fold increase of gamma-glutamyl transferase				

Abbreviations: AE, adverse event; TED, thyroid eye disease.

Source: Amgen (2020), Amgen (2017).^{142, 166}

Table 42: Adverse event probabilities per cycle used in the model for IVMP and IVMP + MMF

Comparator	Adverse event	Roy <i>et al.</i> 2015 ¹⁸⁷	Marcocci <i>et al.</i> 2001 ¹⁸⁸	Aktaran <i>et al.</i> 2007 ¹⁸⁹	Salvi <i>et al.</i> 2015 ¹⁸⁶
		All AEs >5%			Model base-case: Only Grade ≥3 Aes in ≥5%
IVMP & IVMP + MMF	Muscle spasms	0.00%	0.00%	0.00%	0.00%
	Alopecia	0.00%	0.00%	0.00%	0.00%
	Nausea	0.00%	0.00%	0.00%	0.00%
	Sleepiness/fatigue	0.00%	0.00%	4.08%	0.00%
	Diarrhoea	0.00%	0.00%	0.00%	0.00%
	Dry skin	0.00%	0.00%	0.00%	0.00%
	Dysgeusia	0.00%	0.00%	0.00%	0.00%
	Headache	0.00%	0.00%	0.00%	0.00%
	Amenorrhoea	0.00%	0.00%	0.00%	0.00%
	Dizziness	0.00%	0.00%	0.00%	0.00%
	Stomatitis	0.00%	0.00%	0.00%	0.00%
	Abdominal pain	0.00%	0.00%	0.00%	0.00%
	Cough	0.00%	0.00%	0.00%	0.00%
	Influenza	0.00%	0.00%	0.00%	0.00%
	Cushingoid habitus	3.74%	5.42%	0.00%	0.00%
	Weight gain	7.75%	0.00%	4.08%	0.00%
	Hypertension	2.47%	0.00%	0.00%	0.00%
	Depression	2.47%	0.00%	0.00%	0.00%
	Myalgias	2.47%	0.00%	0.00%	0.00%
	Glucose intolerance	0.00%	10.08%	0.00%	0.00%
	Gastritis	0.00%	4.30%	4.08%	0.00%
	Urinary tract infection	0.00%	8.88%	0.00%	0.00%
	Palpitation	0.00%	0.00%	6.19%	0.00%

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	Hyperglycaemia	0.00%	0.00%	6.19%	1.60%
	10-fold increase of aminotransferases	0.00%	0.00%	0.00%	1.60%
	5-fold increase of gamma-glutamyl transferase	0.00%	0.00%	0.00%	1.60%

Abbreviations: AE, Adverse event; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; TED, thyroid eye disease.

B.3.4.5 Disutilities

Adverse event disutilities

Adverse event disutilities are included in the model base-case to capture the negative quality of life impact of experiencing adverse events. Excluding adverse event disutilities is explored in scenario analysis.

The adverse event disutility, the duration of adverse events, and source of disutility values are given in Table 43. For each adverse event, the adverse event disutility values from the relevant literature are divided by the number of days in a year (365.25) to give the disutility per day, and then multiplied by the duration of adverse events reported. The probability of adverse events per treatment, detailed in Table 41 and Table 42, is then used to give the total sum of treatment-specific disutility values. In the model base-case, only adverse event disutility values for $\geq$ Grade 3 adverse events with an incidence of 5% or more are included (Table 44). In the scenario analysis that explored the inclusion of any Grade adverse event with an incidence of 5%, the treatment-specific adverse event disutility values will be calculated for the additional adverse events and incidence rates included.

Table 43: Adverse event disutility values and average duration

Adverse event	Disutility	Average duration (days)	Disutility sources and assumptions	Duration source and assumptions
Muscle spasms	0.035	63	Matza <i>et al.</i> (2019) ¹⁹¹	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Alopecia	0.040	168	Hall <i>et al.</i> (2019) ¹⁹²	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴² , assumed adverse events occur over the course treatment course.
Nausea	0.062	2	Hagiwara <i>et al.</i> (2018) ¹⁹³	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Sleepiness/fatigue	0.030	32	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Diarrhoea	0.047	3	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Dry skin	0.000	75	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Dysgeusia	0.027	23	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Headache	0.027	23	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Amenorrhoea	0.056	168	Disutility for hormone dysfunction assumed same as cushingoid habitus.	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴² , assumed adverse events occur over the course treatment course.
Dizziness	0.027	9	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Stomatitis	0.140	114	Paracha <i>et al.</i> (2018) ¹⁹⁵	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Abdominal pain	0.051	11	NICE TA804 (2022) ¹⁹⁶	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Cough	0.014	75	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Influenza	0.014	59	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴²
Cushingoid habitus	0.056	105	NICE HST14 ¹⁹⁷	Roy <i>et al.</i> (2015), ²⁷ Marcocci <i>et al.</i> (2001), ^{187, 188} assumed adverse events occur over the course treatment course.
Weight gain	0.008	98	Smith-Palmer <i>et al.</i> (2016) ¹⁹⁸	Roy <i>et al.</i> (2015), ²⁷ Aktaran <i>et al.</i> (2007), ²⁹ assumed adverse events occur over the course treatment course.

Hypertension	0.046	112	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Roy <i>et al.</i> (2015), ¹⁸⁷ assumed adverse events occur over the course treatment course.
Depression	0.080	10	Kolovos <i>et al.</i> (2017) ¹⁹⁹	Matza <i>et al.</i> (2015) ²⁰⁰
Myalgias	0.090	3	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Sullivan <i>et al.</i> (2011) ¹⁹⁴
Glucose intolerance	0.000	98	Assumed to be 0.	Marcocci <i>et al.</i> (2001), ¹⁸⁸ assumed adverse events occur over the course treatment course.
Gastritis	0.051	3	NICE TA804 (2022) ¹⁹⁶	Amgen (2017), ¹⁶⁶ Amgen (2020). ¹⁴² , assumed equal to diarrhoea.
Urinary tract infection	0.100	14	NICE TA127 (2007) ²⁰¹	NICE TA127 (2007) ²⁰¹
Palpitation	0.039	1	Sullivan <i>et al.</i> (2011) ¹⁹⁴	Aktaran <i>et al.</i> (2007) ¹⁸⁹
Hyperglycaemia	0.005	84	Drummond <i>et al.</i> (2018) ²⁰²	Aktaran <i>et al.</i> (2007), ¹⁸⁹ assumed adverse events occur over the course treatment course.
10-fold increase of aminotransferases	0.000	168	Disutility assumed to be 0.	Salvi <i>et al.</i> (2015), ¹⁸⁶ assumed adverse events occur over the course treatment course.
5-fold increase of gammaglutamyltransferase	0.000	168	Disutility assumed to be 0.	Salvi <i>et al.</i> (2015), ¹⁸⁶ assumed adverse events occur over the course treatment course.

Abbreviations: HST, highly specialised technology; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

Table 44: Total adverse event disutilities

Treatment	Adverse event disutility
Teprotumumab	0.0000000
IVMP	0.0000184
IVMP + MMF	0.0000184

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

Intravenous administration disutilities

A disutility values per hours of IV infusion is included in the model base-case to capture the negative quality of life impact; the exclusion of IV disutilities is explored in the scenario analysis.

IV disutilities were sourced from Matza *et al.* (2013), which reported a 30-minute and 2-hour infusion disutility value of 0.023 and 0.037, respectively.²⁰³ The IV administration disutility values in the submitted CEM first use the 30-minute IV disutility value (0.023) from Matza *et al.* (2013), and then calculates the remaining duration of IV administration from the difference between the 30-minute and 2-hour IV administration values (1.5 hours) divided by the remaining duration.²⁰³ For example, the 1-hour IV administration was calculated as $0.023 + ((0.037 - 0.023) / 3) = 0.02767$, and the 1.5-hour IV administration $0.023 + ((0.037 - 0.023) / (2/3)) = 0.03233$.

The calculated disutility values were then divided by the number of days in a month to give a daily disutility value, as the values reported in Matza *et al.* (2013) were for a monthly IV administration.²⁰³ The model then applies the calculated daily per administration to the number of IV infusions per cycle. For teprotumumab, patients receive two IV administrations per cycle while on treatment (one infusion every 3 weeks, with a cycle length of 6 weeks), with a duration of 1.5-hours for the first cycle and 1-hour for the subsequent cycles. Therefore, a disutility of $0.0021 (2 * (0.02767 / 30.4))$ is applied in the first model cycle, and a disutility of $0.0018 (2 * (0.03233 / 30.4))$ in cycles two to four. For IVMP and IVMP + MMF, patient receive six administrations per cycle, each f 1-hour in duration. Therefore, a value of $0.0055 (6 * (0.02767 / 30.4))$ is applied per cycle. The IV administration disutility values per cycle included in the model are given in Table 45.

Table 45: IV administration disutility per cycle

Per cycle	IV administration disutility per cycle	Source and assumption
Teprotumumab (cycle 1)	0.00213	Two 1.5-hour IV administration. ²⁰³
Teprotumumab (cycle 2 – 4)	0.00182	Two 1-hour IV administration. ^{170, 203}
IVMP	0.00546	Six 1-hour IV administration. ^{170, 203}
IVMP + MMF	0.00546	

Abbreviations: IV, intravenous; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

Source : Bartalena *et al.* (2021), Matza *et al.* (2013).^{170, 203}

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment acquisition costs

Teprotumumab

The list price for teprotumumab is £[REDACTED] per 500 mg vial. A [REDACTED]% PAS is subsequently applied to teprotumumab to give a drug acquisition cost of £[REDACTED] per vial. The dosing regimen administered for teprotumumab is based on the Phase 2 and Phase 3 OPTIC clinical trials and expected UK SmPC (Appendix C), where patients received 10 mg of teprotumumab per kg of body weight for the first infusion and 20 mg per kg for subsequent infusions (once every three weeks for a total of eight infusions).¹⁸² Using the mean patient weight of 78.07 kg from the pooled data, patients received a dose per administration of 780.70 mg for the first infusion, and a dose per administration of 1,561.40 mg for remaining infusions.

Vial wastage, calculated through method of moments, is used in the base-case to estimate the number of vials that would be used because the average administered dosage does not align with the vial size (Table 46). Method of moments was chosen to model vial wastage as it reflects the true vial wastage based on that observed in the trials. This approach applies a lognormal transformation to the mean weight and standard deviation of all individual patients' weights reported in the pooled Phase 2 and OPTIC trials to derive a lognormal distribution for vial usage. From this, a weighted average for the number of vials used was calculated. A 5% rounding down

threshold is also used in the method of moments calculation; if a patient requires a partial vial to make up their total dose, but this partial vial makes up less than 5% of the total dose, the administered dose would be rounded down to the nearest vial size. This is understood to be the likely application in clinical practice. For example, 3.1 vials would be rounded down to 3 vials because adding the extra 0.1 vial makes up 3.2% (i.e. <5%) of the total dose. Scenario analysis is used to explore no wastage (Table 47).

Compliance, detailed in Section B.3.3, is used in the base-case to calculate the total drug costs in the model per health state, applied to the acquisition costs listed in the tables below. As no compliance data was available for IVMP and IVMP + MMF, the model assumes the same compliance rate as teprotumumab.

Table 46: Teprotumumab acquisition costs per infusion – Method of moments

Infusion	Mean weight (kg)	Dose (mg)	Unit size (mg)	Cost per unit (£)	Dose per administration (mg)	Vials per administration	Cost per administration (£)
Infusion 1	78.07	10.00	500.00	[REDACTED]	780.70	[REDACTED]	[REDACTED]
Infusion 2 – 8		20.00	500.00		1,561.40	[REDACTED]	[REDACTED]

Abbreviations: kg, kilogram; mg, milligram.

Table 47: Teprotumumab acquisition costs per infusion – No wastage

Infusion	Mean weight (kg)	Dose (mg)	Unit size (mg)	Cost per unit (£)	Dose per administration (mg)	Vials per administration	Cost per administration (£)
Infusion 1	78.07	10.00	500.00	[REDACTED]	780.70	[REDACTED]	[REDACTED]
Infusion 2 – 8		20.00	500.00		1,561.40	[REDACTED]	[REDACTED]

Abbreviations: kg, kilogram; mg, milligram.

IVMP

The unit costs for IVMP are given in Table 48. As there are multiple versions available, the least expensive option was selected for the calculations. The dosing regimen for IVMP, based on EUGOGO clinical practice guidelines, recommends 500 mg weekly for the first six weeks, followed by 250 mg weekly for the next six weeks.

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¹⁷⁰The per cycle IVMP costs are described in Table 49, where patients receive six administrations per 6-week cycle.

No vial wastage is applied for IVMP, given there is a fixed dose for administration that aligns with the available unit sizes.

Table 48: IVMP unit costs

Unit size	Unit cost (£)	Source
500 mg, powder and solvent for solution for injection	9.60	BNF (2024) ²⁰⁴
125 mg, powder and solvent for solution for injection	4.75	BNF (2024) ²⁰⁴

Abbreviations: BNF, British National Formulary; IVMP, intravenous methylprednisolone; mg, milligram; MMF, mycophenolate mofetil.

Table 49: IVMP acquisition costs per cycle

Infusion	Dose per admin (mg)	Admin per cycle	Dose per cycle (mg)	Unit size (mg)	Vials per cycle	Cost per unit (£)	Cost per cycle (£)
IVMP dose 1	500.00	6.00	3,000	500.00	6.00	9.60	57.60
IVMP dose 2	250.00		1,500	125.00	12.00	4.75	57.00

Abbreviations: IVMP, intravenous methylprednisolone; mg, milligram.

IVMP + MMF

For IVMP + MMF, the dosing regimen is the same as described above for IVMP, in combination with 1,000 mg MMF oral tablet daily for 24 weeks based on EUGOGO clinical practice guidelines.¹⁷⁰ The unit cost of MMF 500 mg, 50 tablets, is £5.59, which equates to £0.11 per tablet; using the least expensive pack cost available sourced from the BNF.²⁰⁵ The IVMP + MMF acquisition costs per cycle is detailed in Table 50.

No wastage is applied for IVMP + MMF, given there is a fixed dose for administration that aligns with the available unit sizes.

Table 50: IVMP + MMF acquisition costs per cycle

Infusion	Dose per admin (mg)	Admin per cycle	Dose per cycle (mg)	Unit size (mg)	Units per cycle	Cost per unit (£)	Cost per cycle (£)
IVMP dose 1	500.00	6.00	3,000	500.00	6.00 vials	9.60	57.60

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IVMP dose 2	250.00		1,500	125.00	12.00 vials	4.75	57.00
MMF	1,000	42	42,000	500.00	84 tablets	0.11	9.39

Abbreviations: IVMP, intravenous methylprednisolone; kg, kilogram; mg, milligram; MMF, mycophenolate mofetil.
Source: BNF (2024)²⁰⁵

B.3.5.1.2 Treatment administration costs

Teprotumumab and IVMP are administered intravenously (IV). As no specific NHS references costs for IV administrations for autoimmune conditions were found, the model uses the chemotherapy code NHS reference cost SB12Z at a cost of £411.99 for a 1-hour IV administration.

Teprotumumab is administered over 90 minutes for the first two infusions, with the model rounding up to a two-hour infusion period, to reflect that NHS costs are charged on an hourly basis even if the full hour is not used, and 60 minutes per infusion thereafter. IVMP is administered over one or two hours as per EUGOGO 2021 guidelines,¹⁷⁰ with the model conservatively assuming a one-hour infusion for IVMP administration. MMF is administered orally and, therefore, no cost for administration have been assumed. The administration costs for all treatments are described in Table 51.

Table 51: Treatment-specific administration costs

Comparator	Admin duration	Admin cost (£)	Admin per cycle	Total cost per cycle (£)	Admin description	Source
Teprotumumab (Infusion 1- 2)	2 hours	823.98	2	1,647.96	The first and second infusion have an administration time of 1.5-hours. Rounded up to 2-hours.	EOGOGO (2021), ¹⁷⁰ NHS England cost 2022/2023 (SB12Z) ²⁰⁶
Teprotumumab (Infusion 3-8)	1 hour	411.99	2	823.98	From the third infusion onwards, administration time is 1.0 hour	
IVMP	1 hour	411.99	6	2,471.94	Administration time is 1.0 hour	EOGOGO (2021), ¹⁷⁰ NHS

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						England cost 2022/2023 (SB12Z) ²⁰⁶
IVMP + MMF	1 hour	411.99	6	2,471.94	IVMP: Administration time is 1.0 hour	EOGOGO (2021), ¹⁷⁰ NHS reference costs 2022/2023 (SB12Z), ²⁰⁶ SmPC

Abbreviations: EUGOGO, European Group On Graves Orbitopathy; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; NHS, National Health Service.

B.3.5.1.3 Surgery costs

Surgery procedure and complication costs are applied as a one-off cost in the cycle surgery is received, with a proportion of patients transitioning to the surgery state at cycle 26 in the base-case. Patients remain in the Surgery health state for 3.5 years (30 cycles) before moving to the Post-surgery health state.¹⁴¹

The type of surgeries a patient may receive, and the surgery procedure costs are given in Table 52. The respective costs of each surgery is calculated as a weighted average from the relevant National Schedule of NHS Costs 2022/23.²⁰⁶

The average number of surgeries that a patient receives by health state and treatment arm was informed by UK clinicians (Table 53),¹⁴¹ and is used to calculate the surgical procedure costs by active disease health state and treatment arm (Table 54).

The same number of surgeries and total surgery cost is applied across all six active disease health states given a lack of data, with the number and type of surgery informed by UK clinicians.¹⁴¹

Table 52: Surgery cost

Surgical procedure	Cost code	Frequency	Cost (£)	Weighted average cost (£)
OD (elective inpatient)	BZ54B	206	4292.34	5,206.79
	BZ54A	247	4160.11	
	BZ53B	176	5257.22	
	BZ53A	302	4919.26	
	BZ51B	264	5721.44	
	BZ51A	394	6194.10	
	BZ74Z	462	1233.26	2,605.84

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Strabismus surgery (day case)	BZ73A	821	2314.17	
	BZ72A	1933	2848.51	
	BZ71A	952	3030.74	
Eyelid surgery (upper and lower blepharoplasty; day case)	BZ46A	9811	921.62	1,269.37
	BZ45B	12412	1153.98	
	BZ45A	3391	1224.39	
	BZ44B	7290	1737.88	
	BZ44A	3580	1711.00	

Abbreviations: NHS, National Health Service; OD, orbital decompression; TED, Thyroid eye disease.

Source: NHS reference costs (2023).²⁰⁶

Table 53: Average number of surgeries per health state

Average number of surgeries per patient	Small Proptosis, No Diplopia	Large Proptosis, No Diplopia	Small Proptosis, Intermittent/Inconstant Diplopia	Large Proptosis, Intermittent/Inconstant Diplopia	Small Proptosis, Constant Diplopia	Large Proptosis, Constant Diplopia
Teprotumumab						
OD						
Strabismus						
Eyelid						
Total						
IVMP						
OD						
Strabismus						
Eyelid						
Total						
IVMP + MMF						
OD						
Strabismus						
Eyelid						
Total						

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; OD, orbital decompression.

Source: Amgen, Clinical expert opinion (2024)¹⁴¹

Table 54: One-off surgery procedure costs

Treatment	Surgery procedure costs (£)
Teprotumumab	6,966.43
IVMP	11,670.76
IVMP + MMF	11,670.76

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

Surgical complications are categorised separately from adverse events in the CEM, and are applied as a one-off cost on patient entry into the surgery health state, with the same cost applied regardless of the active disease health state the patients were previously in. The incidence rate of surgical complications of any Grade was sourced from the relevant literature (Table 55).^{141, 207-209} The surgery complication unit costs are given in Table 56, sourced from the NHS reference costs 2022/2023.²⁰⁶ The one-off cost for surgery complications (Table 57), is calculated by multiplying the probabilities of complication occurrence for each surgery procedure by the unit surgery complication cost, and the number of surgeries per health state per treatment. The exclusion of surgery complication costs is explored in the scenario analysis.

Table 55: Probability of complication per surgery type

Surgical complications	Incidence complication per surgery		
Complication	Orbital decompression²⁰⁷	Strabismus²⁰⁸	Eyelid surgery²⁰⁹
Post-operative numbness	25.00%	0.00%	0.00%
New post-operative diplopia	19.00%	0.00%	0.00%
Hematoma	0.00%	0.00%	0.50%
Chemosis	0.00%	0.00%	6.00%
Perioperative stroke	0.00%	0.00%	0.00%
Persistent post-operative facial nerve frontal branch palsy	0.00%	0.00%	0.00%
Scleral perforation	0.00%	0.00%	0.00%
Lowerlid malpositioning	0.00%	0.00%	3.00%
Dellen	0.00%	0.00%	0.00%
CSR leakage	0.00%	0.00%	0.00%

Abbreviations: CSR, central serous retinopathy.

Source: Akbari *et al.* (2020), Patrocinio *et al.* (2011).^{208, 209}

Table 56: Unit costs of surgery complications

Complication	Unit cost (£)	Assumption / source
Post-operative numbness	0.00	No cost associated to post-operative numbness
New post-operative diplopia	139.38	Patient will be re-operated/re-treated and will attend a specialist ophthalmology visit. Service code 130 'Total outpatient Attendance' Ophthalmology Service. NHS reference costs 2022/2023. ²⁰⁶
Hematoma	44.65	Costs derived paracetamol and sunglasses as prescribed by NHS. BNF (2024), ²¹⁰ NHS (2024). ²¹¹
Chemosis	124.13	Costs derived from ophthalmology visit and steroid eye drops for the first two days. NHS reference costs 2022/2023, ²⁰⁶ BNF (2024). ²¹²
Perioperative stroke	915.64	Weighted average NHS reference cost 2022/23 for stroke codes AA35A, AA35A, AA35B, AA35B, AA35C, AA35C, AA35D, AA35D, AA35E, AA35E, and AA35F. NHS reference costs 2022/2023. ²⁰⁶
Persistent post-operative facial nerve frontal branch palsy	11898.18	Cost derived from eye drop for three times daily, ointment at night, taping, wraparound glasses for 8 weeks, and weighted average NHS reference cost 2022/23 codes for surgery BZ46A, BZ45B, BZ45A, BZ44B, BZ44A, CA90Z, CA91A, CA91B, CA92A, CA92B, CA93A, CA93B, CA93C, CA94Z, and CA95Z. BNF (2024), ²¹³ BNF (2024), ²¹³ NHS England (2024), ²¹¹ NHS reference costs 2022/2023. ²⁰⁶ NHS England 2023, ²¹⁴ FIRSTAIID.co.uk (2024). ²¹⁵
Scleral perforation	1106.42	Weighted average NHS reference cost 2022/23 codes for surgery BZ46A, BZ45B, BZ45A, BZ44B, and BZ44A. NHS reference costs 2022/2023. ²⁰⁶
Lower lid malpositioning	139.38	Costs derived from ophthalmology visit. NHS reference costs 2022/2023. ²⁰⁶
Dellen	148.53	Costs derived from eye drop for three times daily, ointment at night, taping, wraparound glasses for 8 weeks. BNF (2024), ²¹³ BNF (2024), ²¹³ , NHS England (2024), ²¹¹ NHS England 2023, ²¹⁴ FIRSTAIID.co.uk (2024). ²¹⁵
CSR leakage	466.34	Costs derived from a retinal photograph and one time steroids IV administration. NHS reference costs 2022/2023, ²⁰⁶ BNF (2024). ²⁰⁴

Abbreviations: BNF, British National Formulary; CSR, central serous retinopathy; IV, intravenous infusion; NHS, National Health Service; TED, thyroid eye disease.

Table 57: Surgery complication costs per treatment

Treatment	Health state surgery procedure costs (£)
Teprotumumab	29.23
IVMP	45.92
IVMP + MMF	45.92

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

B.3.5.2 Subsequent treatments

The CEM considers a course of subsequent treatments for all patients in the four most severe health states (large proptosis, no diplopia; large proptosis, intermittent/inconstant diplopia; small proptosis, constant diplopia; large proptosis, constant diplopia). Subsequent treatment costs are applied as a one-off cost in the cycle after the patient completes their primary treatment (cycle 5 for teprotumumab, IVMP + MMF, and cycle 3 for IVMP) and to all patients. Subsequent treatment costs are also applied to any patients that discontinue their primary treatment, regardless of health state, in the cycle at which the patient discontinued. The subsequent treatments considered in the model base-case are informed by Amgen clinical insights given a lack of available market share data.

The unit costs for each subsequent treatment, the total one-off cost of subsequent treatments (including administration costs), and the proportion of subsequent treatments are detailed in Table 58 and Table 59. Administration costs for IVMP are the same as those used for IVMP primary treatment. No administration costs are applied to oral treatments. The exclusion of subsequent treatment costs is explored within the scenario analysis.

Table 58: Subsequent treatment costs

Subsequent treatment	Unit size	Unit cost (£)	Dose per administration (mg)	Number of administrations	Total acquisition cost for the duration of administration (£)	Source
IVMP	Cycle 1: 500 mg, powder and solvent for solution for injection, Cycle 2: 125 mg, powder and solvent for solution for injection.	Cycle 1: 9.60, Cycle 2: 4.75.	Cycle 1: 500, Cycle 2: 250.	Cycle 1: 6, Cycle 2: 6, Total 12.	Cycle 1: 2,529.54, Cycle 2: 2,528.94, Total: 5,058.48.	BNF (2024) ²⁰⁴ . Equivalent to the primary treatment cost of IVMP for two cycles (12 weeks, one administration per week).
						BNF (2024) ²⁰⁴
MMF	50 tablets	5.59	1,000	168	37.56	Daily administration for 24 weeks. BNG (2023) ²⁰⁴
Radiotherapy	NA	287.48	NA	NA	287.48	NHS reference costs 2022/2023, assumed equal to oral surgery service radiotherapy, code 140. ^{141, 206}
Ciclosporin	100 mg, 30 tablets	68.28	586	84	1,119.43	7.5 mg/kg, administer daily for 12 weeks. Prummel <i>et al.</i> (1989), ¹⁵⁹ BNF (2024) ²¹⁶
Azathioprine	50 mg, 56 tablets	1.52	200	336	36.48	100 – 200 mg, daily, for 48 weeks. Rajendram <i>et al.</i> (2018), ²¹⁷ BNF (2024). ²¹⁸

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

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Table 59: Total one-off cost and proportion of patients receiving each subsequent treatment therapy

Subsequent treatment	Total acquisition and administration one-off cost (£)	Subsequent treatment following teprotumumab	Subsequent treatment following IVMP	Subsequent treatment following IVMP + MMF
IVMP	5,058.48			
MMF	37.56			
Radiotherapy	287.48			
Ciclosporin	1,119.43			
Azathioprine	36.48			
Total cost		£4,910.94	£4,650.50	£4,650.50

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

B.3.5.3 Health state unit costs and resource use

Healthcare resource use (HCRU) costs are included in the model to capture the costs associated with the routine monitoring and disease management for moderate-to-severe active TED.

HCRU was identified through UK clinical interviews as no relevant UK data were identified in the available literature.¹⁴¹ Given inconsistencies across the clinician interviews, the model assumes the same HCRU for all treatments, only varied by health state and time. More frequent HCRU is included for the more severe health states, with a cap applied to HCRU such that more severe health states could not have lower resource use than less severe health states. The model also applies separate HCRU frequencies for cycle 1, cycle 2-35, and cycle 36 onwards, to align with changes in HCRU over time reported in the UK clinical interviews.¹⁴¹ Hearing appointments are included for teprotumumab only, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HCRU unit costs are given in Table 60, with the frequency and cost per HCRU per cycle given in Appendix I. The total costs per cycle is calculated as the HCRU cost multiplied by the HCRU frequency for each health state in cycle 1, cycles 2 to 35 and cycle 36, and described in Table 61.

Table 60: Healthcare resource use unit costs

Healthcare resource	Unit cost (£)	Source
Artificial tears	0.20	BNF (2024), £5.59 per pack of 30. ²¹³
Ophthalmic gels/ointments	2.05	BNF (2024). ²¹⁹
CT scans	158.20	NHS reference costs 2022/2023, weighted average, BZ88A-BZ88B. ²⁰⁶
MRI	219.87	NHS reference costs 2022/2023, weighted average, RD01A-RD01B. ²⁰⁶
Ophthalmologist visit	139.38	NHS reference costs 2022/2023, service code 130. ²⁰⁶
Orthoptics visit	139.38	Assumed the same as ophthalmologist visit.
Hormone test	1.61	NHS reference costs 2022/2023, DAPSO4. ²⁰⁶
Endocrinologist visit	199.84	NHS reference costs 2022/2023, service code 304. ²⁰⁶
Primary care visit	49.00	PSSRU 2023 unit costs, assuming a 10-minute appointment. ²²⁰
Hearing appointment	113.67	NHS reference costs 2022/2023, service code 840. ²⁰⁶

Abbreviations: BNF, British National Formulary; CT, computed tomography; MRI, magnetic resonance imaging; NHS, National Health Service.

Table 61: Total resource use cost per health state per cycle

Health state	Total, cycle 1 (£)	Total, cycle 2 to 35 (£)	Total, cycle 36+ (£)
Small proptosis, no diplopia	319.15	171.14	93.62
Large proptosis, no diplopia	657.74	308.84	235.21
Small proptosis, intermittent/inconstant diplopia	657.74	308.84	235.21
Large proptosis, intermittent/inconstant diplopia	821.37	337.29	263.66
Small proptosis, constant diplopia	849.80	366.38	295.88
Large proptosis, constant diplopia	904.08	411.86	341.36
Teprotumumab hearing appointments (all proptosis and diplopia health states)	113.67	6.69	0.00

The Surgery and Post-surgery health states have separate HRCU frequencies to the six active disease health states, independent of treatment regimen. Surgery and Post-surgery HCRU frequencies are informed by UK clinicians.¹⁴¹ The HCRU frequency for surgery and Post-surgery are detailed in Table 62 and Table 63. HCRU are applied for the duration of the surgery health state. For Post-surgery, HCRU are applied either for 26 cycles or indefinitely, depending on the HCRU, detailed in Table 63. The HCRU unit costs for surgery and Post-surgery are assumed equal to those in the active disease health states (Table 60).

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Table 62: Cycles 0 – 26 HCRU frequency and cost per cycle in the surgery health state

Health care resource	Resource use (per cycle) ¹⁴¹	Total costs per cycle (£)	Assumption
Artificial tears (per dose)			Applied daily for the duration patients remain in state.
Ophthalmic gels/ointments (per dose)			Applied daily for the duration patients remain in state.
CT scans			Two CT scans per year, updated to align with the 6-week cycle length.
MRI			Frequency calculated as the mean value from clinician consultation.
Orthoptics			Frequency calculated as the mean value from clinician consultation.
Ophthalmologist visit			Frequency calculated as the mean value from clinician consultation.
Hormone test			Frequency calculated as the mean value from clinician consultation.
Endocrinologist visit			Frequency calculated as the mean value from clinician consultation.
Primary care visit			Frequency calculated as the mean value from clinician consultation.
Total			

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TED, thyroid eye disease.

Source: Amgen (2024)¹⁴¹

Table 63: Cycles 26+ HCRU frequency and cost per cycle in the surgery health state

Health care resource	Resource use (per cycle) ¹⁴¹	Total costs per cycle (£)	Assumption ¹⁴¹
Artificial tears (per dose)			Applied once weekly, for the duration of the patient lifetime.
Ophthalmic gels/ointments (per dose)			Applied once weekly, for the duration of the patient lifetime.
CT scans			Not required for post-surgery.
MRI			Not required for post-surgery.
Orthoptics			Frequency calculated as the mean value from clinician consultation.

			Applied for 3 years (26 cycles).
Ophthalmologist visit			Frequency calculated as the mean value from clinician consultation. Applied for 3 years (26 cycles).
Hormone test			Frequency calculated as the mean value from clinician consultation. Applied for 3 years (26 cycles).
Endocrinologist visit			Frequency calculated as the mean value from clinician consultation. Applied for 3 years (26 cycles).
Primary care visit			Frequency calculated as the mean value from clinician consultation. Applied for 3 years (26 cycles).
Total, post-surgery cycle 1 – 26			
Total, post-surgery cycle 26+			

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TED, thyroid eye disease.
Source: Amgen (2024).¹⁴¹

B.3.5.4 Adverse reaction unit costs and resource use

Adverse event costs are applied to patients on primary treatment, and sourced from the National Schedule of NHS Costs 2022/23 and published literature (Table 64). Where possible, costs from published literature were obtained for the 2023, or inflated to 2023 using the inflation indices sourced from the PSSRU, if 2023 costs were unavailable.²²⁰ The adverse event costs per cycle per treatment (Table 65) was calculated by multiplying the unit costs by the incidence rate (described in Section B.1.5.4). In the CEM base-case, only $\geq$ Grade 3 adverse events occurring in $\geq$ 5% of patients are included. No adverse events met this criterion for teprotumumab, therefore the adverse event cost per cycle for teprotumumab treatments was zero. The adverse event cost for IVMP + MMF was assumed equal to IVMP + MMF. The inclusion of any Grade adverse events that occurred in 5% or more patients is explored in the scenario analysis.

Table 64: Adverse event unit costs

Adverse event	Unit cost (per cycle) (£)	Source and assumptions
Muscle spasms	315.00	Assuming 1 GP visit and an injection of botulinum toxin into the affected muscles every 3 months. ²²⁰⁻²²²
Alopecia	91.26	Minoxidil 1ml applied twice daily for a year. ^{223, 224}
Nausea	128.83	Cost of one enteral feeding nursing service appointments, community health service N16AF in NHS reference costs 2022/2023. ²⁰⁶
Sleepiness/fatigue	0.00	Self-management, no cost. Assuming no underlying medical condition. ²²⁵
Diarrhoea	421.23	NHS reference costs 2022/2023, gastrointestinal infections without interventions, weighted average of FD01F, FD01G, FD01H and FD01J (day case). ²⁰⁶
Dry skin	517.65	NHS reference costs 2022/2023, skin disorders without interventions, weighted average of JD07K, JD07J and JD07H (day case). ²⁰⁶
Dysgeusia	0.00	Self-management, no cost. Assuming no underlying medical condition. ²⁰⁶
Headache	408.22	NHS reference costs 2022/2023, headache, migraine or cerebrospinal fluid leak, weighted average of AA31E, AA31D and AA31C (day case). ²⁰⁶
Amenorrhoea	75.47	NHS reference costs 2022/2023, cost of follicle stimulation hormone IVF02 (day case). ²⁰⁶
Dizziness	408.22	Assumed same as headache.
Stomatitis	514.11	NHS reference costs 2022/2023, non-malignant, ear, nose, mouth, throat, head or neck disorders, without Interventions, with CC Score 0, CBO2F (day case). ²⁰⁶
Abdominal pain	412.62	NHS reference costs 2022/2023, abdominal pain without interventions, FD05B (day case). ²⁰⁶
Cough	116.35	NHS reference costs 2022/2023, specialist nursing, asthma and respiratory nursing/liaison, adult, face to face, N08AF (total other currencies). ²⁰⁶
Influenza	419.69	NHS reference costs 2022/2023, lobar, atypical or viral pneumonia, without interventions, weighted average of DZ11R, DZ11S, DZ11T, DZ11U and DZ11V. ²⁰⁶
Cushingoid habitus	55.00	Assuming 1 GP visit (per surgery consultation lasting 10 minutes). NHS recommends management through down-titration or discontinuation (for steroids). ^{220, 226}
Weight gain	249.00	Assuming 3 dietician appointments. ²²⁰
Hypertension	358.47	NHS reference costs 2022/2023, hypertension, EB04Z (day case). ²⁰⁶
Depression	378.00	Assuming 6 clinical psychologist community therapy sessions. ²²⁰
Myalgias	213.00	Assuming 3 physiotherapist appointments. ²²⁰

Glucose intolerance	55.00	"Assuming 1 GP visit (per surgery consultation). ²²⁰
Gastritis	421.23	NHS reference costs 2022/2023, gastrointestinal infections without interventions, weighted average of FD01J, FD01H, FD01G, FD01F (day case). ²⁰⁶
Urinary tract infection	353.63	NHS reference costs 2022/2023, kidney or urinary tract infections, without Interventions, weighted average of LA04S, LA04R, LA04Q, LA04P(day case). ²⁰⁶
Palpitation	55.00	Assuming 1 GP visit (per surgery consultation lasting 10 minutes). NHS recommends management through down-titration, discontinuation or a change of lifestyle (for steroids). ²²⁰
Hyperglycaemia	55.00	Assuming 1 GP visit (per surgery consultation lasting 10 minutes). NHS recommends management through down-titration, discontinuation or a change of lifestyle (for steroids). ^{186, 220}
10-fold increase of aminotransferases	870.15	Assuming 1 GP visit (per surgery consultation lasting 10 minutes), an ultrasound check (code 812 for diagnostic imaging service), and biweekly blood test for 4 months (code 822 for chemical pathology service). ^{186, 206, 220}
5-fold increase of gamma-glutamyl transferase	870.15	Assuming 1 GP visit (per surgery consultation lasting 10 minutes), an ultrasound check (code 812 for diagnostic imaging service), and biweekly blood test for 4 months (code 822 for chemical pathology service). ^{186, 206, 220}

Abbreviations: GP, general practitioner; NHS, National Health Service.

Table 65: Total adverse event cost per treatment per cycle

Treatment	Total AE cost per cycle for patients on treatment (£)
teprotumumab	0.00
IVMP	28.73
IVMP + MMF	28.73

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

B.3.5.5 Miscellaneous unit costs and resource use

Surgical procedure and complications costs are described as part of the treatment costs in the above Sections.

B.3.6 Severity

We are confident that the impact of TED on patients' lives is severe; the utility scores are low in this population, and we have heard of suicide ideation in this patient group.^{227, 228} The evidence to support a case for the severity modifier however is

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limited, in part due because the severity modifier calculations are reliant on utilities and there are inherent challenges of deriving utility values, especially EQ-5D, for conditions in eyes. We believe however, that the sentiment of the severity modifiers does apply to TED; in that its purpose is to identify conditions that have such severity additional value should be applied.

B.3.7 Uncertainty

Were possible, uncertainty was explored through the validation of parameters and assumptions within the sensitivity and scenario analysis of the economic model. Patient experiences were also validated by TED clinical experts in the UK.¹⁴¹

There are key areas of uncertainty in the economic analysis, which were beyond the control of Company's submission include:

- In active moderate-to-severe TED, uncertainty is exacerbated by low prevalence rates, limited clinical evidence and published data, no NICE precedents, and no other licensed therapies available.^{30, 47} Pooling Phase 2 and Phase 3 OPTIC clinical evidence to increase the patient numbers included in the economic analysis, as well as validation of parameters by TED UK clinical experts, were performed to reduce this uncertainty.
- The limitations of EQ-5D to accurately assess eye conditions and visual impairment is well known,¹⁷⁵⁻¹⁷⁷ and acknowledged by the NICE DSU.¹⁷⁴ Following NICE's hierarchy of preferred HRQoL methods,¹⁶⁵ and lack of available literature or mapping algorithms for GO-QoL to EQ-5D, a health state vignette study using a TTO approach was conducted to calculate utility values used in the economic analysis. The utility values used in the economic analysis were validated by UK experts to reduce this uncertainty.

B.3.8 Managed access proposal

A managed access proposal is not provided.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the base-case analysis in the CEM are given in Table 66.

Table 66: Summary of variables applied in the economic model

Variable	Value	Standard error	Distribution	Lower value	Upper value	Reference to section in submission
Time horizon	48.42	NA	NA			Section B.3.2
Age	51.58	1.34	GAMMA	39.24	63.92	
Weight	78.07	2.07	GAMMA	74.06	82.12	
Percentage male	27.03%	5.41%	BETA	17.14%	38.23%	
Discount rate costs	3.50%	NA	NA			
Discount rate outcomes	3.50%	NA	NA			
Teprotumumab PAS discount (%)	██████████%	NA	NA			Section B.3.5
Acquisition cost teprotumumab cost per cycle (up to cycle 1)	£██████████	NA	NA			
Acquisition cost teprotumumab cost per cycle (cycle 2+)	£██████████	NA	NA			
Teprotumumab number of cycles on treatment	4.00	NA	NA			
Administration cost per cycle with teprotumumab (up to cycle 1)	£1,647.96	£329.59	GAMMA	£1,066.47	£2,353.95	
Administration cost per cycle with teprotumumab (cycle 2+)	£823.98	£164.80	GAMMA	£533.24	£1,176.98	
Teprotumumab compliance	██████████	██████████	BETA	██████████	██████████	Section B.3.3
Teprotumumab discontinuation probability per cycle	██████████	██████████	BETA	██████████	██████████	
Acquisition cost IVMP cost per cycle (up to cycle 1)	£57.60	NA	NA			Section B.3.5
IVMP cost per cycle (cycle 2) (£)	57	NA	NA			
IVMP number of cycles on treatment	2.00	NA	NA	2.00	2.00	

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Administration cost per cycle with IVMP (up to cycle 1)	£2,471.94	£494.39	GAMMA	£,599.71	£3,530.93	
Administration cost per cycle with IVMP (cycle 2+)	£2,471.94	£494.39	GAMMA	£1,599.71	£3,530.93	
IVMP compliance			BETA			
IVMP discontinuation probability per cycle	1.34%	0.27%	BETA	0.87%	1.92%	Section B.3.3
Acquisition cost IVMP + MMF cost per cycle (cycle 1)	£66.99	NA	NA			
Acquisition cost IVMP + MMF cost per cycle (cycle 2)	£66.39	NA	NA			
Acquisition cost IVMP + MMF cost per cycle (cycles 3 - 4)	£9.39	NA	NA			Section B.3.5
IVMP + MMF number of cycles on treatment (IVMP only)	2.00	NA	NA			
IVMP + MMF number of cycles on treatment	4.00	NA	NA			
Administration cost per cycle with IVMP + MMF (up to cycle 1)	£2,471.94	£494.39	GAMMA	£1,599.71	£3,530.93	
Administration cost per cycle with IVMP + MMF (cycle 2+)	£2,471.94	£494.39	GAMMA	£1,599.71	£3,530.93	
IVMP + MMF compliance			BETA			Section B.3.3
IVMP + MMF discontinuation probability per cycle	1.29%	0.26%	BETA	0.83%	1.84%	
Teprotumumab total subsequent treatment costs	£4,910.94	£982.19	GAMMA	£3,178.10	£7,014.81	Section B.3.5
IVMP total subsequent treatment costs	£4,650.50	£930.10	GAMMA	£3,009.56	£6,642.80	
IVMP + MMF total subsequent treatment costs	£4,650.50	£930.10	GAMMA	£3,009.56	£6,642.80	Section B.3.5
Teprotumumab hearing appointments total cost - cycle 1	£113.67	£22.73	GAMMA	£73.56	£162.37	
Teprotumumab hearing appointments total cost - cycles 2 - 35	£6.69	£1.34	GAMMA	£4.33	£9.55	Section B.3.5
Surgery - health state total cost	£639.21	£127.84	GAMMA	£413.66	£913.04	
Post-surgery - total health state cost to be applied for first 26 cycles in health state	£122.72	£24.54	GAMMA	£79.42	£175.29	
Post-surgery - total health state cost to be applied beyond 26 cycles	£13.48	£2.70	GAMMA	£8.72	£19.25	Section B.3.4
Teprotumumab adverse event total disutility	0.00	0.00	BETA	0.00	0.00	
IVMP adverse event total disutility	1.84E-05	3.68E-06	BETA	1.19E-05	2.63E-05	
IVMP + MMF adverse event total disutility	1.84E-05	3.68E-06	BETA	1.19E-05	2.63E-05	

Utility: Small Proptosis, No Diplopia	0.60	0.03	BETA	0.54	0.67	Section B.3.4
Utility: Large Proptosis, No Diplopia	0.46	0.03	BETA	0.40	0.52	
Utility: Small Proptosis, Intermittent/Inconstant Diplopia	0.52	0.03	BETA	0.45	0.58	
Utility: Large Proptosis, Intermittent/Inconstant Diplopia	0.43	0.03	BETA	0.36	0.49	
Utility: Small Proptosis, Constant Diplopia	0.34	0.03	BETA	0.29	0.40	
Utility: Large Proptosis, Constant Diplopia	0.30	0.03	BETA	0.24	0.36	
Utility: Surgery	0.3825	0.0765	BETA	0.2391	0.5372	
Utility: Post-surgery	0.5025	0.1005	BETA	0.3072	0.6974	
Teprotumumab IV administration disutility per cycle 1 (1.5hours)	0.0021	0.0004	BETA	0.0014	0.0030	Section B.3.4
Teprotumumab IV administration disutility per cycle (1 hour)	0.0018	0.0004	BETA	0.0012	0.0026	
IVMP IV administration disutility per cycle (1 hour)	0.0055	0.0011	BETA	0.0035	0.0078	
IVMP + MMF IV administration disutility per cycles (1 hour)	0.0055	0.0011	BETA	0.0035	0.0078	
Teprotumumab: Proportion of patients undergoing surgery - Small Proptosis, No Diplopia	5.00%	1.00%	BETA	3.23%	7.13%	Section B.3.5
Teprotumumab: Proportion of patients undergoing surgery - Large Proptosis, No Diplopia	38.13%	7.63%	BETA	23.84%	53.55%	
Teprotumumab: Proportion of patients undergoing surgery - Small Proptosis, Intermittent/Inconstant Diplopia	5.00%	1.00%	BETA	3.23%	7.13%	
Teprotumumab: Proportion of patients undergoing surgery - Large Proptosis, Intermittent/Inconstant Diplopia	41.25%	8.25%	BETA	25.67%	57.79%	
Teprotumumab: Proportion of patients undergoing surgery - Small Proptosis, Constant Diplopia	43.75%	8.75%	BETA	27.11%	61.15%	
Teprotumumab: Proportion of patients undergoing surgery - Large Proptosis, Constant Diplopia	43.75%	8.75%	BETA	27.11%	61.15%	
Duration of recovery from surgery (cycles)	████	████	GAMMA	████	████	
Cycle at which surgery occurs	████	████	GAMMA	████	████	
Duration of resource use for post-surgery (cycles)	26.00	5.20	GAMMA	16.83	37.14	

Abbreviations: IV, intravenous; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; NA, not applicable; PAS, patient access scheme.

B.3.9.2 Assumptions

A list of the modelling assumptions included in the CEM, and justification for each, is given in Table 67.

Table 67: Summary of assumptions included in the economic model

CEM feature	Assumption	Justification
Model structure and settings	The perspective is from the UK NHS and PSS.	In line with NICE reference case. ¹⁶⁵
	A cycle length of 6 weeks is used.	In line with timepoints at which efficacy was assessed in OPTIC and Phase 2 trials.
	The important costs and outcomes associated with TED are captured by the six health states defined by diplopia and proptosis and by the surgery and post-surgery states.	Patients flowing through the health states capture important differences in costs and quality of life.
	Costs and outcomes are discounted at 3.5%.	In line with NICE reference case. ¹⁶⁵
	Lifetime horizon (assumed to be 48.42 years, assuming a maximum age of 100).	Sufficiently long enough to capture all important differences in costs and outcomes between the intervention and comparators given the chronic nature of the disease, as per the NICE reference case. ¹¹
	Half-cycle correction applied.	To account for uncertainty in the time points at which patients transition.
Clinical effectiveness	Pooled Phase 2 and OPTIC data are used in the base-case for all clinical inputs, including transition probabilities.	Trial populations are generalisable to submission population (active disease). Pooling increases robustness of analysis by maximising sample size of data used.
	Transition probabilities for IVMP and IVMP + MMF are derived from <i>de-novo</i> MAICs conducted by Amgen.	In line with NICE technical support document 2, in the absence of head-to-head trial data. ²²⁹
	For the IVMP transition probabilities, equal or worsening diplopia is assumed to be the same as teprotumumab.	In the absence of data as the MAIC only reported on improving diplopia.
	For the IVMP + MMF transition probabilities, proptosis is derived from two <i>de-novo</i> ITCs conducted by Amgen.	In line with NICE technical support document 2, in the absence of head-to-head trial data. ²²⁹
	For the IVMP + MMF transition probabilities, diplopia was assumed equal to IVMP, as no evidence was available.	Assumption in the absence of an alternative data source. Results for the proptosis endpoint were similar for both MAICs, so no significant

		differences are expected for the diplopia endpoint.
	Treatment discontinuation and compliance for teprotumumab was sourced from pooled Phase 2 and OPTIC Phase 3 clinical trial data. Treatment discontinuation and compliance for comparators was assumed equal to teprotumumab.	Trial discontinuation criteria is assumed to reflect UK clinical practice. No published data reporting discontinuation or compliance was available for IVMP or IVMP + MMF.
	Patients who discontinue treatment no longer accrue primary treatment costs, adverse event costs, or resource use costs, and remain in the health state in which they discontinued treatment.	Discontinuation was informed by all-cause discontinuation values
	Patients remain in their respective health states after 24 weeks.	Small sample size means that transitions are associated with considerable uncertainty. Additionally, there is no long-term follow-up data for comparators, meaning a comparison of long-term outcomes is not possible.
Surgery	Patients enter the surgery state at cycle 26.	Based on feedback from UK clinicians. ¹⁴¹
	The proportion of patients in each health state that move to the surgery state was informed by UK clinical opinion. ¹⁴¹	No published data available.
	The surgery state accounts for patients undergoing multiple surgeries, and considers OD, strabismus surgery, and eyelid surgery.	OD, strabismus surgery, and eyelid surgery are the most common surgeries received by TED patients, as per ATA/ETA guidelines. The average number of surgeries received per patient was based on feedback from UK clinicians. ¹⁴¹
	Patients remain in the surgery state for 30 cycles before transitioning to the post-surgery state.	Based on feedback from UK clinicians. ¹⁴¹
Mortality	General population mortality is applied for all treatment arms.	TED is not associated with increased mortality.
Utilities	Utility values associated with the Surgery and Post-surgery health states are averages of the four lowest utility values and the four highest utility values for the active disease health states.	No published data available. Patients in the Surgery health state are expected to have an improved quality of life post-surgery.
	Utility values are informed by a vignette study specific to active moderate-to-severe TED. ¹⁶⁹	Due to the limited available literature and no EQ-5D available, and following NICE's hierarchy of preferred HRQoL methods. ¹⁶⁵

	IV disutility is applied in the base-case.	To capture impact on quality of life from IV infusions.
	Adverse events disutilities are applied in the base-case.	To capture the impact on quality of life from experiencing adverse events.
	Surgery disutility is not applied in the base-case.	Lack of suitable published estimates to inform surgery disutility value.
Cost and healthcare resource use	Method of moments used for calculating wastage in the base-case. This approach applies a lognormal transformation to the mean weight and standard deviation of all individual patients' weights reported in the pooled Phase 2 and Phase 3 OPTIC clinical trials to derive a lognormal distribution for vial usage. From this, a weighted average for the number of vials used was calculated.	TED is a disease with a relatively low prevalence worldwide, so it is uncertain whether vial sharing will be possible. Method of moments provides a more accurate estimate for wastage. No wastage is explored as scenario analyses.
	Only Grade ≥ 3 AEs occurring in $\geq 5\%$ of the study population are included.	Reflects AEs severe enough to require treatment.
	Subsequent treatment costs are applied to all patients in the four most severe health states (large proptosis, no diplopia; large proptosis, intermittent/inconstant diplopia; small proptosis, constant diplopia; large proptosis, constant diplopia), and to patients who discontinue treatment.	Assumed that patients who are in the two least severe disease health states, who complete their primary treatment course, would not have a severe enough disease to require a subsequent treatment.

Abbreviations: AE, adverse event; CEM, cost-effectiveness model; IPD, individual patient data; IV, intravenous; IVMP, intravenous methylprednisolone; MAIC, match-adjusted indirect comparison; MMF, mycophenolate mofetil; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; TA, technology assessment; TED, thyroid eye disease; UK, United Kingdom.
Source: NICE (2023), NICE (2022), Amgen (2024), Smith *et al.* (2023).^{165, 11, 141, 169}

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results versus IVMP and IVMP + MMF

Table 68 details the base-case results for teprotumumab versus IVMP and IVMP + MMF in treating moderate-to-severe active TED patients. All treatments included in the model resulted in a total number of life years (LYs) of [REDACTED], given TED is a chronic disease that does not directly affect patient mortality.

Teprotumumab treatment resulted in a total of [REDACTED] QALYs over the model lifetime time horizon, an increase of 0.8 QALYs versus both IVMP and IVMP + MMF ([REDACTED] total QALYs each). Teprotumumab treatment resulted in a total cost of £[REDACTED], an increase of £[REDACTED] versus IVMP (£[REDACTED] total cost) and £[REDACTED] (£[REDACTED] total cost) versus IVMP + MMF. The base-case incremental cost-effectiveness ratio (ICER) of teprotumumab was £[REDACTED] versus IVMP and £[REDACTED] versus IVMP + MMF per QALY gained. All results include a [REDACTED]% PAS applied to teprotumumab.

Table 69 details the expected net health benefit (NHB) of teprotumumab, with a NHB Opportunity Cost Threshold (OCT) value of £20,000 resulting in [REDACTED] NHB QALYs for teprotumumab versus both IVMP or IVMP + MMF, and a NHB OCT of £30,000 resulting in [REDACTED] NHB QALYs versus both IVMP and IVMP + MMF. Disaggregated results of the base-case incremental cost-effectiveness analysis are given in Appendix J.

As discussed in detail in Section B.1.3 azathioprine, ciclosporin and orbital radiotherapy (all usually in combination with oral or IV steroids) may also be used to treat moderate-to-severe active TED at second or later lines in the NHS. However, insufficient evidence was available for a formal comparison against these comparators. Given the clinical benefits of teprotumumab are expected to be similar in 2L vs 1L,^{158, 159} whereas the other treatment options used at 2L are expected to show lower efficacy than IVMP and IVMP + MMF irrespective of line of therapy, teprotumumab may conservatively be expected to be no less cost-effective as a second or subsequent treatment vs treatments used at 2L as it is versus IVMP and

IVMP + MMF in the untreated population. As such, generalising the incremental cost-effectiveness ratios for teprotumumab versus IVMP and IVMP + MMF to other 2L therapies would likely underestimate the value of teprotumumab. However, we propose this as a conservative approach in the absence of a formalised comparison.

Table 68: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Teprotumumab						-		
IVMP						0.8		
IVMP+MMF						0.8		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 69: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB OCT at £20,000	NHB OCT at £30,000
Teprotumumab				-		
IVMP				0.8		
IVMP+MMF				0.8		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probability sensitivity analysis (PSA) was conducted to explore uncertainty in the CEM. All inputs were varied simultaneously for 10,000 iterations, based on reported uncertainty values and appropriate distributional information. Where uncertainty parameters (e.g. standard errors, confidence intervals) were not reported, a standard error of 20% around the mean value is assumed. Table 70 presents the mean results of the 10,000 PSA iterations, with the probabilistic base-case ICER for teprotumumab of £[REDACTED] versus IVMP and £[REDACTED] versus IVMP + MMF per QALY gained. The mean probabilistic results are closely aligned to the deterministic results, indicating that the model is robust to parameter uncertainty.

Figure 34 presents the scatter plot for the 10,000 PSA iterations, as well as the mean ICER, for teprotumumab versus both IVMP and IVMP + MMF. The majority of the 10,000 PSA iterations were within the North-East quadrant, demonstrating an increase in QALY gained for patients treated with teprotumumab, at an increased cost.

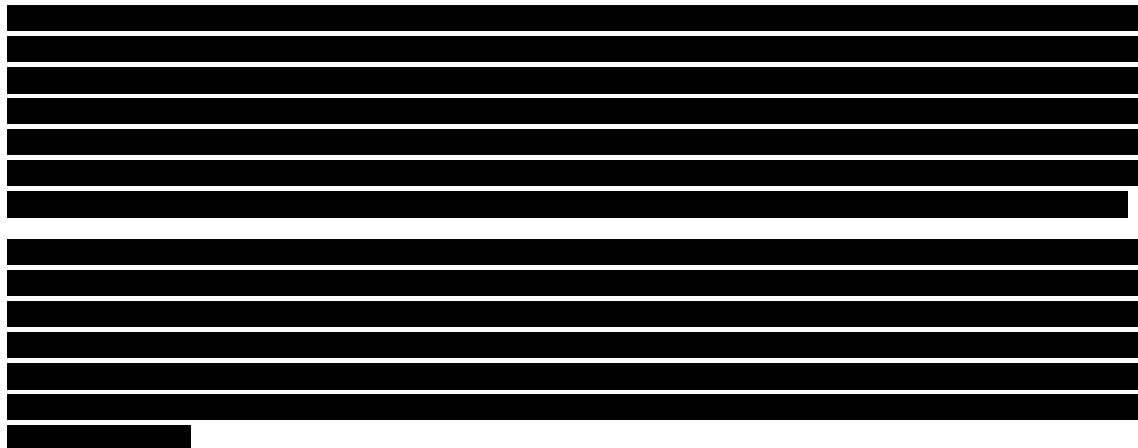
Figure 35 presents the cost-effectiveness acceptability curve (CEAC) for teprotumumab, IVMP, and IVMP + MMF.

Table 70: Probabilistic base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Teprotumumab	[REDACTED]	[REDACTED]	[REDACTED]	-	[REDACTED]
IVMP	[REDACTED]	[REDACTED]	[REDACTED]	0.8	[REDACTED]
IVMP+MMF	[REDACTED]	[REDACTED]	[REDACTED]	0.8	[REDACTED]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 34: Cost-effectiveness plane



Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil, PSA; probabilistic sensitivity analysis.

Figure 35: Cost-effectiveness acceptability curve



Abbreviations: CEAC, cost-effectiveness acceptability curve; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil.

B.3.11.2 Deterministic sensitivity analysis

One-way sensitivity analyses (OWSAs) were conducted to evaluate the sensitivity of the model to individual inputs, holding all other parameters constant. In OWSA, the lower and upper bounds of a parameter were set to +/-20% of the base-case value in the absence of reported confidence intervals. The ten most impactful parameters on the deterministic base-case ICER for teprotumumab versus IVMP and IVMP + MMF are given in Table 71 and Table 72, respectively. Tornado diagrams for teprotumumab versus IVMP and IVMP + MMF are given in Figure 36 and Figure 37, respectively.

Table 71: OWSA results for teprotumumab versus IVMP

Parameter	ICER: Lower bound (£)	ICER: Upper bound (£)	ICER: Difference (£)
Utility: Small Proptosis, No Diplopia			
Utility: Post-surgery			
Age			
Utility: Large Proptosis, Intermittent/Inconstant Diplopia			
Utility: Surgery			
Utility: Large Proptosis, No Diplopia			
Utility: Large Proptosis, Constant Diplopia			
Utility: Small Proptosis, Intermittent/Inconstant Diplopia			
Teprotumumab: Proportion of patients undergoing surgery (%) - Large Proptosis, Constant Diplopia			
Small Proptosis, No Diplopia total cost – cycle 36+			

Abbreviations: intravenous methylprednisolone; IVMP, OWSA, one-way sensitivity analysis.

Figure 36: OWSA tornado diagram for teprotumumab versus IVMP



Abbreviations: ICER, incremental cost-effectiveness ratio; IVMP, intravenous methylprednisolone; OWSA, one way sensitivity analysis.

Table 72: OWSA results teprotumumab versus IVMP + MMF

Parameter	ICER: Lower bound (£)	ICER: Upper bound (£)	ICER: Difference (£)
Utility: Small Proptosis, No Diplopia			
Utility: Post-surgery			
Age			
Utility: Large Proptosis, Intermittent/Inconstant Diplopia			
Utility: Surgery			
Utility: Large Proptosis, No Diplopia			
Utility: Large Proptosis, Constant Diplopia			
Teprotumumab: Proportion of patients undergoing surgery (%) - Large Proptosis, Constant Diplopia			
Utility: Small Proptosis, Intermittent/Inconstant Diplopia			
Small Proptosis, No Diplopia total cost – cycle 36+			

Abbreviations: IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; OWSA, One-way sensitivity analysis.

Figure 37: OWSA tornado diagram for teprotumumab versus IVMP + MMF



Abbreviations: ICER, incremental cost-effectiveness ratio; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; OWSA, one way sensitivity analysis.

B.3.11.3 Scenario analysis

Scenario analyses were performed to investigate uncertainty around the structural assumptions of the model. The deterministic results associated with each scenario are presented in Table 73. Rationale for including each scenario is briefly described in Table 73, with further explanation detailed in the relevant Sections of this submission document. Across all scenarios, ICER estimates were contained within a range of £[REDACTED] to £[REDACTED] for teprotumumab versus IVMP, and £[REDACTED] to £[REDACTED] versus IVMP + MMF.

Scenarios that explored the exclusion of subsequent treatment cost, or surgery complication costs, had a small impact on the deterministic ICER. As did the exclusion IV disutilities, and the scenarios exploring adverse events inclusion/exclusion criteria.

Not including vial wastage in the model reduced the deterministic ICER by more than £[REDACTED] (approximately 16%).

Exploring the use of alternative transition probabilities for IVMP from an independently published MAIC, Douglas *et al.* (2022), increased the ICER by £[REDACTED] (14.7%) versus IVMP.¹⁷¹ This study was not used in the base-case given non-RCTs were included within the independent MAIC, the median proptosis CFB was used over the mean, and difference matched covariates were used. Douglas *et al* Company evidence submission for teprotumumab for treating thyroid eye disease [ID6432]

al. (2022) also did not investigate IVMP + MMF as a treatment option, which resulted in no change in the deterministic ICER versus IVMP + MMF.¹⁷¹ Therefore, the study is limited compared to the MAIC used in the CEM base-case.

Table 73: Scenario analysis results

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER teprotumumab versus IVMP (£)	Impact on base-case ICER teprotumumab versus IVMP + MMF (£)
Base-case	Not applicable	Not applicable	████████	████████
Sourcing data from IVMP <i>de-novo</i> ITC with different covariates	Covariates: Smoking, baseline diplopia	To assess the impact of applying different covariates from those used in the base-case (smoking, baseline diplopia, baseline proptosis).	████████	████████
	Covariates: Smoking, baseline diplopia, baseline proptosis		████████	████████
Data source for the IVMP active population	Douglas <i>et al.</i> (2022). ¹⁷¹	To assess the impact of varying the efficacy for teprotumumab; the MAIC comparison in Douglas <i>et al.</i> 2022 included non-RCT studies, ¹⁷¹ so the <i>de-novo</i> MAIC was preferred for the base-case.	████████	████████
Include costs of subsequent treatments	No	To assess the impact of removing subsequent treatment cost. Subsequent treatments are recommended in the ETA guidelines and included in the base-case.	████████	████████
Include AEs	No	To assess the impact of removing AE costs and disutility.	████████	████████
	Yes (All Grade AEs)	To assess the impact of including AEs for	████████	████████

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		teprotumumab since Phase 2 and OPTIC trials did not report any severe Grade ≥ 3 AEs occurring in $\geq 5\%$ of patients in the study population.		
Model wastage	No wastage	To establish the impact of vial sharing if used in clinical practice. As TED is a disease with a relatively low prevalence worldwide, the base-case considered wastage.		
Include surgery complication costs	No	To assess the impact of removing costs for surgery complications.		
Include IV disutility	No	To assess the impact of removing disutility for IV infusions.		
Discount rate	1.5% for costs and outcomes	To assess the impact of alternative discount rates.		
	1.5% for costs only			
	1.5% for outcomes only			
Cycle surgery occurs at	20	To assess the impact of varying the cycle at which surgery occurs.		
	30			
Surgery recovery time (cycles)	21	To assess the impact of varying the surgery recovery time.		
	39			

Abbreviations: AE, adverse events; IV, intravenous; IVMP, intravenous methylprednisolone; MAIC, match-adjusted indirect comparison; MMF, mycophenolate mofetil; RWE, real-world evidence; TED, thyroid eye disease.

Source Douglas *et al.* (2022).¹⁷¹

B.3.12 Subgroup analysis

No subgroup analysis was performed as part of this appraisal.

B.3.13 Benefits not captured in the QALY calculation

The use of teprotumumab for the treatment of moderate-to-severe TED may result in additional patient benefits not captured in the economic analysis. These include:

- Greater LY and QALYs for teprotumumab as a result of better mental health. The economic model assumes patients have a mortality rate equal to the general population for all treatments. However, TED patients are known to have a higher risk of suicide,^{227, 228} due to physical consequences, self-esteem issues, negative impact on relationships and ability to engage with communities, and loss of independence. This suicide risk appears to be independent of the presence of Graves' disease and population studies suggest that the risk of suicide in TED patients is greater than double that of individuals without graves' disease or TED.²²⁷ Many studies have shown that patients with TED have a significantly lower quality of life, often due to visual impairment (physical disability) and/or perceived disfigurement,²³⁰ factors which are known to be associated with suicide risk.²³¹⁻²³⁴ Teprotumumab treatment has been demonstrated to improve quality of life in TED disease based on GO-QOL scores including sub-scales evaluating visual functioning and perceived physical appearance.
- Teprotumumab treatment could improve a patient's mental health by lessening the severity of TED-related changes to physical appearance, improving visual functioning, and improving overall quality of life and this may in turn result in fewer suicidal events, a benefit which is not captured in the economic analysis. These aspects are not easily captured in the utility and QALY calculations.
- The definition of large proptosis used in the economic analysis was selected based on the numerical equivalence of significant proptosis referenced in ATA/ETA guidelines (≥ 3 mm above the upper limit for race and sex).¹⁶⁷ The inclusion criteria for the Phase 2 and OPTIC Phase 3 clinical trials meant that

some people who were enrolled did not meet the definition of 'large proptosis' at study entry, and were instead enrolled based on their CAS score of >4 and/or other symptoms indicative of moderate-to-severe active TED (lid retraction, soft tissue involvement, diplopia), and entered the model in the 'small proptosis' health state. Despite observing a ≥ 2 mm reduction in proptosis from baseline at week 24 in the trials, these patients were not modelled to experience any improvement in proptosis as they were already in the best possible health state with respect to proptosis at model entry. Consequently, the model underestimates the true benefit of teprotumumab, as the treatment's benefit is not captured for these patients who start and finish in the small proptosis health state.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The CEM was developed in line with the NICE reference case and guidance from the NICE DSU TSDs, where appropriate. The CEM underwent quality control checks from an expert not involved in the development of the model, which included a systematic examination of calculations, model inputs, Visual Basic for Applications coding accuracy and extreme value testing. Additionally, the IVMP and IVMP + MMF transition probability calculations were developed in collaboration with an external health economic modelling expert, who validated the method and performed a quality check of the calculations to ensure accuracy.

This CEM is the first economic evaluation to assess teprotumumab for the treatment of moderate-to-severe active TED. As such, the results of the economic analysis in this appraisal could not be compared to previous studies.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional clinical evidence not described in B.2.2.-B.2.6

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teprotumumab for treating thyroid eye disease [ID6432]

Summary of Information for Patients (SIP)

January 2025

File name	Version	Contains confidential information	Date
ID6432 teprotumumab SIP [noCON].docx	1.0	No	14 January 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic approved name: teprotumumab
Brand name: TEPEZZA®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult patients with active thyroid eye disease (TED) of moderate-to-severe severity.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

At the moment, teprotumumab (TEPEZZA®) is only approved in the United States of America. It is not yet approved in Europe or in any part of the UK. Marketing authorisation in Europe and the UK is pending. The anticipated dates for regulatory approval can be found in section B.1.2. of the company submission (Table 2).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Amgen has been approached by the British Thyroid Foundation (BTF) to be an independent sponsor of a national Thyroid Eye Disease Patient Information Day. This is being organised primarily by the BTF in association with the Thyroid Eye Disease Charitable Trust and The Thyroid Trust.

The aim of the day is threefold (as per the letter of request of sponsorship):

- to inform and educate patients and carers about all aspects of living with a diagnosis of TED and how to live better with it. This will involve talks by medical specialists who are looking after patients at all stages of the diagnosis;
- discussions and presentations about treatment options and what they can expect from the team that is caring for them;
- the opportunity to meet, listen to and talk to other patients who may have been through similar experiences, to share tips and learn from each other and to advocate better for themselves.

The amount of sponsorship requested by the BTF is £30,400. At the time of submission to NICE this is yet to be formally contracted.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Thyroid eye disease (TED), also known as thyroid-associated ophthalmopathy, Graves' ophthalmopathy or Graves' orbitopathy, is a serious and progressive autoimmune disease (a condition where the body's immune system attacks itself) that affects the eyes and the tissues that surround them. This can include the eye muscles, eyelids, tear glands and soft tissues around the eyes.

In TED, the body's immune system mistakenly attacks these tissues, and this causes inflammation (pain, redness and swelling). This can result in a number of different symptoms such as red eyes, dry eyes, itchy eyes, watery eyes, sensation of a foreign body in the eye, and swollen eye lids. There is also an increase in the number and size of the muscle and fat cells surrounding the eyes which can result in increased pressure within the orbit (eye socket). This increased pressure can push the eyes forward so that they "bulge" outwards. This bulging of the eyes can cause significant disfigurement and, in some cases, this can prevent complete closure of the eyes (including during sleep). In addition, the inflammation and increased pressure can mean the muscles that control eye movements cannot function properly. This can mean that eye movements are restricted and that the eyes cannot move together equally and this in turn can cause double vision.

Over time, some symptoms of inflammation (redness, pain and swelling) may improve or go away. However, because of remodelling of the muscle and fat tissues around and behind the eyes, symptoms such as eye bulging and double vision may persist.

In a minority of TED patients, vision can be compromised, most commonly through two associated conditions Dysthyroid Optic Neuropathy (DON) and/or corneal ulceration. In DON, the increased pressure within the eye socket can cause compression of the optic nerve (the nerve that carries visual signals from the eye to the brain) and disruption of its blood supply and function, potentially leading to permanent visual loss. Corneal ulceration refers to the breakdown of the dome shaped outer layer of the eye that covers the pupil and iris (the coloured ring of the eye) and is caused by the inability to fully close the eye, resulting in a lack of lubrication of the eyes surface and subsequent sore formation.^{1,2}

The symptoms and signs of TED can cause significant disfigurement (redness, bulging and malalignment of the eyes) and disability (pain, double vision and visual impairment/loss).^{2,3} These factors combine to produce high morbidity and marked reductions in quality of life (QOL), such as physical functioning, role functioning, social functioning, mental health, health perceptions and pain.^{4,5} The substantial changes in patient QOL due to TED can produce profound psychosocial problems and impact various aspects of patient wellbeing, in particular, anxiety and depression due to the alarming and disfiguring changes in appearance that can result^{6,7} and feelings of isolation.⁸⁻¹⁰

The exact number of patients affected by TED in England remains uncertain. However, a recent European study suggests that there could be around 68,000 TED patients in the UK or 58,000 in England.¹¹⁻¹⁴ TED is five or six times more common in women than in men¹⁵ and most frequently affects people between the ages of 40 to 65.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

TED can be difficult to diagnose, which leads to delays in treatment. Diagnosing TED requires a comprehensive approach as no single clinical finding or laboratory test is definitive. The tests and investigations typically involved in making a diagnosis of TED include a review of the patient's medical history, a physical examination of the eyes, thyroid function tests, imaging (e.g. magnetic resonance imaging), laboratory tests and antibody tests.

The process of diagnosis can be time-consuming and burdensome on the patient. Some patients have reported encountering difficulties early on, facing uncertain diagnoses, prognoses, and treatment decisions^{3,16}:

"It also took many months and many doctor visits to get an accurate diagnosis, which is demoralising and terribly frustrating."

"I was diagnosed with Thyroid Eye Disease in August of 2020. I'd actually never heard of the disease before. It took 3 doctors to finally diagnose me and find a doctor who specialised in it."

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug-drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are currently no treatments specifically approved for TED in the UK. Treatments for active TED, irrespective of disease severity, do not target the underlying cause of the disease. They can provide temporary symptomatic relief, but do not result in meaningful changes in bulging of the eyes (proptosis) and double vision (diplopia).

All medical treatment of TED is accompanied by conservative measures to control known risk factors for TED. This includes smoking cessation support and control of thyroid dysfunction.

Treatment of active moderate-to-severe TED

Most TED clinicians practising in England follow the 2021 clinical practice guidelines for treating patients with TED developed by the European Group on Graves' Orbitopathy, or EUGOGO.¹⁷ These guidelines recommend steroids (intravenous methylprednisolone; IVMP) over 12 weeks, with or without the addition of mycophenolate mofetil (MMF) over 24 weeks as a first treatment.¹⁸ IVMP is a member of a class of treatments called glucocorticoids, whereas MMF is a non-steroidal immunosuppressant treatment.

Glucocorticoids such as IVMP are thought to help reduce inflammation and so help with symptom control, and have been the most common treatment option for acute, moderate-to-severe TED for more than 50 years, even though they are not licensed or approved to treat TED.¹⁹⁻²¹ Glucocorticoids can provide symptomatic relief in TED patients with inflammation, due to their impact on the swelling of superficial soft tissues, and other aspects of disease associated with inflammation,^{22,23} but they have limited impact on double vision, bulging of the eyes and the other potentially disfiguring consequences of TED.

If a patient needs a second treatment (for example, because their condition has not responded to the first treatment, or has not responded sufficiently well), the choice of second treatment depends on the treatment goals for that patient, patient preferences, and the availability of the treatment. Options include a further course of IVMP (with or without MMF), oral steroids, orbital radiotherapy and/or systemic immunosuppressants (such as azathioprine and ciclosporin), none of which are licensed or approved to treat TED. Biologic agents (e.g. rituximab and tocilizumab) may be used in a small number of hospitals but they are not available routinely or consistently throughout the UK.

In summary, the company's understanding is that systemic methylprednisolone (IVMP) with or without MMF is used almost exclusively for people with active, moderate-to-severe TED who have received no prior treatment. It is also used, often at a higher dose, for TED patients who have had an inadequate response to their initial treatment or have experienced deterioration in symptoms or disease progression. For this latter group, ciclosporin or azathioprine (with steroids), or orbital radiotherapy may also sometimes be used.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Smith and colleagues have investigated how TED patients experience living with this condition, and have concluded that TED can have a wide-ranging impact on the lives of patients, regardless of disease activity or duration.³ Symptoms of TED, such as dry or gritty eyes, light sensitivity, bulging eyes, and pressure or pain profoundly impact patients.³

“Eyes do not look straight ahead, comfortable eye position for me after TED is much lower than neutral so to lift my eye up hurts, driving more than 15 minutes is difficult and then this creates tremendous neck pain and ... migraines.”

“When I felt increased pressure at work and home, my symptoms got worse.”

Dry/gritty eye (reported by 65%), light sensitivity (56%), proptosis (43%), and pressure or pain behind the eye (42%) were the most burdensome symptoms reported by 443 patients with acute and chronic TED.³ TED imposes significant restrictions on daily activities such as reading, driving, socialising, and working due to impaired visual function.^{24,25} These restrictions can negatively affect employment, relationships, and self-confidence, often leading to social withdrawal. In 171 patients with recent onset, moderate-to-severe TED, Smith et al. found that 74% of them had difficulty reading, 61% experienced difficulties driving, 95% reported a change in their appearance and 66% reported that their condition had adversely affected their self-confidence.^{26,27}

Other noted challenges include difficulty driving and moving around outdoors, particularly with light sensitivity, uneven surfaces, and depth perception issues^{3,28-32}:

“I am worried about crossing roads and definitely don’t go out on my own. I always go out with my sister. I wouldn’t dream of going shopping on my own.”

“I started experiencing visual problems which affected my daily life. I slowly stopped reading because I couldn’t track the words on the page. Eventually, I stopped driving, relying on others for transportation.”

“I started having problems completing everyday activities. Driving also became difficult. I drove with one eye closed due to severe double vision. I quit driving long distances and anywhere I was not familiar.”

A 2014 Danish study found that patients with TED were at significantly higher risk of sickness absence, lower probability of returning to work after sickness absence and higher risk of unemployment and disability pension compared to people with other types of thyroid disease and the general population.³³

As well as causing visual dysfunction and, in severe cases, threatening sight altogether, proptosis can dramatically change a patient's appearance. This can have a profound effect on patients' quality of life.

More than 70% of TED patients reported that the disease interfered with their vision, and 60-95% felt that changes in their appearance significantly affected their psychosocial functioning.²⁸⁻³⁰

In a separate study, people with TED reported higher levels of potential cases of clinical anxiety (37%) and depression (26%) compared with patients with other chronic diseases or facial disfigurements. Appearance-related quality of life and mood were particularly affected.³⁴ Other studies have reported how the impact of an altered appearance due to TED leads to social withdrawal, isolation, and a decrease in confidence and self-esteem.^{3,25}

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The underlying causes and disease course of TED are not fully understood. However, TED is an autoimmune condition (a condition where the body's immune system inappropriately attacks itself). Antibodies are small proteins that are normally produced by the body's immune cells (B cells). They bind to specific targets on things which the body recognises as foreign/alien such as bacteria and viruses. This "tagging" of foreign entities with antibodies assists in the process of the immune system recognising them and removing them from the body. In TED, it is believed that there is abnormal production of antibodies that bind to and activate specific targets on the surface of normal (non-alien/non-foreign) cells within and around the eye socket. These cells can include muscle, fat, immune cells (T and B cells) and fibroblasts which help to create and maintain connective tissues. Binding of these antibodies to their targets and the subsequent activation of these cells results in two key outcomes. Firstly, there is an increase in the production of specialised signalling molecules called "cytokines". These cytokines activate the immune system and lead to symptoms of inflammation (redness, heat, pain and swelling). Secondly, signalling pathways are activated that lead to the increase in the number and size of fat and muscle cells as well as an increase in production of some of the constituents of connective tissue. In turn, this remodelling of the tissues within and around the orbit (eye socket) leads to crowding and increased pressure that can give rise to the bulging eyes (proptosis) and restriction of eye movement (double vision) associated with TED. One of the targets thought to play a key role in this process, through its activation by antibodies, is the insulin like growth factor 1 receptor (IGF-1R).

Teprotumumab is a manufactured (laboratory created) antibody that also targets the IGF-1R. However, instead of activating the IGF-1R, teprotumumab blocks its activation. In doing so, it is believed that it can reduce the production of inflammatory cytokines, tissue remodelling and therefore many of the symptoms associated with TED. Teprotumumab has demonstrated statistically significant reductions in bulging of the eyes, double vision and the inflammatory symptoms of TED in randomised controlled trials. In addition, reduction in these symptoms was also associated with significant improvements in patient-reported quality of life scores, including those evaluating self-rated appearance and visual-functioning.

There is significant unmet medical need in TED, and specifically for new medicines with improved effectiveness and better tolerability that treat the underlying cause of the disease. Current management of TED comprises the use of off-label interventions (that is, treatments that do not have a licence specifically for treating TED) with a limited evidence base that are not suitable, or available, for all patients. Current treatments may help with symptom improvement but fail to target the underlying disease, and so do not significantly alter the long-term disease outcome.³⁵

Teprotumumab is the first and only medicine that targets the underlying causes of TED and has the potential to positively affect the course of the disease. Teprotumumab not only reduces the inflammation associated with TED, it treats the underlying cause of TED, thereby modifying the course of the disease, reducing disability and improving the function of the eye.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No
- If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, teprotumumab is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Teprotumumab is given to patients as an intravenous infusion using an infusion pump. It is administered into a vein, usually through a small plastic tube called a cannula, which is placed into the back of the hand or in the arm.

Teprotumumab must be administered by a healthcare professional and under the supervision of a physician experienced in the diagnosis and treatment of TED with access to appropriate medical support to manage potential reactions, such as any serious infusion-related reactions.

Teprotumumab dosing is based on the patient's actual body weight. The recommended dose of teprotumumab is 10 mg/kg of body weight for the initial dose followed by 20 mg/kg of body weight for 7 additional doses given once every three weeks as an intravenous infusion. For the first 2 infusions, the diluted solution is administered as an intravenous infusion over at least 90 minutes. If well tolerated, infusions 3 to 8 can be administered over 60 minutes every three weeks.

Most of the other treatments already being used to treat TED symptoms are also administered by IV infusion, so the administration method of teprotumumab is not expected to have any additional burden on patients or their caregivers. An intravenous course of steroid infusions usually lasts for about 12 weeks, with weekly infusions. So, treatment with teprotumumab would mean fewer and less frequent hospital visits than for a full course of steroid treatment.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Teprotumumab has been evaluated in a clinical development programme consisting of several studies including a phase 2 randomised controlled trial (RCT) [NCT01868997], a phase 3 OPTIC RCT [NCT03298867]), an open-label extension study from OPTIC (OPTIC-X) for moderate-to-severe acute TED, and a phase 4 study in the United States (US) in patients with chronic TED. Furthermore, teprotumumab was also evaluated in the treatment of Japanese patients with moderate-to-severe acute TED in the OPTIC-J study.

Links to the three studies in moderate-to-severe acute TED relevant to the population in this NICE appraisal are provided here:

- Teprotumumab (RV 001) Treatment in Patients With Active Thyroid Eye Disease (phase 2, completed)
<https://clinicaltrials.gov/study/NCT01868997?term=OPTIC&intr=Teprotumumab&rank=10>
- Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC)(phase 3, completed)
<https://clinicaltrials.gov/study/NCT03298867?term=OPTIC&intr=Teprotumumab&rank=2&tab=results>
- Treatment of Graves' Orbitopathy to Reduce Proptosis With Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X)
<https://clinicaltrials.gov/study/NCT03461211?term=OPTIC&intr=Teprotumumab&rank=1&tab=results>

A US trial to investigate a sub-cutaneous formulation of teprotumumab is ongoing:
<https://clinicaltrials.gov/study/NCT06248619?term=OPTIC&intr=Teprotumumab&rank=4>

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Teprotumumab significantly improved response rates for double vision (diplopia) and eye bulging (proptosis) when compared with placebo (dummy treatment) in two double-blind randomised, placebo-controlled clinical trials (a phase 2 study and the phase 3 OPTIC study). The combined outcomes from a pooled data analysis of these two studies reported significantly better clinical results in patients treated with teprotumumab compared to placebo at Week 24 as follows:

- Reduction in eye bulging: a response rate of 77% for patients treated with teprotumumab vs. 15% for patients given placebo.
- Reduction in double vision: 70% for teprotumumab vs. 31% for placebo
- The proportion of patients achieving an overall response, which was defined as a reduction of at least 2 mm in the bulging of the eye AND a reduction of at least 2 points in the Clinical Activity Score [CAS]: 74% for teprotumumab vs. 14% for placebo.
- Disease inactivation (defined as achieving a CAS] of 0 or 1): 62% for teprotumumab vs. 22% for placebo.

All of these results were statistically significant, confirming that teprotumumab is better than placebo for treating moderate-to-severe active TED.

Teprotumumab also leads to meaningful improvements in QOL (measured as improvements in the Graves' Orbitopathy Quality of Life [GO-QOL] questionnaire visual-functioning, appearance and combined scales) in patients with TED. Further information is given in section 3f below.

There has been no direct comparison of teprotumumab and any of the other current treatment options for active, moderate-to-severe TED listed in section 2c) above. However, there is very limited evidence and data to support the efficacy of these options in patients with TED. Steroids like IVMP can provide transient symptomatic relief in TED patients due to their impact on inflammation including superficial soft-tissue swelling.^{22,23} However, while inflammation improves over time, the bulging of the eyes may not return to normal, with a significant percentage of patient cases (ranging from 14% to 41.2%) having permanent double vision and experiencing worsening or long-term visual impairment.³⁶⁻³⁸ Additionally, steroids are only appropriate for short term use as extended treatment can be associated with high rates of adverse reactions.³⁹⁻⁴³

There is currently no robust evidence to demonstrate the impact of glucocorticoids on the hallmarks of TED: proptosis and/or diplopia. Studies on the use of glucocorticoids in TED suggest modest improvements in proptosis and diplopia, however these are not considered to be clinically meaningful.⁴⁴ A meta-analysis of the published literature on the efficacy of IV glucocorticoids at the EUGOGO-recommended dose over a 12-week period in patients with acute, moderate-to-severe TED found a modest, but not clinically meaningful effect, on proptosis and diplopia.⁴⁴

Immunomodulatory agents can also reduce inflammation in active TED but have limited, if any, effect on the long-term consequences of disease, such as functional disability and facial disfigurement.

The company has carried out indirect treatment comparisons between teprotumumab and the current standard of care for TED: intravenous steroids (IVMP) with or without mycophenolate mofetil (MMF). The methods and results of these indirect comparisons are presented in section B.2.9 of the company submission. The indirect comparisons suggest that teprotumumab may be more effective at treating TED than these other treatments but the results are confidential.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease-specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The impact of teprotumumab treatment on patients' health-related quality of life was measured in the phase 2 and phase 3 (OPTIC) trials and the effects measured using an instrument known as the GO-QOL (Graves' Orbitopathy Quality of Life) questionnaire.

The GO-QOL questionnaire measures disease-specific aspects of QOL in TED patients. It includes two domains (eight questions each): the impact of double vision and decreased visual acuity on visual-functioning, and the psychosocial consequences of having an altered appearance. The sum of the scores on each subscale and an overall combined score are calculated and transformed to a scale from zero to 100, with 0 indicating worst health state and 100 indicating best health state. A mean change of 6 points or more is considered clinically meaningful.⁴⁵⁻⁴⁷

In the phase 2 trial in patients with active moderate-to-severe TED, teprotumumab treatment resulted in improvements in the GO-QOL visual-functioning score compared with placebo, demonstrating that teprotumumab improved symptoms related to vision. The

improvement in scores was large enough to be considered clinically meaningful or relevant. A consistent trend toward improvement on the GO-QOL appearance subscale was also observed in the group of patients treated with teprotumumab, but the result did not reach statistical significance.⁴⁸

In the phase 3 OPTIC trial, patients who received teprotumumab had a better overall score on the GO-QOL compared to those who received placebo, meaning that they reported improved quality of life. Scores on the visual and appearance subscales were also significantly better with teprotumumab than with placebo by the end of the trial.⁴⁷

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Teprotumumab was generally well-tolerated across the clinical studies and most adverse events were of mild or moderate severity. Serious adverse events were uncommon and the most recent cumulative safety update confirms that the benefit-risk profile of teprotumumab remains favourable for the thyroid eye disease indication.

The most common adverse reactions observed in the teprotumumab clinical trials were: muscle spasms (experienced by 27.6% of patients receiving teprotumumab in the clinical trials), diarrhoea (14.5%), hearing impairment (13.8%), alopecia (13.2%), hyperglycaemia (13.2%), fatigue (12.5%), nausea (10.5%), headache (10.5%), dry skin (9.9%), dysgeusia (a taste disorder where foods can taste metallic, sweet, sour or bitter, 8.6%), COVID-19 (6.6%), ear discomfort (6.6%) and nail disorder (5.9%). Overall, most of these side effects were of mild to moderate severity, were temporary, and were easily managed or treated.

The most common serious adverse reactions observed in the teprotumumab clinical trials were diarrhoea, exacerbations of existing inflammatory bowel disease (observed in two patients), or infusion-related reactions.

Events associated with hearing impairment including hearing loss have been observed in the teprotumumab clinical trials. People taking teprotumumab need their hearing assessed before, during and after treatment, and should discuss the benefits and risks of treatment with their clinician.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
- Teprotumumab will be the first treatment specifically for people with moderate-to-severe TED. Currently available treatments only reduce inflammation and help with symptom reduction, whereas teprotumumab blocks a key receptor involved in the underlying mechanism of TED. This means it reduces symptoms and treats the

underlying cause of disease to reduce longer-term complications such as double vision (diplopia) and eye bulging (proptosis).

- Teprotumumab will be the only licensed treatment for the disease in the UK. Other treatments are used 'off-label', which means they are not approved specifically to treat TED. Teprotumumab will therefore be the only treatment for TED with a patient information leaflet specifically describing how it should be used and for how long, providing clarity and reassurance for patients.
- Teprotumumab significantly improved response rates on diplopia and proptosis vs. placebo, as demonstrated in two randomised, double-blind, placebo-controlled studies (phase 2 and phase 3 OPTIC). The integrated outcomes from a pooled data analysis of the two trials reported significantly better clinical results with teprotumumab compared to placebo on proptosis response rate (77% vs 15%; $p < 0.0001$), diplopia response rate (70% vs 31%; $p < 0.0001$), overall response rate (74% vs 14%; $p < 0.001$), and disease inactivation (i.e., achieved CAS of 0 or 1) (62% vs 22%; $p < 0.001$) after 24 weeks of treatment. In general, teprotumumab was well-tolerated by patients, with the majority of adverse events being temporary, of mild to moderate severity, and did not result in discontinuation from the study.
- The improvement in proptosis with teprotumumab over placebo was consistent across various subgroups, including age, gender, smoking status, time since diagnosis of TED, time since diagnosis of Graves' Disease and baseline CAS.
- Teprotumumab treatment also leads to meaningful improvements in QOL in patients with TED.
- Teprotumumab's dosing frequency (once every 3 weeks x 8) is less frequent than for the main comparator IVMP (once a week for 12 weeks), meaning fewer and less frequent hospital visits and so less of a burden for TED patients and their carers.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Teprotumumab is generally well tolerated but, as with all treatments teprotumumab can be associated with some side effects. It is important to note that not every patient will experience side effects and that, where they do occur, they can affect each person differently.

As noted above, the most common side effects observed in the clinical trials included muscle spasms (experienced by 27.6% of patients receiving teprotumumab), diarrhoea (14.5%), hearing impairment (13.8% - this includes, amongst others: hearing loss, sensitivity to sounds, tinnitus [ringing in the ears] and autophony [the perception of the echoing of one's own voice]), alopecia (13.2%), hyperglycaemia (13.2%), fatigue (12.5%), nausea (10.5%), headache (10.5%), dry skin (9.9%), dysgeusia (a taste disorder where foods can taste metallic, sweet, sour or bitter, 8.6%), COVID-19 (6.6%), ear discomfort (6.6%) and nail disorder (5.9%). Overall, most of these side effects were of mild to moderate severity, were temporary, and were easily managed or treated.

Teprotumumab is administered as an intravenous infusion, which means the patient must travel to an appropriate outpatient clinic once every 3 weeks. However, other treatments for TED are also administered intravenously and so the method of administration for teprotumumab is no different to the current treatment options. In fact, as noted in section 3h) above, the dosing schedule for teprotumumab is less burdensome on patients and their carers than the dosing schedule for IVMP.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition:

- The economic model is informed by the Phase 2 and Phase 3 OPTIC clinical trials for teprotumumab for the treatment of TED.^{49,50} Evidence for the comparator treatments of IVMP and IVMP + MMF were informed by the available literature.
- The model categorises people into separate disease health states according to their level of proptosis (eye bulging) and diplopia (double vision) scores, with cost and quality of life outcomes applied to each health state. People can move between these health states over time, reflecting improvements or worsening of their disease.
- The disease health states use in the model align with the outcomes of the Phase 3 OPTIC trial,⁵⁰ and were validated by UK clinicians, who commented that the health states used would capture meaningful changes in the disease.⁵¹
- As there is no evidence for patient movement beyond 24 weeks, for either teprotumumab or comparators, the model assumes that patients remain in the disease health state they were in at 24 weeks for the duration of their lifetime.
- The model also captures patients who may receive surgery(ies) as part of their treatment options. This is captured by including additional health states for surgery and post-surgery, which patients can move to outside of the disease health states. Patients who move to surgery and post-surgery health states ultimately remain in the post-surgery health state for the durations of their lifetime, as patients in these health states may have different costs and quality of life experiences that the disease health states described above.
- As TED is a chronic disease, which lasts for the entire patient's lifetime, the model has a lifetime time horizon (estimating the costs and quality of life for the entire patient's lifespan up to age 100).

Modelling how much a treatment improves quality of life:

- Teprotumumab is a first-in-class treatment, with the only available alternatives being off-label therapies that target some of the symptoms of TED and not the underlying disease. Therefore, patients treated with teprotumumab is expected to be greater than those treated with the comparators, which is seen in the economic analysis.
- Patients treated with teprotumumab had no side effects (adverse events) greater or equal to Grade 3 (a measure of severity), which occurred in 5% or more patients; a standard cut-off and modelling practice outlined in NICE guidance.⁵²
- Quality of life was captured through utility values (a measure of quality of life, with a utility value of 1 representing perfect health and a value of 0 representing death) and reported as quality-adjusted life years (QALYs); calculated as the utility value multiplied by the estimated patient's lifespan (life years). Utility values were based on the model's health states, and not by treatment. Patients who remain in less severe health states have a higher utility value and generate more QALYs. In the economic analysis, more patients treated with teprotumumab remained in the less severe health states, compared to the comparators, therefore, generated more QALYs.

Modelling how the costs of treatment differ with the new treatment:

- Teprotumumab resulted in an increase in QALYs at an increased cost compared with IVMP and IVMP + MMF. The cost-effectiveness, as measured by the incremental cost-effectiveness ratio (ICER, difference in costs divided by the difference in QALYs) is confidential.
- Teprotumumab does not quantitatively meet the current criteria for consideration of a severity weight, which increased NICE's ICER threshold. However, given that the severity modifiers were designed to incentivise innovation in underserved disease areas, and teprotumumab is an innovative first-in-class treatment that meets an unmet clinical need for moderate-to-severe active TED patients, we believe teprotumumab matches the objectives which the severity modifiers initially set out to be achieved.
- The net budget impact of introducing teprotumumab into the NHS is not expected to exceed NICE's budget impact test of £20,000,000 per year in any of the first five years of its use in the NHS.
- Teprotumumab is given once every three weeks for eight intravenous (IV) infusions, compared to the comparator treatment component IVMP that is administered weekly for 12 weeks. Patient's treatment with teprotumumab, therefore, have fewer intravenous infusions, which is expected to improve the patients' wellbeing and reduce any associated costs and time. IV disutilities, the negative effect of an experiencing an IV infusion, is included in the economic analysis, however, the additional cost and time to the patient is not captured.

Uncertainty:

- There is limited clinical and economic data available for moderate-to-severe TED, with no published cost-effectiveness analysis available. Therefore, several modelling assumptions have been made due to a lack of clinical data. Where possible, modelling assumptions were validated by UK clinical experts.
- Uncertainty in the economic analysis was also explored through a series of sensitivity and scenario analysis; these are presented in the Company submission documents.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

There are currently no medicines specifically approved for TED in the UK. If licensed, teprotumumab will be the first and only medicine to be licensed to treat TED and the first and only intervention that targets the underlying pathophysiology of TED. Clinical management of all active TED patients, irrespective of disease severity, currently consists of off-label treatments which do not target the underlying cause of the disease, but focus on relieving symptoms and inflammation, with non-meaningful changes in eye bulging (proptosis) and double vision (diplopia).

Teprotumumab is expected to represent a step change in treatment because, not only does it reduce the inflammation associated with TED, but the mechanism of action helps with the underlying autoimmune pathogenesis of TED, thereby modifying the course of the disease, reducing disability and improving ocular function. Teprotumumab has demonstrated statistically significant reductions in proptosis, diplopia and the inflammatory symptoms of TED (as measured by the Clinical Activity Score [CAS]) in randomised controlled trials, with associated significant improvements in patient-reported quality of life scores. The economic analyses focus on aspects of the patient treatment experience that we can measure from clinical data and expert opinion. The economic analyses in themselves do not fully and accurately capture the broader aspects of clinical unmet need in TED, nor the broad benefits of teprotumumab as a first-in-class treatment for moderate-to-severe active TED patients. Currently, the only viable alternative treatment options focus exclusively on treating the symptoms and not the underlying disease. This is further emphasised in the severity modifier calculations, where we believe teprotumumab matches the objectives that the severity modifiers initially set out to be achieved, but do not fall within the quantitative thresholds.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

[Find more general information about the Equality Act and equalities issues here](#)

Disease severity in active TED is measured through the Clinical Activity Score (CAS).¹⁷ One of the key limitations with the CAS is that some signs of inflammation, such as redness, are more difficult to detect in people who have black skin. Data suggests that darker skinned patients present with fewer external exam findings suggestive of active TED compared to white patients, but the rate of compressive optic neuropathy and decompression surgery are similar.^{53,54} Therefore, the CAS may underappreciate disease activity in darker skinned patients.^{53,54}

Given the company submission includes moderate-to-severe active TED, which is often defined clinically according to the CAS, it is important to ensure that any recommendations do not make it more difficult for people with black or brown skin to

access teprotumumab. There is a risk that their CAS assessment does not reflect their clinical disease activity level (i.e. they may be assessed as having inactive disease when they have clinically active disease), and as such a risk of them being excluded from accessing teprotumumab due to their race.

This is also one of the reasons why the cost-effectiveness model (CEM) structure includes health states based on a combination of TED symptomatic proptosis and diplopia score, validated through UK clinical experts, and not CAS.

TED is also more prevalent in women, with an estimated 0.54 to 0.9 cases per 100,000 men per year and 2.67 to 3.3 cases per 100,000 women per year.^{15,17} Therefore, there is greater clinical evidence available for women compared to men.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Patient organisation websites:

- <https://www.btf-thyroid.org/listing/category/thyroid-eye-disease-ted>
- <https://tedct.org.uk/>
- <https://www.nrib.org.uk/your-eyes/eye-conditions-az/thyroid-eye-disease/>

Teprotumumab clinical trial information and results:

- Phase 2 trial Teprotumumab (RV 001) Treatment in Patients With Active Thyroid Eye Disease
<https://clinicaltrials.gov/study/NCT01868997?term=OPTIC&intr=Teprotumumab&rank=10>
- Phase 3 OPTIC study Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study
<https://clinicaltrials.gov/study/NCT03298867?term=OPTIC&intr=Teprotumumab&rank=2&tab=results>
- Treatment of Graves' Orbitopathy to Reduce Proptosis With Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X)
<https://clinicaltrials.gov/study/NCT03461211?term=OPTIC&intr=Teprotumumab&rank=1&tab=results>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE:
<https://www.eupati.eu/guidance-patient-involvement/>

- EFPIA – Working together with patient groups:
<https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative.
<https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

BTF, British Thyroid Foundation
 EUGOGO, the European Group on Graves' Orbitopathy
 GO-QOL, the Graves' Orbitopathy Quality of Life questionnaire
 IVMP, Intravenous Methylprednisolone
 MMF, mycophenolate mofetil
 NICE, the National Institute for Health and Care Excellence
 QOL, Quality of Life
 RCT, Randomised Controlled Trial
 TED, Thyroid Eye Disease
 US, United States

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

- 1 Smith, T. J. & Hegedus, L. Graves' Disease. *N Engl J Med* 375, 1552-1565 (2016).
<https://doi.org/10.1056/NEJMra1510030>
- 2 Szelog, J., Swanson, H., Sniegowski, M. C. & Lyon, D. B. Thyroid Eye Disease. *Mo Med* 119, 343-350 (2022).
- 3 Smith, T. J. et al. How patients experience thyroid eye disease. *Front Endocrinol (Lausanne)* 14, 1283374 (2023). <https://doi.org/10.3389/fendo.2023.1283374>
- 4 Gerding MN, T. C., Dekker FW, et al. . Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. . *Thyroid*. 1997;7(6):885-9. (1997).
- 5 Terwee C, W. I., Tan S, et al. . Long-term effects of Graves' ophthalmopathy on health-related quality of life. . *Eur J Endocrinol*. 2002;146(6):751-7. (2002).
- 6 Bartley GB, F. V., Kadrmas EF, et al. Long-term follow-up of Graves ophthalmopathy in an incidence cohort. . *Ophthalmology*. 1996;103(6):958-62. (1996).
- 7 Coulter I, F. S., Krassas GE, Perros P. . Psychological implications of Graves' orbitopathy. . *Eur J Endocrinol*. 2007;157(2):127-31. (2007).
- 8 Amgen. ABOUT THYROID EYE DISEASE (TED). 2023; Available from: <https://www.tepezzahcp.com/about-thyroid-eye-disease/>. (2023).
- 9 Amgen. PSYCHOLOGICAL IMPACT OF THYROID EYE DISEASE (TED). 2023; Available from: <https://www.tedimpact.com/thyroid-eye-disease-symptoms/patient-burden>. (2023).
- 10 Patel, A., Yang, H., & Douglas, R. S. . A New Era in the Treatment of Thyroid Eye Disease. . *Am J Ophthalmol*, 208, 281-288.
<https://doi.org/10.1016/j.ajo.2019.07.021> (2019).

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- 12 Laurberg, P., et al. . *J Clin Endocrinol Metab*. 2012;97:2325–32. doi: 10.1210/jc.2012-1275. (2012).
- 13 Perros, P., et al., . Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. . *Orphanet J Rare Dis* 2017 Apr 20;12(1):72. doi: 10.1186/s13023-017-0625-1. (2017).
- 14 Zaletel, K., et al. . *Croat Med J*. 2011;52:615–21. doi: 10.3325/cmj.2011.52.615. (2011).
- 15 Bartalena, L., Piantanida, E., Gallo, D., Lai, A. & Tanda, M. L. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. *Front Endocrinol (Lausanne)* 11, 615993 (2020). <https://doi.org/10.3389/fendo.2020.615993>
- 16 AMGEN. *Thyroid Eye Disease (TED) Patient Experiences*, <<https://www.tepezza.com/about-tepezza/patient-experiences>> (2023).
- 17 Bartalena, L. et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 185, G43-g67 (2021). <https://doi.org/10.1530/eje-21-0479>
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teprotumumab for treating thyroid eye disease [ID6432]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6432 teprotumumab Company response to EAG clarification letter [redacted]	2.0	No	26 February 2025

Section A: Clarification on effectiveness data

Literature searches

A.1 Appendix D states that searches were run on 9.6.23 and updated on 11.9.24 for the clinical effectiveness SLR. Only the original search strategies appear to have been provided in this submission (Tables 5-9).

a) Please provide the full search strategies for all update searches conducted.

Search strategies were the same for both the original clinical SLR (conducted 9.6.23) and the updated clinical SLR (conducted 11.9.24). Please see the below updated tables for MEDLINE, EMBASE, Cochrane, and DARE searches.

Search Strategy in MEDLINE:

#	Search terms	Hits 9/6/23	Hits 11/9/24
1	graves ophthalmopathy/	2982	3366
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyroid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	5599	6025
3	or/1-2	5599	6025
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glyccorticoid* or glyccorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	343664	355712
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitison or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab,kw,kf,rn.	58291	59642
6	exp meprednisone/ or (prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or detla cortene beta or "deltisone b" or "deltisona b" or "sch 4358" or sch4358).ti,ab,kw,kf,rn.	103971	106465
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw,kf,rn.	16827	17703
8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	291274	305184
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathioprim or azathioprin*2 or azathioprim or azathiopurine or azthropsin or aziatioprina or aztox or azatrillem or azopi or azoran or azothioprin or azothioprine or colisan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	722917	760743

10	orbital radiotherapy.ti,ab,kw,kf,rn.	259	273
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halprya or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw,kf,rn.	30653	32946
12	(tocilizumab or actemra or atlizumab or "bat 1806" or bat1806 or lusinec or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw,kf,rn.	121	132
13	(teprotumumab or "hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza).ti,ab,kw,kf,rn.	231	294
14	(batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	14	23
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw,kf,rn.	0	1
16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw,kf,rn.	0	1
17	(VB-421 or "VB 421" or VB421).ti,ab,kw,kf,rn.	0	0
18	(afibercept or "abp 938" or abp938 or "alt 19" or alt19 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or "bay 865321" or bay865321 or "chs 2020" or chs2020 or eylea or "fyb 203" or fyb203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw,kf,rn.	3563	3914
19	(secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw,kf,rn.	2292	2613
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapammune or rapamune or rapmycin or "sila 9268a" or sila9268a or tarzifyx or "tavl 18" or tav18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw,kf,rn.	26058	27072
21	rapamycin.ti,ab,kw,kf,rn.	36368	38758
22	exp betamethasone/ or (betamethason* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsoport or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or methasone or "nsc 39470" or nsc39480 or ophthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw,kf,rn.	9808	10022
23	((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin*2).ti,ab,kw,kf,rn.	1594	1655
24	(vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw,kf,rn.	4	4
25	(linstinib or "osi 906" or soi906 or osi906aa).ti,ab,kw,kf,rn.	95	96
26	(bimotoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw,kf,rn.	113	124
27	exp decompression, surgical/ or ((orbital or ophthalm*) adj (operation or decompression or surgery or surgical procedure*).ti,ab,kw,kf,rn. or (decompression adj2 surgery).ti,ab,kw,kf, or (strabismus adj2 (operation or surgery)).ti,ab,kw,kf,kw.	41013	43066
28	((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw,kf,rn.	1147	1237
29	exp atorvastatin/ or (astator or ator or atorab or atorin or atorlip or atorvavidid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or Lipitor or liprimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw,kf,rn.	11484	12041
30	exp doxycycline/ or (adoxa or amernycin or aprilon or atrax or azudoxat or bactidox or bannodoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoin or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doinmycin or dosil or dotur or doxacinil or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxicycline or doxilil or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxycen or doxychel or doxycin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdixin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxine or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramicina or tenutan or tolexine or "tolexine ge" or toymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or vibramycin? or vibraveineuse or	20274	21478

	vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw,kf,rn.		
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw,kf,rn.	12194	12707
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or clytezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulio or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulinno or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw,kf,rn.	11225	12049
33	exp etanercept/ or (avent or benepali or brenzys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatocept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw,kf,rn.	10011	10261
34	("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw,kf,rn.	61	124
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw,kf,rn.	39412	41895
36	(K1-70 or K170 or "K1 70").ti,ab,kw,kf,rn.	56	58
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw,kf,rn.	3	3
38	or/4-37	1541542	1617495
39	3 and 38	2158	2323
40	exp Randomized Controlled Trial/ or exp Random Allocation/	684677	712603
41	exp Double-Blind Method/ or exp Single-Blind Method/	207036	213155
42	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	971769	1003805
43	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	80597	85607
44	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/	382555	396969
45	exp Multicenter Study/	334468	354135
46	exp Placebos/	39468	39920
47	exp Cross-Over Studies/	55166	57474
48	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	269848	280223
49	randomized controlled trial.pt.	594048	621250
50	controlled clinical trial.pt.	95326	95603
51	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1429768	1539727
52	(random* adj2 allocat*).tw.	43582	46794
53	blind*.ti,ab,kw.	347387	364856
54	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1020846	1077294
55	prospective studies/	660232	696798
56	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	488963	511694
57	trial.ti.	286466	313030
58	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	161139	171257
59	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	54412	58271
60	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	272860	285219
61	(single arm or single group).ti,ab,hw,kf.	17633	20539
62	(basket adj2 trial*).ti,ab,hw,kf.	333	401
63	observational study/	142501	161150
64	observational studies as topic/	8796	10014
65	clinical studies as topic/	784	843
66	controlled before-after studies/	726	762
67	cross-sectional studies/	468316	514176
68	historically controlled study/	227	236
69	interrupted time series analysis/	1836	2188
70	cohort studies/	328960	346634
71	longitudinal studies/	165247	175376
72	prospective studies/	660232	696798
73	retrospective studies/	1122105	1228484
74	follow-up studies/	691749	702570
75	case-control studies/	328064	338410
76	single-case studies as topic/	98	117

77	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	218886	247913
78	cohort*.ti,ab,kf.	853579	956446
79	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	531194	569792
80	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	169119	180641
81	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	344855	374040
82	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	677467	755361
83	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	158941	169315
84	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	637	637
85	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	232451	251127
86	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	108835	121934
87	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	4934	5409
88	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	433820	491372
89	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3276	3725
90	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	20250	22918
91	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	1699	1824
92	((uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic* or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab,kf.	110299	115542
93	or/40-92	6854374	7303328
94	39 and 93	1098	1194
95	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	5046791	5270808
96	case reports/	2339517	2428574
97	(animal* not human*).sh,hw.	5083987	5212432
98	95 or 96 or 97	9992502	1034061 5
99	94 not 98	1005	1095
100	limit 99 to english language	906	995
101	100 and 2023:2024.(sa_year).		131

Search Strategy in EMBASE:

#	Search terms	Hits 9/6/23	Hits 11/9/24
1	endocrine ophthalmopathy/	6746	7442
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyroid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6608	7204
3	or/1-2	8570	9314
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	985607	1051831
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitison or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or Meticortone or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or ertilone or winpred).ti,ab,kw,kf,rn.	204564	217525
6	exp meprednisone/ or (prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or delta cortene beta or "deltisone b" or "deltisona b" or "sch 4358" or sch4358).ti,ab,kw,kf,rn.	346825	369148
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw,kf,rn.	88042	97075

8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulmini* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	514430	539990
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprime or azarex or azasan or azathiodura or e or azathioprim or azathioprin*2 or azathioprim or azathiopurine or azthropsin or azatioprina or aztox or azatrimem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazepine or thioprine or transimmune or zytrim).ti,ab,kw,kf,rn.	954582	1011603
10	orbital radiotherapy.ti,ab,kw,kf,rn.	326	343
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halprya or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw,kf,rn.	110983	122540
12	exp tocilizumab/ or (tocilizumab or actemra or atlizumab or "bat 1806" or bat1806 or lulinex or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw,kf,rn.	26787	30708
13	exp teprotumumab/ or ("hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza or teprotumumab).ti,ab,kw,kf,rn.	390	563
14	exp batoclimab/ or (batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	51	82
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw,kf,rn.	9	19
16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw,kf,rn.	3	5
17	(VB-421 or "VB 421" or VB421).ti,ab,kw,kf,rn.	1	1
18	exp aflibercept/ or (aflibercept or "abp 938" or abp938 or "alt 19" or alt19 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or "bay 865321" or bay865321 or "chs 2020" or chs2020 or eylea or "fyb 203" or fyb203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw,kf,rn.	9466	10577
19	exp secukinumab/ or (secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw,kf,rn.	7665	8936
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapamune or rapamune or rapamycin or "sila 9268a" or sila9268a or tarzifxy or "tavt 18" or tav18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw,kf,rn.	22605	26625
21	rapamycin.ti,ab,kw,kf,rn.	80257	82521
22	exp betamethasone/ or (betamethason* or adbeon or becasone or begrogeol or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsoport or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or methasone or "nsc 39470" or nsc39480 or ophthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw,kf,rn.	26827	28492
23	exp thymocyte antibody/ or (((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin* 2).ti,ab,kw,kf,rn.	35378	37880
24	exp vunakizumab/ or (vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw,kf,rn.	13	21
25	exp linstinib/ or (linstinib or "osi 906" or soi906 or soi906aa).ti,ab,kw,kf,rn.	198	199
26	exp bimatoprost/ or (bimatoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw,kf,rn.	236	263
27	exp strabismus surgery/ or exp decompression surgery/ or ((orbital or ophthalm*) adj (operation or decompression or surgery or surgical procedure*).ti,ab,kw,kf,rn. or (decompression adj2 surgery).ti,ab,kw,kf. or (strabismus adj2 (operation or surgery)).ti,ab,kw,kf,kw.	71451	76516
28	exp eyelid reconstruction/ or ((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw,kf,rn.	7050	7550
29	exp atorvastatin/ or (astator or ator or atorab or atoris or atorlip or atoravidid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or	46449	50209

	lipibec or Lipitor or lipimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw,kf,rn.		
30	exp doxycycline/ or (adoxa or amermycin or aprilon or atrax or azudoxat or bactidox or bannodoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoine or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doinmycin or dosil or dotur or doxacin or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxycycline or doxilil or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxycein or doxychel or doxydin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdoxin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxyne or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramycina or tenutan or tolexine or "tolexine ge" or torymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or vibramycin? or vibraveineuse or vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw,kf,rn.	69562	75718
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw,kf,rn.	62491	67154
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or cyltezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fzyoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulo or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulinno or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw,kf,rn.	46346	50943
33	exp etanercept/ or (avent or benepali or breznys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatoccept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw,kf,rn.	38801	41001
34	exp efgartigimod alfa/ or ("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw,kf,rn.	210	392
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw,kf,rn.	57492	61515
36	(K1-70 or K170 or "K1 70").ti,ab,kw,kf,rn.	93	93
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw,kf,rn.	5	5
38	or/4-37	2708193	2877450
39	3 and 38	3873	4286
40	exp Randomized Controlled Trial/ or exp randomization/	863387	919377
41	exp double blind procedure/ or exp single blind procedure/	260797	277425
42	exp clinical trial/ or exp controlled clinical trial/ or exp phase 4 clinical trial/ or exp phase 3 clinical trial/ or exp phase 2 clinical trial/	1853138	1944266
43	exp Multicenter Study/	379620	403824
44	exp placebo/	404089	417806
45	exp crossover procedure/	75413	79612
46	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	367143	386860
47	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	444247	474463
48	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1992722	2138090
49	(random* adj2 allocat*).tw.	54908	58759
50	blind*.ti,ab,kw.	507495	532902
51	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1391997	1468953
52	prospective study/	881169	940179
53	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	597027	624603
54	trial.ti.	404727	436876
55	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	352423	383212
56	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	70625	75665
57	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	396865	419749

58	(single arm or single group).ti,ab,hw,kf.	34127	39570
59	(basket adj2 trial*).ti,ab,hw,kf.	779	946
60	observational study/	330758	391926
61	cross-sectional study/	566950	663871
62	cohort analysis/	1044558	1217876
63	longitudinal study/	194518	221126
64	prospective study/	881169	940179
65	retrospective study/	1477439	1682159
66	follow up/	2059198	2245376
67	exp case control study/	225297	242148
68	quasi experimental study/	11384	12996
69	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	351214	394279
70	cohort*.ti,ab,kf.	1483946	1639633
71	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	818794	880254
72	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	271946	291220
73	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	497776	537546
74	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	1157058	1280173
75	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	215400	227887
76	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	705	713
77	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	355347	385180
78	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	166883	187892
79	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5853	6373
80	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	578884	652194
81	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3627	4072
82	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	25466	28623
83	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2377	2543
84	((uncontrolled or non randomi#ed or nonrandomi#ed or pragmatic) adj1 (study or studies)).ti,ab,kf.	16848	18414
85	or/40-84	9849375	10625410
86	39 and 85	1824	2062
87	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3759866	3950416
88	case report/	2911202	3039993
89	(animal* not human*).sh,hw.	4852079	5009319
90	87 or 88 or 89	11091863	11548916
91	86 not 90	1517	1711
92	limit 91 to english language	1391	1578
93	92 and 2023:2024.(sa_year).	-	236

Search Strategy in Cochrane Central Register of Controlled Trials:

#	Search terms	Hits 9/6/23	Hits 11/9/24
1	graves ophthalmopathy/	144	199
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyrioid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyrioid associated eye disease*2 or thyroid eye disease*2 or Dysthyrioid Ophthalmopath*3).mp.	417	502
3	or/1-2	417	502
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glyocorticoid* or glyocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw.	45001	
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitison or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab,kw.	10093	

6	(prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or detla cortene beta or "deltisone b" or "deltisone b" or "sch 4358" or sch4358).ti,ab,kw.	14102	
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw.	4383	
8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclosporin* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulmini* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw.	29480	
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azaahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprime or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrimem or azopi or azoran or azothioprin or azothioprime or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprime or thioazepine or thioprime or transimune or zytrim).ti,ab,kw.	44893	
10	orbital radiotherapy.ti,ab,kw.	26	
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halprya or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw.	5689	
12	(tocilizumab or actemra or atlizumab or "bat 1806" or bat1806 or lusinec or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw.	185	
13	(teprotumumab or "hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza).ti,ab,kw.	44	
14	(batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw.	25	
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw.	5	
16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw.	0	
17	(VB-421 or "VB 421" or VB421).ti,ab,kw.	1	
18	(afibercept or "abp 938" or abp938 or "alt 19" or alt19 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or bay 865321 or bay865321 or "chs 2020" or chs2020 or eylea or "fyt 203" or fyt203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw.	1133	
19	(secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw.	1124	
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapammune or rapamune or rapmycin or "sila 9268a" or sila9268a or tarzifxy or "tamt 18" or tamt18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw.	4637	
21	rapamycin.ti,ab,kw.	1389	
22	exp betamethasone/ or (betamethason* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsopart or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or methasone or "nsc 39470" or nsc39480 or ophthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw.	2997	
23	((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin*2).ti,ab,kw.	594	
24	(vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw.	12	
25	(linstinib or "osi 906" or soi906 or soi906aa).ti,ab,kw.	19	
26	(bimotoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw.	75	
27	exp decompression, surgical/ or ((orbital or ophthalm*) adj (operation or decompression or surgery or surgical procedure*)).ti,ab,kw. or (decompression adj2 surgery).ti,ab,kw,kf. or (strabismus adj2 (operation or surgery)).ti,ab,kw,kf,kw.	2653	
28	((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw.	102	
29	exp atorvastatin/ or (astator or ator or atorab or atoris or atorlip or atorvavidid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or Lipitor or	5610	

	liprimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tabor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw.		
30	exp doxycycline/ or (adoxa or amernmycin or apprilon or atrax or azudoxat or bactidox or bannodoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoïn or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doïnmycin or dosil or dotur or doxacinlin or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxicycline or doxilil or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxyen or doxychel or doxylin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdoxin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxyne or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramycina or tenutan or tolexine or "tolexine ge" or torymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or vibramycin? or vibraveineuse or vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw.	2340	
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw.	1206	
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or cyltezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulio or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulino or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw.	3751	
33	exp etanercept/ or (avent or benepali or brenzys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatocept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw.	2354	
34	("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw.	98	
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw.	2277	
36	(K1-70 or K170 or "K1 70").ti,ab,kw.	1	
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw.	0	
38	or/4-37	14911 8	
39	3 and 38	277	
40	animals/ not (humans/ and animals/)	2672	3663
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	9926	1573
42	40 or 41	12595	5236
43	39 not 42	274	502
44	limit 43 to english language	258	
45	#43 with Publication Year from 2023 to 2024	-	15

Search Strategy in Cochrane Database of Systematic Reviews:

#	Search terms	Hits 9/6/ 23	Hits 11/9 /24
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyroid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	11	6

Search Strategy in DARE:

#	Search terms	Hits 9/6/ 23	Hits 11/9 /24
Search DARE: Any field	(Graves ophthalmopathy or graves orbitopathy* or thyroid-associated ophthalmopathy* or thyroid associated ophthalmopathy* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopathy*)	7	-

A.2 Appendix G (Section G.1.1.2) states that CDSR, CENTRAL and DARE were searched for the cost-effectiveness/HCRU SLR, but these search strategies have not been provided.

a) Please confirm whether these resources were searched, and if so please provide the full search strategies for both the original and update searches.

For the economic/HCRU SLR (detailed in Appendix G), MEDLINE, Embase, EcoLit, NHS EED, and HTA databases searches were conducted for the original SLR (May 22nd 2023) and updated SLR (October 3rd 2024). Detailed search strategies for each of these are detailed in Appendix G of the submission documents.

A.3 Appendix H states that searches were run on 9.6.23 and updated on 3.10.24 for the HRQoL SLR. Only the original search strategies appear to have been provided in this submission (Tables 39-46).

a) Please provide the full search strategies for all update searches conducted.

For the HRQoL/Utilities SLR (detailed in Appendix H), MEDLINE, Embase, Cochrane, EconLit, DARE, NHS EED, and HTA database searches were conducted for the original SLR (June 9th 2023) and the updated SLR (October 3rd 2024). Detailed search strategies for the updated SLR are given in the below tables.

Search Strategy in MEDLINE (updated search):

#	Search terms	Hits
1	graves ophthalmopathy/	3,381
2	(Graves ophthalmopathy*3 or graves orbitopathy*3 or thyroid-associated ophthalmopathy*3 or thryoid associated ophthalmopathy*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopathy*3).mp.	6,127
3	or/1-2	6,127
4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	1,460,716
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	85,813
6	(quality adj4 life).ti,ab.	429,584
7	(quality adj2 well?being).ti,ab,kw,kf.	594

8	Quality-Adjusted Life Years/	16,903
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	25,541
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	22,658
11	Patient Reported Outcome Measures/	16,319
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	51,242
13	PRO.ti,ab,kw,kf.	273,708
14	exp health surveys/	639,260
15	exp health status/ or health status indicators/	511,770
16	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).ti,ab,kw,kf.	19,146
17	(utilit* or disutilit*).ti,ab,kw,kf.	295,754
18	disability adjusted life.ti,ab,kw,kf.	6,535
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	8,119
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	5,443
21	sg.ti,ab,kw.	15,117
22	willingness to pay.ti,ab,kw,kf.	9,830
23	(TTO or WTP or DCE).ti,ab,kw,kf.	13,354
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	47,701
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	735,036
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	108,405
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	68,946
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	652
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	42
30	(15D or 15-D or 15 dimension).ti,ab,kw.	6,423
31	(euro qol or eq 5d or euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw.	18,930
32	health utilit*.ti,ab,kw.	3,040
33	(HSUV or HSUVs).ti,ab,kw.	118
34	(hui or hui1 or hui2 or hui3).tw.	2,120
35	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or GO quality of life scale or GLS).ti,ab.	5,248
36	or/4-35	3,042,922
37	3 and 36	984
38	case reports/	2,437,267
39	animals/ not (humans/ and animals/)	5,229,551
40	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	707,935
41	or/38-40	8,321,587
42	37 not 41	940
43	limit 42 to english language	882
44	limit 43 to yr="2023 -Current"	146

Search Strategy in Embase (updated search):

#	Search terms	Hits
1	endocrine ophthalmopathy/	7,483
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyroid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	7,238
3	or/1-2	9,358
4	exp "Quality of Life"/ or exp questionnaire/ or exp "quality of life assessment"/	1,637,518
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	151,567
6	(quality adj4 life).ti,ab.	669,935
7	(quality adj2 well?being).ti,ab,kw,kf.	939
8	quality adjusted life year/	38,488
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	36,923
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	38,113
11	patient-reported outcome/	66,254
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	79,823
13	PRO.ti,ab,kw,kf.	413,486
14	exp health survey/	291,868
15	exp health status/ or health status indicator/	346,628
16	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).ti,ab,kw,kf.	34,285
17	(utilit* or disutilit*).ti,ab,kw,kf.	412,060
18	disability adjusted life.ti,ab,kw,kf.	7,838
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	10,268
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	7,778
21	Standard Gamble/ or sg.ti,ab,kw.	22,807
22	willingness to pay.ti,ab,kw,kf.	14,635
23	(TTO or WTP or DCE).ti,ab,kw,kf.	20,148
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	73,118
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	948,265
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	162,996
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	103,348
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	1,074
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	73
30	(15D or 15-D or 15 dimension).ti,ab,kw.	8,057
31	european quality of life 5 dimensions questionnaire/	10,798
32	(euro qol or eq 5d or euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw.	33,887
33	health utilit*.ti,ab,kw.	5,006
34	(HSUV or HSUVs).ti,ab,kw.	228

35	(hui or hui1 or hui2 or hui3).tw.	3,422
36	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or GO quality of life scale or GLS).ti,ab.	12,181
37	or/4-36	3,935,474
38	3 and 37	1,380
39	case report/	3,047,580
40	animal/ not (human/ and animal/)	1,231,031
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	2,270,875
42	or/39-41	6,404,785
43	38 not 42	1,263
44	limit 43 to english language	1,176
45	limit 44 to yr="2023 -Current"	202

Search Strategy in Cochrane CENTRAL (updated search):

#	Search terms	Hits
#1	MeSH descriptor: [Graves Ophthalmopathy] explode all trees	199
#2	((("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thyroid associated" NEXT ophthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	502
#3	#1 OR #2	502
#4	[mh animals] NOT ([mh humans] AND [mh animals])	3663
#5	(note or case report or editorial or short or short survey or survey or book or chapter):pt	1573
#6	#4 OR #5	5236
#7	#3 NOT #6	502
#8	#3 NOT #6 with Publication Year from 2023 to 2024, in Trials	82

Search Strategy in CDSR (updated search):

#	Search terms	Hits
1	((("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thyroid associated" NEXT ophthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	6
2	Limited to last 2 years	0

Search Strategy in EconLit (updated search):

#	Search terms	Hits
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thyroid associated ophthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Search Strategy in DARE (updated search):

#	Search terms	Hits

Search DARE: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thyroid associated ophthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	17
2023-2024		0

Search Strategy in NHS EED (updated search):

#	Search terms	Hits
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thyroid associated ophthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Search Strategy in HTAs (updated search):

#	Search terms	Hits
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2
2	2023-2024	0

Decision problem

A4. Priority question. The company submission (CS) lacks a formal comparison with any comparator except methylprednisolone, with or without mycophenolate on the basis that: *“The other comparators (azathioprine, ciclosporin, orbital radiotherapy) are used less frequently at second and later lines, and the evidence base for their use is lacking...”* (Table 1, CS). Instead the company provide a brief summary of some evidence to support the claim that: *“the outcomes observed in the clinical studies and in the MAIC versus IVMP and IVMP [intravenous methylprednisolone] + MMF [mycophenolate mofetil] are generalisable to other comparators at second line...”* (p. 125)

- a) Please provide a list of all treatments currently used in the population in the decision problem (DP) i.e. people living with active moderate to severe thyroid eye disease, with percentage use.

As stated in Document B of the Company’s submission, there are currently no pharmacological treatments specifically approved for TED in the UK. Based on extensive conversations with clinicians treating TED across UK centres, our understanding of the treatments used in the population with active moderate to severe TED is outlined below and summarised in Table 1. We have also added

estimates for the percentage use for each treatment by line of therapy, given different treatments may be used at first line compared with second line.

IVMP with or without MMF is used in approximately 95% of the first-line population. Other treatments are usually used if there is a clinical contraindication to high dose steroids (IVMP). As such, the remaining 5% of patients will get a mix of radiotherapy, azathioprine, ciclosporin, rituximab or tocilizumab, potentially in combination with oral steroids depending on the clinical profile and perceived risk of steroids for the individual patient. The choice of treatment will vary by centre.

Clinical practice at second-line also varies depending on the treatment centre, with some centres continuing with IVMP with or without MMF, and other centres adding treatments such as azathioprine, ciclosporin or radiotherapy to oral or IV steroids. Radiotherapy and azathioprine seem to be more commonly used than ciclosporin. The EUGOGO guidelines do not recommend MMF in combination with IVMP at second-line,¹ however conversations with UK clinicians indicate that MMF is commonly used at second line in NHS practice. Steroids, either IV or oral, are used alone or in combination in almost all patients, regardless of line of therapy.

Although it is listed as a comparator in the NICE scope, the EUGOGO guidelines state that triamcinolone should only be used if people are contraindicated to systemic glucocorticoids because it has a significant risk of adverse events (for example intraocular pressure elevation, increased orbital lipomatosis, or retrobulbar haemorrhage).¹ Advice from UK clinicians is that triamcinolone is only rarely used in NHS practice, and they prefer to use oral steroids over triamcinolone if people are contraindicated to IV steroids. As such, we have not suggested it as a relevant comparator for this appraisal.

Rituximab and tocilizumab are only available via individual funding requests, which as per our discussions with UK clinicians, are rarely approved or implemented in clinical practice, owing to the time taken to process such requests.

As such, it is thought they are used in <1% of patients at first- or second-line. Given they are not nationally available, we have not suggested them as relevant comparators in its submission.

Table 1: Interventions used to treat active moderate to severe TED in UK clinical practice

Intervention	Percentage use 1L	Percentage use 2L	Company comment
Intravenous methylprednisolone (IVMP)	██████	██████	IVMP with or without MMF is mainstay treatment for active moderate to severe TED. It is used in almost all patients at 1 st line, and in a large proportion of patients who require a second line treatment.
IVMP with mycophenolate mofetil (MMF)	██████	██████	
Orbital radiotherapy (with oral or IV steroids)	██████	██████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Ciclosporin (with oral or IV steroids)	██████	██████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Azathioprine (with oral or IV steroids)	██████	██████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Oral steroids alone	██████	██████	Usually only used if people are unable to have IV steroids.
Rituximab	██████	██████	Not available nationally (only via individual funding request) and rarely used. As such we have not proposed rituximab or tocilizumab as comparators for this appraisal.
Tocilizumab	██████	██████	
Triamcinolone	██████	██████	Not routinely used in UK clinical practice. As such, we have not proposed triamcinolone as a comparator for this appraisal.

b) Please provide a full systematic review of all clinical effectiveness evidence for all relevant comparators, regardless of frequency of use in the population eligible for teprotumumab.

The company has already provided a full systematic review of all clinical effectiveness evidence for all interventions of interest for the treatment of thyroid eye disease (TED) in its original submission (see B.2.1 and Appendix D). In the clarification call on 10 February 2025, the EAG confirmed that for this question, they are not asking us to revisit the existing systematic literature review but would instead like us to discuss the evidence around the comparators in more detail.

The systematic review was broader in scope than the present decision problem (for example, the included population was not limited by disease activity, phase or severity), and includes all potentially relevant comparators for teprotumumab as a treatment for active, moderate-to-severe TED, including unlicensed interventions used off-label and investigational compounds. The full list of interventions included in the systematic review is presented in CS, Document B, Table 7.

The company's understanding of the interventions used to treat active moderate-severe TED in the UK is presented in our response to Question A4A. As stated previously, IVMP with or without MMF is the main first-line treatment option and, usually in higher doses, is also considered the main option for those patients needing a second treatment. Lesser-used interventions at 2L include ciclosporin, radiotherapy and azathioprine (all usually in combination with IV or oral steroids) but we understand their usage in the UK to be much lower than IVMP +/- MMF. Advice received from UK clinicians has confirmed that rituximab, tocilizumab and triamcinolone are rarely used in UK practice, and as such, will not be discussed here.

The evidence base for all of these interventions is somewhat limited due to the fact that none are licensed specifically to treat TED. As the clinical SLR shows, the majority of the published evidence base for the population of interest is for IVMP +/- MMF. As a result, the matching-adjusted indirect comparison, cost-effectiveness model and budget impact analysis are all based on IVMP +/- MMF as the primary comparator where the evidence base, albeit limited, is sufficient to support those analyses.

The evidence base for the other interventions is much more limited, and it is unclear whether or not they are efficacious in active, moderate to severe TED. The key evidence identified is summarised below:

Radiotherapy and Azathioprine

The CIRTED study (Rajendram et al., 2018) investigated the efficacy of radiotherapy and azathioprine in patients who had received a 24-week course of oral prednisolone.² CIRTED was a multicentre, double-blind, randomised controlled trial conducted at six centres in the UK in 126 adult patients with active, moderate-to-severe TED and, according to clinical advice received, is considered the best available evidence for radiotherapy and azathioprine.

Patients all received a 24-week course of oral prednisolone (80 mg per day, reduced to 20 mg per day by 6 weeks, 10 mg per day by 15 weeks, and 5 mg per day by 21 weeks) and were randomly assigned via remote computerised randomisation to receive either radiotherapy or sham radiotherapy and azathioprine or placebo in a 2 × 2 factorial design. The primary outcomes were a binary composite clinical outcome score and an ophthalmopathy index at 48 weeks, and a clinical activity score at 12 weeks.

The adjusted odds ratio (OR_{adj}) for improvement in the binary clinical composite outcome measure was 2.56 (95% CI 0.98–6.66, p=0.054) for azathioprine and 0.89 (0.36–2.23, p=0.80) for radiotherapy. The ophthalmopathy index, clinical activity score, and numbers of adverse events (161 with azathioprine and 156 with radiotherapy) did not differ between treatment groups.

In the longer-term follow-up of a subset of 68 of the 126 patients from the original CIRTED trial (Taylor et al, 2023),³ 3-year outcomes remained suboptimal with ongoing poor quality of life and high numbers of patients requiring surgery. No additional benefit was seen at 3 years for patients randomized to azathioprine or radiotherapy with regard to a binary clinical composite outcome measure (BCCOM), modified European Group on Graves' Orbitopathy score, or Ophthalmopathy Index. Clinical Activity Score (CAS), Ophthalmopathy Index, and Total Eye Score improved over 3 years (P < .001). However, quality of life at 3 years remained poor. Of 64

individuals with available surgical outcome data, 24 of 64 (37.5%) required surgical intervention.

Radiotherapy

The SLR identified three other studies that evaluated radiotherapy outcomes.

Nicosia et al. evaluated the long term efficacy and toxicity of orbital radiotherapy plus concomitant systemic steroids in a population of 40 patients with moderate-to-severe TED not responsive or resistant to high dose systemic steroids or with severe diplopia.⁴

The authors reported overall improvement of TED symptoms, in particular, a regression at 1-year of diplopia in 32.5% eye movement impairment in 42.5%, eyesight in 27.5% and a 2-point reduction in CAS. After a median time of 56 months 21.9% of the patients underwent orbital decompression for relapse of GO, 4.8% received surgical correction of strabismus, and 2.4% received eyelid lipectomy. The authors concluded that orbital radiotherapy was associated with long-term efficacy and was well tolerated.

However, the study has a number of limitations and the results should be treated with caution. Firstly, it was a retrospective study. Secondly, it was non-comparative with the absence of a control group. Thirdly, data regarding serum anti-TSH receptor autoantibodies and both the dose and duration of pre-radiotherapy high-dose steroids were not available.

Wu et al. (2015) evaluated the effect of radiotherapy on moderate and severe TED in a prospective, double blind,⁵ self-controlled study in a single hospital outpatient ophthalmology clinic in China. For each patient, one eye was chosen at random to receive radiotherapy (the experimental eye). The other eye received pseudo radiotherapy (the control eye). Only the operator of the radiotherapy knew which eye was the experimental eye and which was the control eye. Patients and ophthalmologists were blinded to this fact.

Outcomes were assessed using various objective and quantitative indexes including T2 signal intensity ratios of orbital MRI inferior rectus and ipsilateral temporal muscle (T2SIR), extraocular muscles (EOM) volume, and the degree of exophthalmos. There were significant improvements in T2SIR, EOM volume, and degree of exophthalmos in the experimental eyes compared with the control eyes. The authors concluded that radiotherapy was an effective treatment for active, moderate-to-severe TED. However, the absence of an objective control group and the single site nature of this study are all major limitations.

Stoyonova et al. (2023) assessed changes in the therapeutic response,⁶ ocular manifestations of TED and quality of life of 26 patients during the first year following orbital radiotherapy. At baseline, all patients underwent comprehensive ocular examination and thyroid hormone and antibody testing. Radiotherapy was then performed with a total dose of 20 Gy, divided into 10 sessions of 2 Gy each with concomitant oral intake of low-dose glucocorticoids. Therapeutic response and individual ocular manifestations were evaluated 1, 3, 6 and 12 months after radiotherapy, and quality of life (QoL) at 3, 6 and 12 months by a disease-specific questionnaire. One month after radiotherapy, 61.6% of patients had a therapeutic response of some kind (either full or partial). At 12 months, the proportion of full responders had reached 57.5%. All individual ocular manifestations improved significantly 1-3 months after radiotherapy. QoL related to visual functioning increased significantly at 6 months, whereas QoL related to appearance improved significantly at 12 months. The small sample size and lack of control group are major limitations of this study, and as such is it difficult to draw robust conclusions on the efficacy of radiotherapy in active moderate-to-severe TED.

Azathioprine

Apart from the CIRTED study and CIRTED follow-up studies described above, no other evidence for azathioprine was included in the SLR.

Ciclosporin

No studies for ciclosporin as a treatment for TED were identified in the SLR.

In conclusion, the majority of the evidence for possible interventions for TED relates to IVMP +/- MMF. The CIRTED study constitutes the main source of evidence for radiotherapy and azathioprine but shows limited or unclear efficacy. The other radiotherapy studies identified are less robust sources of evidence; all indicate a potential improvement but are associated with major limitations. The SLR did not identify any other studies for azathioprine or ciclosporin. Overall, the evidence base for these interventions is extremely limited and, where it exists, tends to be of poor quality.

c) Please perform indirect treatment comparisons (ITCs) and a cost effectiveness analysis (CEA) for all of these comparators.

As stated in the CS, Document B.1.3.3.4, IVMP (12 weeks) with or without MMF (24 weeks) is the main treatment prescribed in the UK for previously untreated patients with moderate-to-severe active TED. Other treatments are very rarely used in the UK as initial treatment and are usually used in a smaller number of patients as a second treatment. IVMP +/- MMF is therefore the main comparator for teprotumumab in UK clinical practice and is the key comparator relevant to this appraisal. For this reason, the company submission, including the ITC and CEA, is focused on the comparison of teprotumumab versus IVMP and IVMP+MMF.

While the company acknowledges that the EAG has requested a comparison with other treatments (orbital radiotherapy, ciclosporin, azathioprine), the company considers that it would be challenging to generate robust comparative effectiveness evidence against these comparators. Although a full ITC feasibility assessment and ITC is not feasible against these comparators within the timeframe of the EAG responses, the company has reviewed the clinical SLR extraction tables to initially assess if an ITC may be feasible between teprotumumab and orbital radiotherapy, ciclosporin, azathioprine at any line of therapy in patients with moderate-to-severe active TED.

The clinical SLR identified the CIRTED study,² which, as discussed in Question A4B, is the best evidence for radiotherapy and azathioprine according to clinical advice to the company. However, to conduct a robust ITC for this appraisal, proptosis and

diplopia outcomes are required to be reported. The CIRTED study does not report appropriate data in terms of diplopia response or change from baseline in proptosis, and instead reports outcomes in the form of a binary composite clinical outcome score,² meaning that CIRTED does not provide the necessary data for an ITC.

Aside from CIRTED, there were no studies in the SLR reporting relevant outcomes in the moderate-to-severe active TED for azathioprine, and no studies for ciclosporin.

The SLR did, however, report data for three additional studies reporting evidence for radiotherapy in moderate-to-severe active TED:

- Nicosia et al., 2019⁴
- Stoyanova et al., 2023⁶
- Wu et al., 2015⁵

As previously described, these studies are weaker sources of evidence for radiotherapy than CIRTED. CIRTED is a UK-based, randomised controlled trial with a large sample size (n=126). Each of the three studies are weaker sources of evidence due to their trial design, setting, and small sample size. Nicosia et al. is a single-arm study assessing the long-term efficacy of radiotherapy plus steroids in 40 patients in Italy.⁴ Wu et al. evaluated the effect of radiotherapy in 51 patients as part of a randomised, self-controlled trial set in China.⁵ Stoyanova et al. is a single-arm study assessing the response to radiotherapy in 26 moderate-to-severe active TED patients in Bulgaria.⁶

An assessment of these studies found that an ITC between teprotumumab and radiotherapy would be challenging and have high uncertainty. Wu *et al.* does not specify the timepoints when proptosis scores were collected, nor does it provide any data on diplopia,⁵ and therefore would not provide the necessary data for an ITC. Nicosia et al. includes patients other than those with moderate-to-severe active TED.⁴ Patients with sight threatening TED were included, with one patient receiving orbital decompression for severe optic nerve compression related to acute blindness.⁴ Furthermore, proptosis and diplopia measurements are reported in a three-to-six-month range post radiotherapy, further hindering the possibility of a

robust ITC due to the lack of a specific timepoint for the data collection.⁴ Finally, Stoyanova et al.⁶ was a single-arm design and had a small sample size, which would lead to uncertain comparative effectiveness estimates if an ITC were to be conducted. Given that orbital radiotherapy, azathioprine, and ciclosporin are much less widely used than IVMP (with or without MMF) in clinical practice, and there is a lack of robust clinical trial evidence supporting their use, an ITC would be challenging to perform, uncertain, and unlikely to be influential for NICE committee decision-making.

In the absence of a formal comparison, the company has conducted three scenario analyses to explore a simplified estimation of the cost-effectiveness of teprotumumab at second line for radiotherapy, ciclosporin, and azathioprine:

- Scenario one: Treatment and administration cost for radiotherapy applied in addition to the IVMP and IVMP + MMF costs.
- Scenario two: Treatment and administration cost for ciclosporin applied in addition to the IVMP and IVMP + MMF costs
- Scenario three: Treatment and administration cost for azathioprine applied in addition to the IVMP and IVMP + MMF costs

The switch to apply these scenarios is included on cell G61 on the 'settings' sheet.

In each scenario, only the treatment and administration costs were updated. Based on clinical advice to the company, in clinical practice, once a patient has progressed from initial treatment with IVMP+/-MMF, they would receive radiotherapy, azathioprine, or ciclosporin in combination with steroids (in most cases IV steroids). So, the treatment and administration costs for radiotherapy, ciclosporin, and azathioprine were applied in the scenarios in addition to the IVMP and IVMP + MMF costs.

Subsequent treatment was disabled for all three scenarios to avoid double counting, given that these scenarios represent second-line treatment. Efficacy was conservatively assumed to be the same as at first line (i.e. the same as the IVMP and IVMP + MMF). All other inputs, such as adverse events, were assumed to be the

same as IVMP and IVMP + MMF at first line, which is a conservative assumption since a combination therapy is likely to have more adverse events.

Results for each scenario are presented in Table 2 using the PAS price. In scenarios one and three, the ICERs increase slightly from the base case ICERs (1.9% and 2.6% increase for the combination with IVMP, and 2.1% and 2.7% increase for the combination with IVMP + MMF, respectively). The ICER for scenario two decreases from the base case (-0.3% for the combination with IVMP and -0.1% for the combination with IVMP + MMF, respectively). All changes are within 3% of the base case ICER, suggesting that the cost-effectiveness results at second line are similar to first line.

The slight increase in the ICER for scenarios one and three is due to the exclusion of subsequent treatment costs, which in the base case are primarily applied to patients in the four most severe health states and therefore impact comparators more than teprotumumab. The ICER decreases for scenario two as ciclosporin is more expensive than radiotherapy and azathioprine, so the ICER decrease from the additional treatment and administration cost is greater than the increase from the exclusion of subsequent treatment costs.

Table 2: Second line scenario analysis results (PAS price)

	Incremental costs (£)	Incremental QALYs (£)	ICER (£)
Scenario 1: IVMP +/- MMF in combination with radiotherapy			
IVMP and radiotherapy	██████	0.8	██████
IVMP + MMF and radiotherapy	██████	0.8	██████
Scenario 2: IVMP +/- MMF in combination with ciclosporin			
IVMP and ciclosporin	██████	0.8	██████
IVMP + MMF and ciclosporin	██████	0.8	██████
Scenario 3: IVMP +/- MMF in combination with azathioprine			
IVMP and azathioprine	██████	0.8	██████

IVMP + MMF and azathioprine	██████	0.8	██████

We consider that these scenarios give a valid and conservative simplified estimate of the comparative clinical and cost effectiveness of teprotumumab versus radiotherapy, ciclosporin, or azathioprine at second-line therapy. These scenarios are conservative because, while the treatment effect of teprotumumab is similar across first- and second-line (see response to Question A5), the treatment effect of radiotherapy, ciclosporin, or azathioprine in combination with steroids at second-line is likely to be lower than that for IVMP +/-MMF at first-line. This is because second-line patients have failed IVMP +/- MMF and so are a more treatment-resistant population and their efficacy would be expected to be lower than at first-line. This rationale is further expanded upon in our response to Question A5 below. In addition, the CIRTED trial¹ indicates no benefit of radiotherapy or azathioprine over steroids, stating “it is not unreasonable to assume that their efficacy is not likely to be any better than IVMP with or without MMF”. This conclusion has been validated with a UK clinician for the purpose of this clarification response.

A5. Priority question. In Section B.3.10.1 it is stated that “Given the clinical benefits of teprotumumab are expected to be similar in 2L vs 1L, whereas the other treatment options used at 2L are expected to show lower efficacy than IVMP and IVMP + MMF irrespective of line of therapy, teprotumumab may conservatively be expected to be no less cost-effective as a second or subsequent treatment vs treatments used at 2L as it is versus IVMP and IVMP + MMF in the untreated population.” The references provided do not appear to provide direct evidence to support the assertion. Please provide clinical evidence that teprotumumab is similarly effective in 2L and 1L and that it is more effective than alternative 2L therapies. Provide evidence that it is cost-effective as a 2L treatment.

The pivotal teprotumumab trials enrolled only patients with active, moderate-to-severe TED who had not received prior treatment, i.e. as a first treatment. However, as stated above and in the CS, there is no single treatment option or standard of care, for TED patients in need of a second treatment. TED is also a very heterogeneous

disease. Therefore, the company comments in Section B.3.10.1 are intended to reassure clinicians that teprotumumab is expected to be an effective treatment for active, moderate to severe TED, irrespective of line of therapy or the patient's prior treatment history.

Teprotumumab is already recommended as a second-line treatment in the EUGOGO guidelines (subject to licensing).¹

Published evidence

Men et. al. conducted a multicentre retrospective study of sixty-six US patients treated with teprotumumab for moderate-to-severe TED after failing therapy with corticosteroids, orbital radiation, surgical decompression, biologics or other steroid-sparing medications.⁷ Treatment failure was defined as an incomplete response to or reactivation after previous treatment. Only patients who received at least four infusions of teprotumumab were included in the analysis. The vast majority of patients (88%) had active disease.

Patients with treatment-resistant TED demonstrated a significant improvement after teprotumumab in each of the primary study outcomes. The proptosis, CAS, and diplopia responses in this recalcitrant patient population were 85.9%, 93.8%, and 69.1%, respectively. Patients experienced a mean reduction in proptosis of 3.1 ± 2.4 mm and mean improvement in CAS of 3.8 ± 1.6 . The degree of proptosis reduction, diplopia response, and CAS improvement in the recalcitrant group were similar to those of treatment naïve patients from the pivotal clinical trials. Patients with a prior history of orbital decompression, however, demonstrated poor improvement in diplopia and less reduction in proptosis than surgery-naïve patients.⁷ These results indicate that teprotumumab is an effective treatment option for patients with TED recalcitrant to prior medical therapies.

Toro-Tobon and colleagues conducted a retrospective case-control study evaluating the clinical outcomes and safety of teprotumumab and tocilizumab in patients with corticosteroid-resistant TED.⁸ Thirty-seven patients with active moderate to severe steroid-resistant TED treated with teprotumumab or tocilizumab (cases) were

compared with steroid-naïve patients treated with similar therapy (controls). Thirty-one patients received teprotumumab (13 cases and 18 controls) and 6 received tocilizumab (cases). At week 24, in the teprotumumab cases, 81% had proptosis response (reduction of ≥ 2 mm), 45.5% had resolution of diplopia, 85.7% had disease inactivation (CAS < 3), and 58.3% reverted to mild disease severity. There were comparable results in teprotumumab controls, with no significant differences between subgroups. In the tocilizumab cases, 50% had a proptosis response, 16.7% resolution of diplopia, 100% disease inactivation, and 75% returned to mild disease. The authors concluded that teprotumumab and tocilizumab improved inflammation in patients with moderate to severe TED who had failed previous steroid therapy. Additionally, the teprotumumab cases demonstrated similar improvement in proptosis and diplopia to the teprotumumab controls.⁸ The studies conducted by Toro Tobon et al. and Men et al. provide evidence to support the company's contention that teprotumumab is clinically effective irrespective of line of therapy in active moderate-to-severe TED.

A retrospective review by Ugradar et al. 2022 demonstrates the efficacy of teprotumumab in addressing proptosis in patients with previous exposure to glucocorticoids (intravenous and oral) and radiotherapy.⁹ 31 patients with chronic stable TED (> 2 years), who had received ≥ 3 infusions of teprotumumab were included in the analysis. The mean (SD) duration of TED was 81 months (56) and the mean (SD) number of infusions received by each patient was 7 (2). Mean (SD) reduction in proptosis for each study orbit was 3.5 mm (0.4) and 3 mm (0.3) for the fellow orbit. The CAS response was 90% for the study orbit and 87% for the fellow orbit. Of the 15 patients who had diplopia at baseline, 67% had a clinically significant response, while 47% had complete resolution following treatment. Following teprotumumab, mean (SD) reduction of muscle tissue was 2011 mm³ (1847) in the study orbit and 1620 mm³ (1759) in the fellow orbit. The mean (SD) reduction of fat volume was 2101 mm³ (1681) in the study orbit and 1370 mm³ (1181) in the fellow orbit.

The authors concluded that teprotumumab significantly reduces proptosis, inflammation, diplopia, strabismus and orbital soft tissue volume in patients with

chronic TED. Although in the chronic population so less relevant to the current decision problem, this study demonstrates the efficacy of teprotumumab in patients with previous exposure to glucocorticoids and radiotherapy.

Mechanism of action

Teprotumumab has a novel mechanism of action targeting the IGF-1R axis, which is considered to underpin some of the pathogenesis of TED.^{10, 11} This, in conjunction with published data demonstrating teprotumumab's efficacy in patients who are not steroid naïve, indicates that the efficacy of teprotumumab at second line would be similar to the efficacy observed in treatment-naïve patients.

Whilst the exact pathogenesis of TED is not fully understood, there is a strong body of pre-clinical and clinical data that implicates the TSHR/IGF1-R receptor complex.¹²⁻¹⁵ This receptor complex is expressed on orbital fibroblasts and its stimulation by autoantibodies is thought to result in pro-inflammatory cytokine release alongside the activation of cellular signalling pathways. This results in the expansion of extra-ocular muscle and fat tissue alongside the production of hyaluronan. In addition, studies have demonstrated the overexpression of IGF-1R on the immune cells (T and B lymphocytes) of TED patients.^{12, 16-22}

Analysis of orbital fat shows an increase in the proportion of fibroblasts contributing to adipogenesis (fat cell production) in TED patients compared to controls. This was also associated with significant alterations in immune cell composition. Furthermore, transcriptomic profiling of orbital fat has demonstrated significant alterations in the IGF-1R signalling pathway between TED patients and controls, while pharmacological inhibition of the IGF-1R receptor resulted in a reduction in adipogenesis in orbital fibroblasts from TED patients in vitro.²³

Teprotumumab inhibits the activation of the TSHR/IGF1-R receptor complex and as such, addresses a key aspect in the pathogenesis of TED. By targeting the IGF1-R, teprotumumab has demonstrated clinical efficacy in reducing inflammation (CAS score), proptosis and diplopia in TED patients.²⁴ Furthermore, imaging studies

further support the role of teprotumumab in reducing intraocular muscle and fat volumes.²⁵

Current treatments for active moderate-to-severe TED consist of steroids or other steroid-sparing agents which are untargeted and exert their effects via immunosuppressive and anti-inflammatory processes rather than targeting the underlying pathogenic mechanisms of TED.^{14, 26} As a result, outside of their anti-inflammatory effects, steroids are not considered to directly reduce extra-ocular muscle and fat volumes.^{14, 26} In keeping with this, there is a lack of evidence within the literature with regard to the effectiveness of steroids in treating features of TED that stem from the increase in orbital tissue volume such as proptosis.^{14, 26} In addition, given their untargeted mechanism of action, high dose steroids are associated with a range of off target side effects including weight gain, psychiatric morbidity, hyperglycaemia, hypertension and immunosuppression.²⁷

Given this, further exposure to therapies in the second line that exert their effects through similar untargeted mechanisms to those therapies used in the first line are unlikely to demonstrate superior efficacy. Indeed, efficacy would be expected to be lower given that these patients have already failed to respond to alternative prior therapies that have a similar overarching mechanism of action (untargeted immunosuppression and anti-inflammatory effects).

Conversely, given the novel and targeted mechanism of action of teprotumumab, it would be expected to have similar efficacy whether used in treatment naïve patients or those that had received prior untargeted immunosuppressive or anti-inflammatory therapies. This is because teprotumumab targets cellular pathways that are upstream and distinct from those effected by currently available TED treatments.^{10, 11, 28} This proposition is supported by clinical evidence of the efficacy of teprotumumab in patients who have failed to respond to previous lines of therapy, particularly with regard to proptosis response.^{7, 8, 29}

In conclusion, the available evidence and UK expert clinical opinion support the hypothesis that the efficacy of teprotumumab as a second-line treatment is expected

to be similar to that observed at first-line. Conversely, the efficacy of ciclosporin, radiotherapy and azathioprine is unclear, especially at second-line, and even when given in combination with steroids. It is highly unlikely that any of these treatments when used at second line would be more efficacious than IVMP +/- MMF used at first line. This conclusion was validated with a UK clinician for the purposes of this clarification response.

Therefore, assuming the treatment effects from the IVMP and IVMP + MMF ITCs can be generalised to other comparators used at second line is a conservative assumption, which the company is proposing given the lack of potential to do a formal ITC or economic analysis.

We have used the IVMP +/- MMF treatment effects and true comparator costs for radiotherapy, azathioprine and ciclosporin (in combination with IV steroids) in simplified scenario described in our response to A4c.

Systematic review

A6. Please confirm how quality appraisals were conducted. Specifically, please detail number of reviewers involved, whether this was conducted independently, and how any disagreements were resolved.

For the clinical SLR, risk of bias (RoB) assessment was carried out according to Version 2 of the Cochrane risk-of-bias tool for randomised trials. This is the most up-to-date version of the Cochrane risk-of-bias tool designed, validated for RCTs, and recommended by the Cochrane Handbook. RoB was carried out by one reviewer.

For the economic/HCRU and HRQoL/Utilities SLRs, quality appraisals were conducted by one reviewer and were checked for accuracy by an independent researcher. It was planned that any discrepancies between review decisions would be resolved by consensus and/or escalation to a third independent reviewer; however, no discrepancies occurred. Quality appraisal of included studies was conducted using validated checklist depending upon study design:

- HSUV or HRQoL were assessed using the NICE recommended tool for the quality assessment of individual HSUV studies
- Cost and HCRU were assessed using the Schnitzler checklist, a consensus-based tool developed to critically appraise cost-of-illness (COI) studies.

Economic evaluations were assessed using Drummond checklist, a widely used tool that evaluates economic evaluations based on criteria like study design, data collection, analysis, and interpretation.

A7. Please confirm the quality appraisal tool that was used in appraising the included studies. Please justify the use of this tool.

Please see the response to A6, which also includes the quality appraisal tools used for the SLRs.

Clinical effectiveness evidence

A8. Priority question. Please provide evidence to demonstrate the generalizability of the trial populations to the relevant clinical population in England and Wales:

a) Please provide any available baseline characteristics for UK based participants in the two pivotal studies (a phase 2 randomised controlled trial (RCT) [NCT01868997] and the phase 3 OPTIC RCT [NCT03298867].

No UK-based patients were enrolled in the Phase 3 OPTIC study. A total of [REDACTED] UK patients ([REDACTED] of all study subjects) were enrolled in the Phase 2 RCT (Table 3).

Table 3: UK study enrolment (ITT Analysis Set)

	Phase 2 study			Phase 3 OPTIC			Pooled analysis		
Total study enrolment	Placebo (N = 45) n (%)	TEPRO (N = 43) n (%)	Overall (N = 88) n (%)	Placebo (N = 42) n (%)	TEPRO (N = 41) n (%)	Overall (N = 83) n (%)	Placebo (N = 87) n (%)	TEPRO (N = 84) n (%)	Overall (N = 171) n (%)
United Kingdom	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The demographic and baseline characteristics for these UK-based patients are provided in the embedded file below.



b) Please provide data for the characteristics of the patients as would be treated in clinical practice in England and Wales.

The study subjects enrolled in the two pivotal trials are expected to be representative of the TED patients who would be treated with teprotumumab in clinical practice.

Firstly, all study subjects were adults, had received a diagnosis of Graves' disease and had active thyroid eye disease of moderate to severe severity at baseline; that is, they had a CAS equal to or greater than 4. Subjects who were not symptomatic, had a CAS lower than 4, or who had received previous medical or surgical treatment for thyroid eye disease were excluded (but previous treatment with <1g methylprednisolone was allowed with a 6-week washout). It is anticipated that these are the patient characteristics that would make an NHS patient suitable for treatment with teprotumumab.

Both studies enrolled adult patients from tertiary or otherwise specialist orbital clinics at 28 sites across the USA and Europe. A high proportion of Caucasian or Western subjects, and UK clinicians have advised the submitting company that the baseline characteristics, demographics and previous medical histories of the study subjects are broadly representative of the TED patients they would treat in clinical practice.

As was noted in the CS, teprotumumab has also been investigated in Asian TED patients in the OPTIC-J study. However, subjects in that study are not thought to be representative of patients who would be treated in the UK due to differences in subject ethnicity, the typical disease course in Asian patients and the treatment pathway in Asian countries. For these reasons, OPTIC-J was not included in either the pooled clinical or economic analysis.

In the clarification call, the generalisability of assumptions around the patient weight used in the model was also raised as an area for further clarification. The model

uses the average baseline weight from all patients in the pooled analysis (78.07 kg). The mean weight of the UK patients specifically from the pooled analysis was similar (77.65 kg). UK clinicians indicate that this is a reasonable estimate for the average weight of a TED patient in the NHS although some clinicians felt that their patient population has a lower average weight given that these patients are predominantly female and with recent onset hyperthyroidism, one of the key symptoms of which is weight loss.

Indirect treatment comparison (ITC)

A9. Priority question: The EAG cannot find the summary statistics for either the intervention or the comparator studies used in the matching-adjusted indirect comparison (MAIC) in either Document B or Appendix D.

- a) Please provide the mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm (IVMP; IVMP plus MMF) before matching. Given that several IVMP studies were used for the comparator arm please clarify how they were combined in order to estimate these statistics. Please provide the sample size for each arm. Please also provide standardised mean difference for the comparison of the intervention arm and the comparator arm before matching.**

To estimate pooled baseline characteristics from included IVMP studies, a weighted average of each baseline characteristic was calculated based on the sample sizes of the studies involved. The sum of weighted baseline characteristic values was divided by the total sample size. This was performed for all baseline characteristics. If a study did not report a specific characteristic, it was excluded from the weighted average calculation. Four of these baseline characteristics were identified as either prognostic factors or treatment effect modifiers for TED, meaning they were the covariates that the studies were matched when performing the MAIC.

In the base case, the studies were matched on four covariates: smokers (%), baseline diplopia rate (%), baseline proptosis (mm) and proportion of patients who have received radioiodine therapy (RIT) (%). As standard deviation (SD) does not provide useful information for binary covariates, we provide this for baseline proptosis only. The mean and SD for teprotumumab were obtained from individual

patient data (IPD). For IVMP studies the standard deviations from all included IVMP studies were pooled to obtain a single value, using the following formula:

$$S_{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2 + \dots + (n_k - 1)s_k^2}{n_1 + n_2 + \dots + n_k - k}}$$

n – sample size

k – total groups

s – standard deviation

As the comparator arm of IVMP + MMF included only one study, the SD was obtained from the study publication.

Table 4 below presents means and SD of covariates before matching for the studies included for the change from baseline proptosis outcome. The standardised mean difference for proptosis between teprotumumab and comparators is presented in Table 5.

Table 4: Covariates before matching for studies included for the proptosis outcome

	Intervention arm: teprotumumab (n=83)	Comparator arm: IVMP (n=282)	Comparator arm: IVMP + MMF (n=76)
Smoker (%)	24.10	30.51	53.00
Baseline diplopia (%)	79.52	51.48	66.00
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	20.74 (2.89)	21.09 (3.45)
RIT (%)	7.23	14.38	18.00

Abbreviations: IVMP – Intravenous methylprednisolone; MMF – Mycophenolate mofetil; mm – millimeters; n – number; RIT - received radioiodine therapy; SD – Standard deviation

Table 5: Standardised mean difference for the change from baseline in proptosis outcome for teprotumumab and comparators

Teprotumumab vs IVMP	0.76
Teprotumumab vs IVMP + MMF	0.58

Abbreviations: IVMP – Intravenous methylprednisolone; MMF – Mycophenolate mofetil

A different set of studies was included for the diplopia outcome, which resulted in a different mean and SD for the covariates. The values are presented in Table 6 below. The comparator IVMP+MMF was not analysed for this outcome due to lack of data.

Table 6: Covariates before matching for studies included for the diplopia outcome

	Intervention arm: teprotumumab (n=83)	Comparator arm: IVMP (n=101)
Smoker (%)	24.10	23.96
Baseline diplopia (%)	79.52	71.47
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	21.16 (2.76)
RIT (%)	7.23	17.59

Abbreviations: IVMP – Intravenous methylprednisolone; mm – millimeters; n – number; SD – Standard deviation

The standardised mean difference cannot be obtained for the diplopia outcome as the analysis compared the odds ratio of response.

b) Please provide mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm (IVMP; IVMP plus MMF) after matching. Please provide the effective sample size for each arm. Please also provide the standardised mean difference for the comparison of the intervention arm and the comparator arm after matching.

In the base case analysis for the proptosis outcome, studies were matched on four covariates (smokers, baseline diplopia, baseline proptosis, and RIT). Table 7 presents the effective sample size (ESS) and covariates after matching. For ease of comparison, the means before matching are also included in the table.

Table 7: Covariates after matching for studies included for the proptosis outcome (teprotumumab versus IVMP)

	Teprotumumab baseline characteristics		IVMP baseline characteristics
	Before MAIC	After MAIC – 4 covariate adjustment	
ESS	n = 83	n = 31.40	n = 282
Smoker (%)	24.10	30.51	30.51

Baseline diplopia (%)	79.52	51.48	51.48
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	20.74 (2.97)	20.74 (2.89)
RIT (%)	7.23	14.38	14.38

Abbreviations: IVMP – Intravenous methylprednisolone; MAIC – Matching adjusted indirect comparison; mm – millimeters; n – number; SD – Standard deviation

In the base case for teprotumumab vs IVMP+MMF, the studies were matched on three covariates (smokers, baseline diplopia, and baseline proptosis). The ESS and means for the covariates are presented in Table 8.

Table 8: Covariates after matching for studies included for the proptosis outcome (teprotumumab versus IVMP + MMF)

Covariate	Teprotumumab baseline characteristics		IVMP + MMF baseline characteristics
	Before MAIC	After MAIC – 3 covariate adjustment	
ESS	n = 83	n = 30.57	n = 76
Smoker (%)	24.10	53.00	53.00
Baseline diplopia (%)	79.52	66.00	66.00
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	21.09 (3.14)	21.09 (3.45)

Abbreviations: IVMP – Intravenous methylprednisolone; MAIC – Matching adjusted indirect comparison; MMF – Mycophenolate mofetil; mm – millimeters; n – number; SD – Standard deviation

The ESS and covariates for teprotumumab before and after matching, based on the IVMP diplopia response rate population are presented in Table 9.

Table 9: Covariates after matching for studies included for the diplopia outcome (teprotumumab versus IVMP)

Covariate	Teprotumumab baseline		IVMP baseline characteristics
	Before MAIC	After MAIC – 4 covariate adjustment	
ESS	n = 83	n = 49.48	n = 101
Smoker (%)	24.10	23.96	23.96
Baseline diplopia (%)	79.52	71.47	71.47
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	21.16 (3.01)	21.16 (2.76)
RIT (%)	7.23	17.59	17.59

Abbreviations: IVMP – Intravenous methylprednisolone; MAIC – Matching adjusted indirect comparison; mm – millimeters; n – number; SD – Standard deviation

The standardised mean difference cannot be obtained for the diplopia outcome as the analysis compared the odds ratio of response.

A10. Priority question: Please conduct a simulated treatment comparison (STC) as a sensitivity analysis on the basis that it is listed as a method of population adjustment alongside MAIC in NICE TSD 18.

Owing to the lack of a common comparator and wide use of this type of analysis in HTA submissions, an unanchored MAIC was conducted and submitted as part of this appraisal to compare the effectiveness of teprotumumab with IVMP and teprotumumab with IVMP + MMF in accordance with NICE Decision Support Unit Technical Support Document 18.³⁰

NICE do not express any general preference for population reweighting or outcome regression methods, with both MAIC and STC methods being suggested as options to consider for estimating comparative efficacy.³⁰ There is little evidence in the literature to suggest that one methodology is superior to the other and MAICs have been applied widely in health technology assessments before.³¹⁻³³ Given the timeframe and NICE not suggesting a preferred method, the company considers the MAIC analysis with a number of scenario analyses explored is sufficient in providing comparative effectiveness data relevant to the submission and therefore the company is not able to conduct a further STC during clarification response stage.

For the purposes of this clarification response, validation from a UK clinician was sought. The clinician agreed that the results of the MAIC are clinically plausible given the lack of robust evidence for IVMP+MMF compared to evidence from the OPTIC trial for teprotumumab.

A11. Priority question: Please provide details of the methods for the pooling of the outcomes of the intervention arm of the IVMP RCT studies.

As described in the Appendices to Document B Section D1.4.7, for both outcomes the treatment effects from IVMP studies were meta-analysed to obtain a pooled treatment effect.

The metafor package was used to perform the meta-analyses, using a model assuming that the estimated treatment effect is given by

$$y_i = \theta_i + e_i,$$

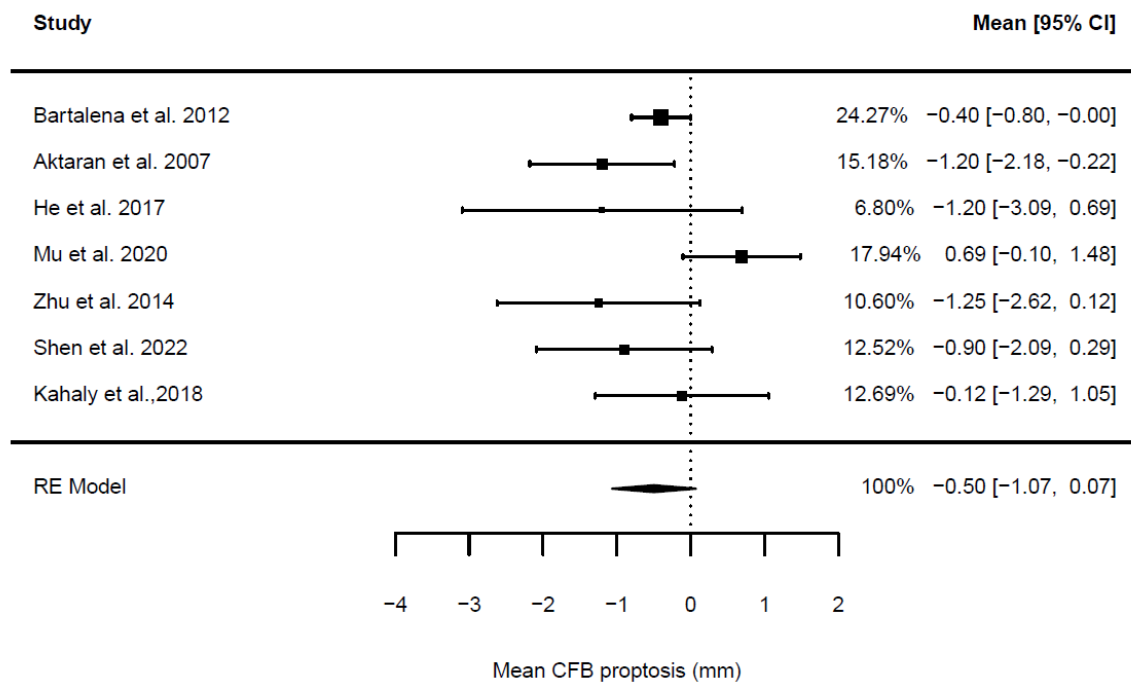
where y_i is the observed effect in the i -th study, θ_i is the unknown true effect, e_i is the sampling error, and $e_i \sim N(0, v_i)$ where v_i is the sample variance. The y_i are assumed to be unbiased, normally distributed estimates of their corresponding true effects. Due to the heterogeneity amongst studies being combined, the random-effects model was considered the most appropriate. In this model, θ_i is defined as follows

$$\theta_i = \mu + u_i,$$

where θ_i represents the observed values of the treatment effect for the individual, μ is the overall mean or the fixed effect, u_i is the term for the random effect (capturing the deviation of the individual from the overall mean).³⁴

In the base case analysis for the proptosis outcome, seven IVMP RCT studies were included. The pooled treatment effect is presented in Figure 1 below, demonstrating a mean change from baseline proptosis of -0.50 mm. The result was not statistically significant, as the CI crosses 0 (95% CI: [-1.07, 0.07]).

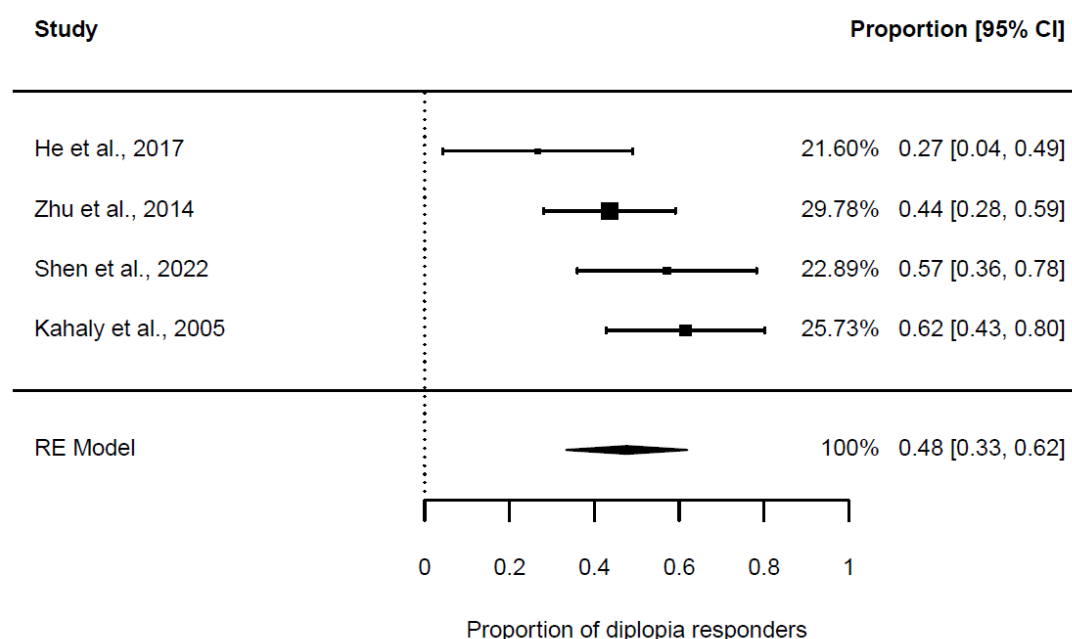
Figure 1: Forest plot for mean change from baseline proptosis outcome



Abbreviations: CFB – Change from baseline; CI – Confidence interval; mm – millimeter

In the base case analysis for the diplopia outcome, four IVMP RCT studies were included. The pooled proportion of diplopia responders is presented in Figure 2 below with a mean rate of 48%. There was minimal overlap between the included studies as demonstrated by the box and whisker plots in Figure 2 below. The pooled treatment effect was statistically significant (95% CI: [0.33, 0.62]).

Figure 2: Forest plot for diplopia response rate outcome



Abbreviations: CFB – Change from baseline; CI – Confidence interval; mm – millimeter

A12. In section B.2.9.1.1 it is stated that “Treatment effect modifiers and prognostic variables were identified both from a previous ITC comparing teprotumumab with IVMP (Douglas et al., 2022) and an Amgen clinical expert, and then were further validated with three external key opinion leaders.” Please clarify that the variables considered were restricted to those collected and reported in Douglas rather than based on clinical rationale. Please also discuss whether any approaches to causal design were used such as directed acyclic graphs?

Treatment effect modifiers and prognostic factors were identified from the ITC conducted by Douglas et al., 2022 and then reviewed and supplemented by Amgen’s medical expert.³⁵ The revised list was shared with 4 TED clinicians, who were asked to confirm and classify the potential covariates as prognostic factors or treatment effect modifiers (TEMs) and rank them by level of importance (very important,

somewhat important, not important). Covariates considered for inclusion are presented below:

- Smoking
- Diabetes
- Thyroid function
- Duration of TED symptoms
- Baseline proptosis
- Diplopia at baseline %
- Radioiodine therapy (RIT) of Grave's disease
- Age
- Gender
- TSH/TSI/TRAb levels
- High cholesterol levels

The most important prognostic factors/TEMs identified by clinicians were diplopia at baseline, smoking, baseline proptosis in mm, RIT in TED, thyroid function and diabetes. Covariate selection was based on the order of importance determined by clinical opinion and on the availability of data from the IVMP studies. Taking into consideration the availability of data, the final list of covariates that were adjusted for was as follows: smoking, baseline diplopia, baseline proptosis and RIT.

No approaches to causal design were used, however, propensity score matching and sandwich estimation was employed to address confounding and ensure reliable estimates of treatment effects.

A13. Priority question: The company stated that non-RCT IVMT studies were excluded from the ITC: "...because RCTs were considered the gold standard as they are designed to eliminate bias and ensure internal validity through randomisation and double-blinding." (Appendix D, p. 61) However, the internal validity is irrelevant given that the ITC was unanchored, i.e. did not use the unbiased treatment effect vs. the comparator in any of the RCTs.

a) Please conduct ITCs that include single arm studies, either experimental or observational.

As described in Section B 2.9.1. of Document B submission, three scenario analyses were conducted on the MAIC to explore the uncertainty associated with the base case analysis of teprotumumab versus IVMP. Scenario 2 included both randomised controlled trials (RCTs) and real-world evidence (RWE) studies. Xu et al. was the only single arm experimental study identified from the clinical SLR.³⁶ It was a prospective pilot study and was included in this scenario for the change from baseline proptosis outcome.

Identifying the single arm study did not affect our choice of analysis. The analysis that was performed here replicated the pooling conducted in the Douglas publication.³⁵ Pooling allowed more data to be incorporated for the IVMP comparator arm rather than conducting one anchored MAIC with the single arm study. NICE DSU TSD 18¹ states that "A sizable proportion (40%) of analyses applied MAIC to single-arm trials, or in situations with no common comparator. The only choice in such a scenario is to perform an unanchored indirect comparison." indicating that an anchored approach would not be considered with single arm studies. Therefore, the single arm prospective study was analysed with RWE studies.

The outcomes from all included IVMP studies were meta-analysed to obtain a pooled treatment effect. The pooled treatment effect was then used in the matching-adjusted indirect treatment comparisons to obtain the relative effects of teprotumumab vs IVMP. The RWE studies included retrospective observational studies and prospective studies. As stated in Document B Section B.2.9.3, the results of these analyses showed teprotumumab to be more effective at reducing proptosis (mean difference in CFB: [REDACTED] mm [95% CI: [REDACTED]]) and achieving diplopia response rate (OR [REDACTED] [95% CI [REDACTED]]). As these analyses have been conducted and shared with NICE, no further analyses have been conducted as part of the EAG requests.

Three non-RCT studies were included for the change from baseline proptosis outcome and are presented in Table 10.

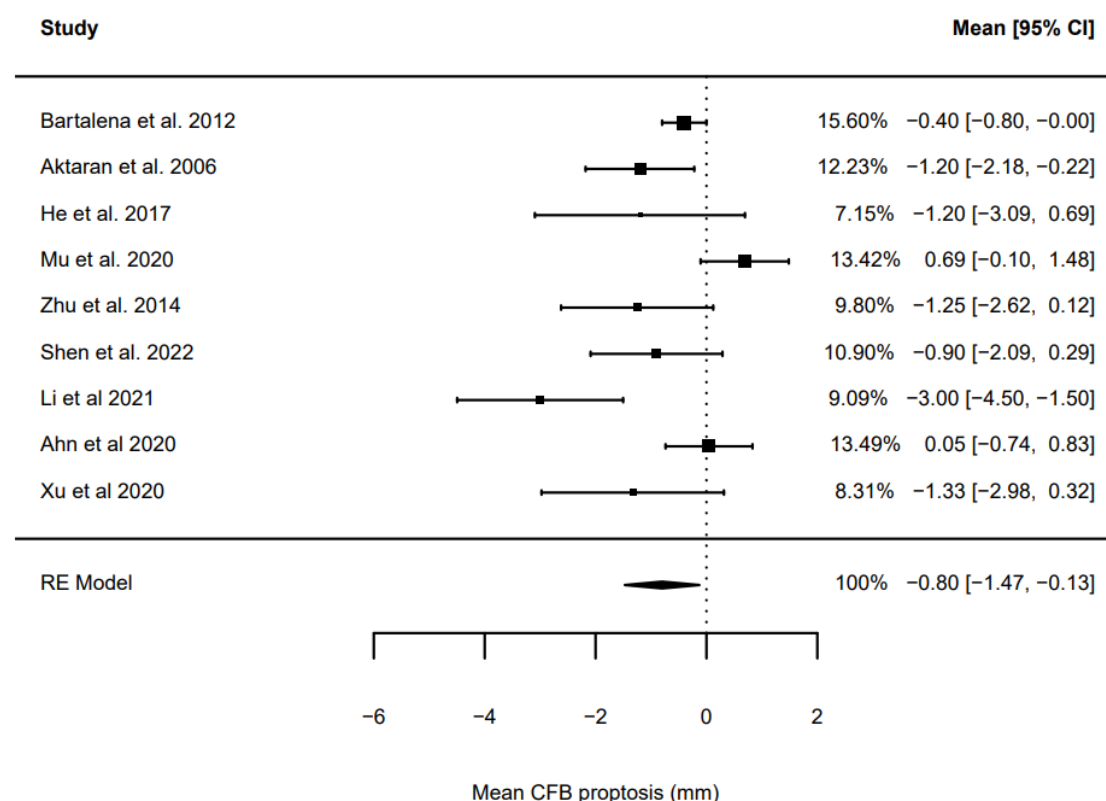
Table 10: Non-RCT studies included for the proptosis outcome.

Study	Study design	Treatment arm
Ahn et al., 2020 ³⁷	Retrospective observational study	IVMP
Xu et al., 2023 ³⁶	Prospective study	IVMP
Li et al., 2021 ³⁸	Prospective study	IVMP

Abbreviations: IVMP – Intravenous methylprednisolone

Figure 3 shows the pooled treatment effect of all studies included for the proptosis outcome in this scenario after performing a meta-analysis.

Figure 3: Forest plot for mean change from baseline proptosis outcome including RCT and non-RCT studies



Abbreviations: CFB – Change from baseline; CI – Confidence interval; mm – millimeter

Scenario analysis including RCT and RWE studies showed teprotumumab to be more effective at reducing proptosis. The results comparing scenario 2 to base case are presented in Table 11.

Table 11: Mean difference in change from baseline proptosis MAIC results (teprotumumab vs IVMP)

	ESS	Mean difference in change from baseline proptosis (mm) (SE)	95% Lower CI	95% Upper CI
Base case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	██████	██████	██████	██████
Unadjusted results	N/A	██████	██████	██████
Scenario 2 (RCTs and RWE)				
Adjusted results	██████	██████	██████	██████
Unadjusted results	N/A	██████	██████	██████

Abbreviations: CI – Confidence interval; mm – millimeter; N/A – Not applicable; RCT – Randomized controlled trial; RIT – Radioiodine treatment; RWE – Real world evidence; SE – Standard error

Three non-RCT studies were included for the diplopia response outcome, with two of those being single-arm studies. The studies are presented in Table 12.

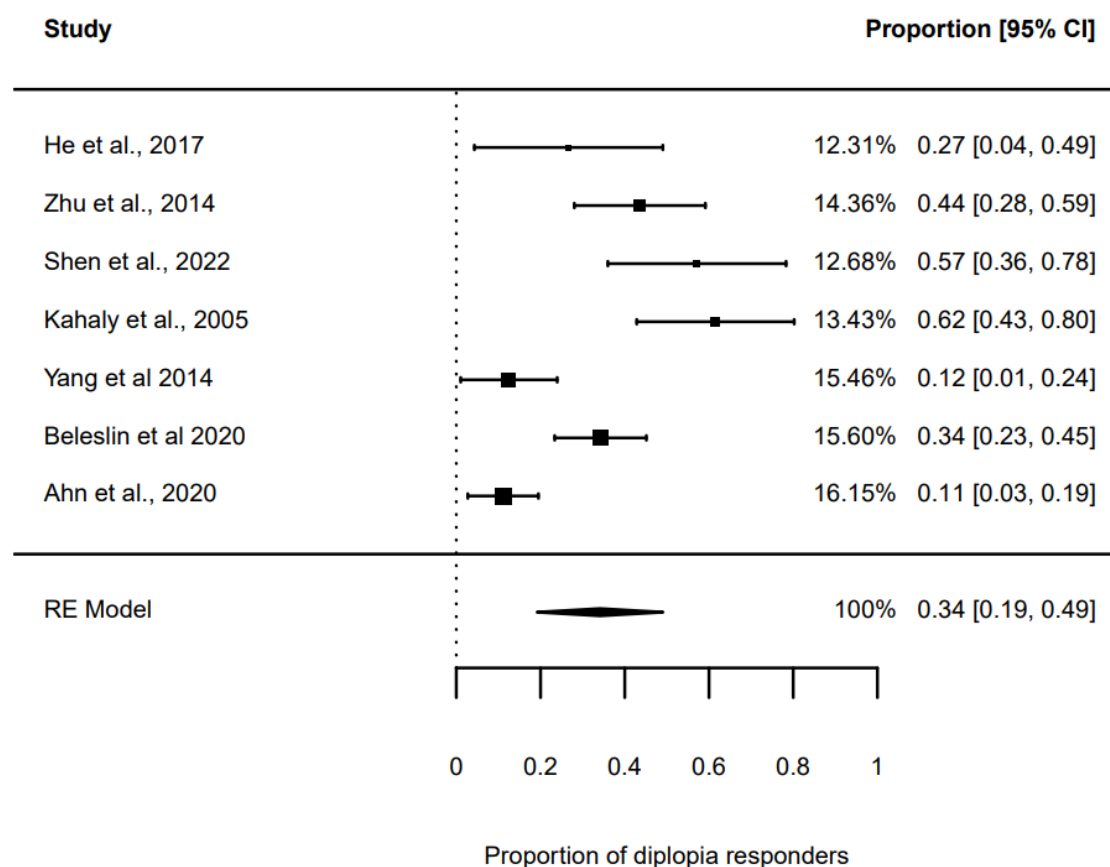
Table 12: Non-RCT studies included for the diplopia outcome.

Study	Study design	Study arms
Ahn et al., 2020 ³⁷	Retrospective observational study	IVMP
Yang et al., 2014 ³⁹	Retrospective observational study	IVMP
Beleslin et al., 2020 ⁴⁰	Retrospective observational study	IVMP
		IVMP + prednisone

Abbreviations: IVMP – Intravenous methylprednisolone

Figure 4 below shows the pooled treatment effect of all studies included for the diplopia outcome in this scenario. Baseline characteristics for the studies were pooled using a weighted average approach.

Figure 4: Forest plot for diplopia response rate outcome including RCT and non-RCT studies



Abbreviations: CFB – Change from baseline; CI – Confidence interval; mm – millimeter

Scenario analysis including RCT and RWE studies showed that teprotumumab increased the odds of achieving a diplopia response compared to IVMP as shown in Table 13.

Table 13: Diplopia response rate MAIC results (teprotumumab vs IVMP)

	ESS	OR	95% Lower CI	95% Upper CI
Base case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	██████	██████	██████	██████
Unadjusted results	N/A	██████	██████	██████
Scenario 2 (RCTs and RWE)				
Adjusted results	██████	██████	██████	██████
Unadjusted results	N/A	██████	██████	██████

b) Please examine the effect of study design on the outcomes of the ITCs.

As seen in the results presented above, including RWE studies resulted in teprotumumab still being more effective compared to IVMP at reducing proptosis and achieving diplopia response. The observed relative treatment effect increased for the diplopia outcome but decreased for the proptosis outcome when RWE was included.

RWE studies were included in the analysis to produce a bigger sample size, however after matching, the ESS was lower than in the base case (RCTs only). This might be the result of greater variety in baseline characteristics within patients included in the RWE studies. Observational studies are more prone to confounding and selection bias, which may distort the ITC outcomes, therefore we would recommend using the MAIC that excludes RWE.

Adverse events

A14. Priority question. Please provide data on all adverse events at grade 3 or higher in the two pivotal studies (a phase 2 randomised controlled trial (RCT) [NCT01868997] and the phase 3 OPTIC RCT [NCT03298867]).

Please see the following documents, which provide all adverse events for any grade in the Phase 2 and OPTIC clinical trials. These documents also include all serious adverse events, irrespective of grade and incidence rate in response the question below.

[REDACTED]

[REDACTED]

A15. Priority question. Please provide percentage data on all reported serious adverse events (SAE) irrespective of grade that occurred in any patient, i.e., not only those SAEs that occurred in >5% the two pivotal studies (a phase 2 randomised controlled trial (RCT) [NCT01868997] and the phase 3 OPTIC RCT [NCT03298867]).

A summary of all Serious Treatment-Emergent Adverse Events for the Safety Population in the Phase 2 pivotal trial is presented in Table 14.

Table 14: Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population) – Phase 2 study

System Organ Class/Preferred Term	Placebo (N=44) n (%)	Teprotumumab (N=43) n (%)	Total (N=87) n (%)
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■

Note: the denominator for percentages is the number of subjects in each treatment group. At each level of summarisation, a subject who experienced more than one serious TEAE was counted only once. All serious TEAEs were coded by using MedDRA Version 14.

^a A TEAE was defined as an AE with onset at the time of or following start of treatment with study drug or an AE starting before the start of treatment but increasing in severity following the start of treatment.

^b Verbatim description included “suspected” Hashimoto’s encephalopathy.

A summary of all Serious Treatment-Emergent Adverse Events for the Safety Population in the Phase 3 OPTIC trial is presented in Table 15.

Table 15: Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population) – Phase 3 OPTIC

System Organ Class/Preferred Term	Placebo (N=42) n (%)	Teprotumumab (N=41) n (%)	Total (N=83) n (%)
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■
■	■	■	■

██████	██████	██████	██████
██████	██████	██████	██████

Note: the denominator for percentages is the number of subjects in each treatment group. At each level of summarisation, a subject who experienced more than one serious TEAE was counted only once. All serious TEAEs were coded by using MedDRA Version 14.

a TEAEs are defined as AEs occurring or worsening after the first dose on Day 1 through to 3 weeks following the last dose of study drug.

Section B: Clarification on cost-effectiveness data

Model structure

B 1. Patients can only enter the surgical state at [REDACTED]. Please provide rationale for why transition to surgery state can only happen at [REDACTED] and not throughout the follow-up time.

The disease pathway was described in Section B1.3.1. in Document B of the submission. The point at which surgery occurs is reflective of the change in the disease course from active to inactive (chronic) TED. To reflect that surgery is only conducted in patients when they are in the inactive disease stage, there is a delay to when patients receive surgery in the model. [REDACTED] corresponds to a period of 3 years, incorporating the additional wait-time for surgery and was informed by UK clinicians.⁴¹ Patients remain in the surgery state for 30 cycles, reflecting an average time period of 3.5 years (between 3 to 4 years) to complete all surgeries, as per UK clinician consultation. It is assumed all patients transition to surgery at [REDACTED] and not at other points beyond this as more granular data on the timepoints at which patients receive surgery were not available. Furthermore, scenarios included in the company model to explore the timing of when surgery occurs show minimal impact on the ICER. Updating the cycle at which surgery occurs to cycle 20 increases by ICERs for IVMP and IVMP+MMF by ~1%, and to cycle 30 decreases the ICER by <1%. Therefore, a simplified approach was adopted and deemed appropriate.

Treatment effectiveness

B 2. Priority question. The methods used to estimate the transition matrices for IVMP and IVMP+MFF are not clearly described in the company submission. Provide a comprehensive description, including calculations, of how the

treatment effects from the MAIC were combined with the IPD data on teprotumumab to create the transition matrices for IVMP and IVMP + MFF.

As proptosis and diplopia are separate outcomes from the ITC, separate IVMP transition matrices were derived for the proptosis and diplopia endpoints.

To generate the IVMP proptosis transition probabilities, pseudo IPD was created by estimating the predicted mean difference between the teprotumumab and IVMP proptosis scores for each subject at each time point, based on the reported mean difference from the ITC and the change from baseline (CFB) of the teprotumumab proptosis scores for that subject over time. The pseudo IPD was calculated as follows:

1. The mean difference for each subject was calculated as a percentage of the CFB in proptosis at week 24 in the teprotumumab IPD.
2. The predicted mean difference applied at each timepoint was calculated by multiplying the absolute CFB in proptosis in the teprotumumab IPD at each timepoint by the percentage calculated in step 1.
3. The predicted mean difference at each timepoint was then subtracted from the corresponding teprotumumab proptosis measurement to derive the pseudo IPD.

Proptosis transition probabilities for IVMP were created from the pseudo IPD using the observed patient counts over each 6-week cycle. The methodology used was the same as for the teprotumumab transition probabilities, whereby patients were classified at each timepoint into either small or large proptosis based on whether their proptosis score was <3mm or ≥3mm above the upper limit of normal for their race and sex (CS, Section B.3.3.1).

Since the ITC compared endpoints for IVMP and teprotumumab at two different timepoints due to their differing treatment lengths (week 12 and week 24, respectively), it was assumed that the IVMP treatment effect increases twice as fast as teprotumumab, such that IVMP reaches its maximum treatment effect at week 12 and teprotumumab at week 24. Therefore, to derive the IVMP transition probability

matrix for week 1 – 6, the pseudo IPD patient transitions for week 1 – 12 were used, and to derive the IVMP transition probability matrix for week 6 – 12, the pseudo IPD patient transitions for week 12 – 24 were used.

For the week 12 – 18 and week 18 – 24 transitions, the model assumes IVMP patients remain in the same state, since they are no longer on treatment. This is likely a conservative assumption in favour of IVMP as it means the maximum IVMP treatment effect is applied for two cycles during which the maximum treatment effect for teprotumumab has not yet been reached.

As the diplopia response output from the ITC is in the form of an odds ratio (OR), it could not be applied to the teprotumumab IPD in the same way as the proptosis output. Therefore, the OR from the ITC was used along with teprotumumab diplopia IPD to calculate a relative risk (RR) of improving diplopia Grade for IVMP compared to teprotumumab. The RR was then applied to the teprotumumab diplopia transition probabilities. The following steps were used to calculate the RR:

1. The probability of improving diplopia score for teprotumumab (P_{trt}) over the full treatment course (week 1 – 24) was calculated from the teprotumumab IPD. This was calculated as the proportion of subjects experiencing an improvement in diplopia of one or more grades between baseline and week 24 divided by the total number of subjects.
2. The probability of improving diplopia score for IVMP (P_{comp}) over the full treatment course (week 1 – 12) was calculated by applying the reported OR from the ITC to the odds of improving diplopia score for teprotumumab over the full treatment course (week 1 – 24).
3. The RR of improving diplopia Grade for IVMP vs teprotumumab was calculated according to the following equation: $RR = P_{comp}/P_{trt}$.

For transitions to a health state which reflects a reduction in diplopia score (e.g. from constant diplopia to intermittent/inconstant diplopia), the teprotumumab diplopia transition probability was multiplied by the RR. As diplopia response in the ITC was defined as a ≥ 1 Grade reduction, to be able to apply the OR in the model it was assumed that the OR refers to the odds of any Grade of diplopia reduction greater

than or equal to one (i.e. the same odds was applied for moving from Grade 3 to Grade 2, Grade 3 to Grade 1, or Grade 3 to Grade 0, independent of the size of the diplopia reduction).

The ITC only reported the odds of improving diplopia Grade, and not of worsening or remaining the same, since the only commonly reported outcome across the IVMP studies was the proportion of patients who had a diplopia response. Therefore, it was assumed that the IVMP probabilities for diplopia worsening or remaining the same were the same as for teprotumumab. This is a conservative assumption in the absence of data.

As with the IVMP proptosis transition probabilities, since treatment effect for IVMP is assumed to increase twice as fast as for teprotumumab, to generate the IVMP diplopia transition matrix for week 1 – 6, the RR was applied to the teprotumumab diplopia transition matrix for week 1 – 12, and to generate the IVMP diplopia transition matrix for week 6 – 12, the RR was applied to the teprotumumab diplopia transition matrix for week 12 – 24. As with the proptosis transition matrices, since IVMP is assumed to reach maximum treatment effect at week 12, IVMP patients are assumed to remain in the same diplopia state between week 12 and week 24.

The separate transition probability matrices for proptosis and diplopia are combined into one 6x6 matrix for IVMP for each transition to align with the structure of the teprotumumab transition matrices, assuming independence of endpoints.

For the IVMP+MMF transitions, the approach is broadly similar, except the matrices do not need to be adjusted to account for differing time points since the ITC outputs for teprotumumab and IVMP+MMF were both recorded at week 24. Therefore, the timepoints of the teprotumumab IPD used are aligned with the timepoints of the IVMP+MMF transition matrices being generated, and the remain in state assumption is not required between week 12 and week 24.^{24, 42}

In response to question B18, the full calculations for deriving the IVMP and IVMP+MMF transition matrices are now included in the model.

B 3. Priority question. Clearly describe how uncertainty in the treatment effects from the MAIC were propagated through the model. Clarify whether only mean estimates of treatment effect were used.

The model only included the mean estimates of treatment effect from the MAIC. However, in response to question B18 we have updated the model so that the MAIC outputs are varied in the PSA according to their standard errors to capture this uncertainty; this approach is detailed in the response to question B18.

B 4. Priority question. Please provide the long-term follow-up results for both the phase 2 and the OPTIC RCT Phase 2 trial (NCT01868997)

The phase 2 study was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study that consisted of 3 parts: a Screening Phase of 4 weeks; a double-blind Treatment Phase of 24 weeks; and an off-treatment Follow-up Period of 48 weeks, with no additional treatment for TED during at least the first 12 weeks, unless medically indicated.

The study results at Weeks 24 and 28 have already been provided by the submitting company in CS, Document B, section 2.6. This clarification response provides additional details of the efficacy and safety results at Week 28 and at Week 72. The off-treatment Follow-up Period (Weeks 28-72) is detailed in an addendum to the CSR.⁴³

The purpose of the study addendum was to evaluate subjects off-treatment following the blinded 24-Week Treatment Phase with teprotumumab or placebo in subjects diagnosed with active TED. The off-treatment Follow-up Period was designed to assess safety, including evaluation of the possibility of an acute disease activity rebound effect off treatment, during the initial 30-day Follow-up Period (Week 24 to Week 28), and evaluate continued short-term response of teprotumumab after 4 weeks of treatment discontinuation at Week 28. Continued teprotumumab treatment effect as well as worsening of disease requiring additional treatment was then further evaluated in the long-term follow-up at Week 72. In the Follow-up Period, subjects attended clinic visits at Weeks 28, 36, 48, 60, and 72 for safety assessments; efficacy was measured at Weeks 28 and 72 only.

Efficacy results

Efficacy was assessed by overall response criteria (using the same definition of response as at Week 24), proptosis and by CAS (7-point version of the scale).^{43, 44}

Response analysis

There was [REDACTED] at Week 28, 30 days following the Week 24 double-blind treatment phase, for subjects receiving teprotumumab.⁴⁴

The Week 24 primary endpoint, the proportion of responders, remained statistically significantly higher for teprotumumab [REDACTED] compared to placebo [REDACTED] at Week 28, with the difference in the proportion of responders in favour of teprotumumab of [REDACTED] a greater response difference than seen at Week 24.^{43, 44}

Secondary Endpoints

The Week 24 teprotumumab proportion of proptosis responders considered statistically significant and clinically meaningful continued to be observed off-treatment at Week 28 ([REDACTED] in the teprotumumab group compared to XXX in the placebo group, [REDACTED]). This was a larger response than what was seen at the end of the double-blind treatment period (Week 24). The mean change from baseline had similar results.^{43, 44}

The majority ([REDACTED]) of subjects from the teprotumumab group who met proptosis response criteria at Week 24 maintained improvement relative to baseline ([REDACTED]) and did not require additional TED treatment or surgical intervention up to 48 weeks off treatment. [REDACTED] had elective TED surgery 2 weeks before their Week 72 visit; therefore, no Week 72 data was collected.^{43, 44}

[REDACTED] of subjects from the teprotumumab group who met proptosis response criteria at Week 24 did not maintain improvement relative to baseline ([REDACTED]) during the 48-week off-treatment Follow-up Period. XXX of these subjects received steroids and [REDACTED] received steroids in addition to surgical intervention.^{43, 44}

■■■■ of subjects from the teprotumumab group who met proptosis response criteria at Week 24 did not maintain improvement relative to baseline during the 48-week off-treatment Follow-up Period. ■■■■ of these subjects received steroids and X received steroids in addition to surgical intervention. In comparison, during this 48-week off-treatment Follow-up Period, ■■ subjects from the placebo group required surgical intervention, ■■ in combination with steroids and ■■ with addition of rituximab; ■■ additional subject was treated with steroids only.^{43, 44}

The safety profile of teprotumumab did not change during the off-treatment Follow-up Period.

Phase 3 OPTIC trial (NCT03298867)

At the end of the Double-Blind Treatment Period (Week 24) in the Phase 3 OPTIC trial, subjects who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter an open-label extension study (OPTIC-X). Proptosis responders, as well as non-responders who chose not to enrol in OPTIC-X, entered a Follow-Up Period of an additional 48 weeks, during which no study drug was administered. Clinic visits were scheduled for Weeks 28, 36, 48, 60 and 72 (Months 7, 9, 12, 15 and 18) during the Follow-Up Period. Subjects who were responders at Week 24 but who met the re-treatment criteria due to a relapse during the Follow-Up Period could have enrolled in OPTIC-X.

Determination of relapse was based on the following criteria: increase in proptosis of ≥ 2 mm in the study eye since Week 24, or an increase in Clinical Activity Score (CAS) of ≥ 2 points since Week 24 with an absolute CAS of ≥ 4 in the study eye following the Week 24 Visit. In addition to the criteria, the Investigator was to consider the subject's symptomology to ensure a relapse had occurred (e.g., new onset of double vision).

Of the ■■ subjects in the placebo group who completed the Week 24 Double-Blind Treatment Period, ■■ enrolled in OPTIC-X and 4 continued into the 48-week Follow-up Period, of whom ■■ subject discontinued early and ■■ completed the Follow-up Period. Of the ■■ subjects in the teprotumumab group who completed Week 24,

only ■ enrolled in OPTIC-X and ■ continued into the 48-week Follow-up Period. ■ discontinued early and ■ completed the Follow-up Period.^{45, 46}

With the exception of biomarker results, data from the 24-week Double-Blind Treatment Period (primary trial analysis) were reported in the Week 24 CSR dated 24 April 2019. Results through to the final visit (Week 72) of the 48-week treatment-free Follow-Up Period were reported in a CSR addendum dated 03 August 2020 (the Week 72 CSR addendum).^{45, 46}

Week 72 efficacy results

The following efficacy outcomes were evaluated:^{45, 46}

- Proptosis responder rate (defined as 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);
- Overall responder rate (defined as subjects with ≥ 2 mm reduction in proptosis AND ≥ 2 point reduction in CAS from Baseline, provided there was no corresponding deterioration [≥ 2 mm/point increase] in proptosis or CAS in the fellow eye);
- CAS categorical responder rate (defined as subjects with a reduction to a CAS of 0 or 1 [no or minimal inflammatory symptoms]);
- Proptosis as a continuous variable:
- Diplopia categorical responder rate (defined as 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); and
- Graves' Ophthalmopathy Quality of Life (GO-QoL).

The efficacy endpoints at Week 72 are presented in Table 16. Few placebo subjects (n = ■) responded to treatment at Week 24 and entered the Follow-Up Period, precluding meaningful interpretation of the data for those subjects.^{45, 46}

The response to treatment achieved for the primary and secondary responder endpoints at the end of the Week 24 Double-Blind Treatment Period was also observed for the majority of the teprotumumab subjects at the end of the off-treatment Follow-Up Period (Week 72).^{45, 46}

Table 16: Efficacy Endpoints at Week 72 (ITT Population; Observed Cases)

Outcome	Placebo (N = 3)	Teprotumumab (N = 21)
Primary		
Proptosis responder rate, n/N (%)		
Secondary		
Overall responder rate, n/N (%)		
CAS categorical responder rate, n/N (%)		
Average change from Baseline in proptosis (mm) through Week 72, mean (SD)		
Diplopia responder rate, n/N (%)		
Average change from Baseline in GO-QoL overall score through Week 72, mean (SD)		

Abbreviations: CAS, clinical activity score; GO-QoL, Graves' Ophthalmopathy Quality of Life; ITT, intent-to-treat; SD, standard deviation.

Note: Although 20 teprotumumab subjects completed the 48-week Follow-Up Period of the study, 1 additional subject (US-103-006) had evaluable data that fell within the Week 72 Visit window and was included in analysis.

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

In addition, the maintenance of response for additional endpoints was assessed in subjects who were responders at Week 24 (see Table 17). Sustained response was defined as subjects who continued to meet the Week 24 response definition and received no additional TED treatment at the time of the visit.

Table 17: Maintenance of Response at Week 72 (Week 24 Responders)

	Placebo	Teprotumumab
Sustained proptosis responder rate, n/N (%)		
Sustained overall responder rate, n/N (%)		
Sustained CAS categorical responder rate, n/N (%)		
Sustained diplopia responder rate, n/N (%)		
Sustained diplopia Grade 0 responder rate, n/N (%)		

Abbreviation: CAS, clinical activity score

For sustained responder rates, a subject missing the Week 72 evaluation was considered a non-responder.

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

Mean increases from Baseline in the GO-QoL overall score remained consistent in teprotumumab subjects during the Follow-Up Period (██████ at Week 28 for █████ subjects, █████ at Week 48 for █████ subjects, and █████ at Week 72 for █████ subjects). In addition, mean increases in the GO-QoL subscale scores of visual functioning (██████ at Week 28 for █████ subjects, █████ at Week 48 for █████ subjects, and █████ at Week 72 for █████ subjects) and appearance (██████ at Week 28 for █████ subjects, █████ at Week 48 for █████ subjects, and █████ at Week 72 for █████ subjects) were also observed. The increases at each measured time point were well above the minimal clinically important difference for the GO-QoL instrument and represent moderate to large changes. A 10-point difference in GO-QoL scores is considered a moderate change and a 20-point difference is considered a large change.^{45, 46}

Week 72 safety results

The safety analysis evaluated Adverse Events (AEs), concomitant medication use, physical and ophthalmic examinations, vital signs, immunogenicity testing, clinical safety laboratory evaluations (haematology, chemistry, thyroid panel and urinalysis) and electrocardiograms (ECGs).

██████ occurred during the Follow-Up Period. Serious AEs were experienced in █████ teprotumumab subjects (*Intercostal neuralgia* and *Optic neuropathy*) during the Follow-Up Period, which were considered severe in intensity and not related to study drug. █████ of the teprotumumab subjects experienced an AE that led to discontinuation from study. █████ of the AEs experienced in placebo subjects was serious or led to discontinuation from study.^{45, 46}

In the Follow-Up Period, 26 (██████%) of the █████ teprotumumab subjects experienced at least 1 AE, 7 (██████) of whom had AEs considered treatment-related. Severe AEs were experienced in 3 (██████) teprotumumab subjects (serious AEs of *Intercostal neuralgia* and *Optic neuropathy* and a non-serious AE of *Hypothyroidism*) that were considered not related to study drug. Among the X placebo subjects in the Follow-Up Period, 3 (██████) experienced at least 1 AE that was mild or moderate in intensity. █████ of the AEs in the placebo group was considered related to study drug.^{45, 46}

The most common AEs reported during the Follow-Up Period in teprotumumab subjects were mild events associated with fingernails including *Onychoclasia* (■ subjects), *Koilonychia* (■ subject), *Nail disorder* (■ subject), and *Onychoclasia* and *Nail discolouration* (■ subject). The AEs of *Onychoclasia* were described as brittle or splitting nails. Among the ■ subjects with nail-related events, ■ had events that were considered related to study drug and ■ had events that were noted as ongoing. ■ of the placebo subjects experienced these types of AEs.^{45, 46}

AEs of special interest (hyperglycaemia, muscle spasms, diarrhoea and hearing impairment) were evaluated in the Follow-Up Period.^{45, 46}

- > ■ teprotumumab subjects had an AE or fasting glucose value associated with hyperglycaemia during the Follow-Up Period. The subject with the AE of moderate *Diabetes mellitus* had an HbA1c value at Baseline suggestive of impaired glucose tolerance (■%), with values above the normal range during the Double-Blind Treatment Period and the Follow-Up Period; all fasting glucose values were within the normal range. The subject was treated with metformin, which was ongoing when the subject discontinued from the study due to relapse. The subject with the shift in fasting glucose had a Grade 1 elevation during the Double-Blind Treatment Period and the Follow-Up Period but was within the normal range at Week 72; no antidiabetic agent was prescribed for this subject at any time during the study.
- > ■ had an AE of *Muscle spasms* during the Follow-Up Period that was considered mild in intensity, related to study drug, and noted as resolved.
- > ■ had an AE of *Hypoacusis* during the Follow-Up Period that was considered mild in intensity, not related to study drug, and resolved after completion of OPTIC-X.
 - No AEs associated with diarrhoea were reported during the Follow-Up Period.
- > AEs of special interest that were ongoing at the end of the Double-Blind Treatment Period were noted as resolved for ■ subjects with *Muscle spasms*, ■ subjects with events associated with hearing impairment, and ■ subject with *Hyperglycaemia*.

- No clinically significant changes in laboratory values, vital signs, ECGs, physical (pretibial myxoedema) examinations or ophthalmic examinations were observed during the Follow-Up Period.
- > ███ teprotumumab-treated subjects were confirmed positive at Week 72 for anti-teprotumumab antibodies; however, neither sample had sufficient antibodies (<1) for quantitative assessment.

Conclusions

By study design, subjects who did not have a proptosis response at Week 24, and those who relapsed during follow-up, were eligible to leave the study and enrol in the separate extension study (OPTIC-X) where all subjects received a course of teprotumumab treatment. As few subjects who had originally been randomised to placebo were responders at Week 24, few (n=██) participated in the Follow-Up Period and it is therefore not possible to draw conclusions from this population.^{45, 46}

For subjects who were originally randomised to receive teprotumumab, most had a proptosis response at Week 24, and were not immediately eligible for the extension study (OPTIC-X) and therefore entered the Follow-Up Period. Subjects who relapsed during follow-up were eligible to move into OPTIC-X and some subjects discontinued for other reasons; taken together, ███ subjects originally randomised to teprotumumab had evaluable data at Week 72.^{45, 46}

Of those with Week 72 data, ███ of teprotumumab subjects were proptosis responders. The mean decrease from Baseline in proptosis remained consistent with Week 24 during the Follow-Up Period (-████ mm at Week 24 for ███ subjects, -████ mm at Week 28 for ███ subjects, and -████ mm at Week 72 for ███ subjects).^{45, 46}

Among teprotumumab subjects who had data at the Week 72 Visit, the overall responder rate was ███% (████), the CAS categorical responder rate was ███ (████) and the diplopia responder rate was ███ (████).^{45, 46}

Mean increases from Baseline in the GO-QoL overall score remained consistent in teprotumumab subjects during the Follow-Up Period. In addition, mean increases in

the GO-QoL subscale scores of visual functioning and appearance were also observed.

The maintenance of effect was observed in analyses of additional endpoints for teprotumumab subjects who were responders at Week 24. At the end of the off-treatment Follow-Up Period, the response to treatment achieved for the primary and secondary responder endpoints at the end of the Double-Blind Treatment Period was maintained for ████████ of teprotumumab subjects without the need for additional TED treatment for proptosis, diplopia, and CAS. Lack of data was imputed as lack of maintenance; accordingly, subjects who lacked Week 72 data were counted as non-responders, including █ subject who had a Week 24 proptosis response but chose not to enrol in the Follow-Up Period.^{45, 46}

█ subjects who relapsed during the Follow-Up Period prior to Week 72 (█ of whom enrolled into OPTIC-X to receive a second course of teprotumumab) and █ subjects who discontinued for other reasons.^{45, 46}

In summary, the response to treatment achieved for the primary and secondary responder endpoints at the end of the Double-Blind Treatment Period was also observed for the majority of the teprotumumab subjects at the end of the off-treatment Follow-Up Period with no observed change in the overall safety profile.

Week 120 results

Subjects who completed the Week 72 visit (█ in the placebo group and █ in the teprotumumab group) were contacted 6 and 12 months later via phone or email by research staff to enquire if any treatment for TED has been received since last study contact. If yes, the subject was questioned regarding the type of treatment received and outcome/response. The objective of the Treatment-Free Follow-Up Contact Period was to ascertain whether study subjects had received further medication, surgical or other interventional procedures for their TED during that period.⁴⁷

A second CSR addendum presents the final follow-up analysis of the trial (Week 120 addendum), as all subjects who completed the Week 72 Visit either completed the additional Follow-Up Contact Period (Week 96 and Week 120) or were unable to be

contacted during this period; these follow-up data were collected after the cut-off date for the Week 72 CSR addendum (21 January 2020).⁴⁷

In addition, this Week 120 addendum presents results pertaining to an exploratory endpoint of the trial: evaluation of the effect of teprotumumab on the mean change from Baseline to Week 24 of the Double-Blind Treatment Period in biomarkers (i.e., thyroid autoantibodies).

A total of [REDACTED] study subjects ([REDACTED] from the placebo group and [REDACTED] from the teprotumumab group) completed the Week 72 visit and entered the Treatment-Free Follow-Up Contact Period. All [REDACTED] had a successful Week 96 contact and [REDACTED] ([REDACTED] from the placebo group and [REDACTED] from the teprotumumab group) had a successful Week 120 contact.⁴⁷

Results of the contact evaluation

[REDACTED] of the [REDACTED] 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-Blind Treatment Period.⁴⁷

- > [REDACTED] received commercial teprotumumab (TEPEZZA) intravenously every 3 weeks from Day 626 (approximately 16 months after the last dose of double-blind teprotumumab) to Day 773, resulting in resolution of bulging in both eyes, but pain and pressure still ongoing in the left eye. Teprotumumab (TEPEZZA) was approved by the United States Food and Drug Administration 10 weeks prior to Day 626 for this subject.
- > [REDACTED] underwent eyelid surgery on Day 513 (1 year after the last dose of teprotumumab) that resulted in improvement in TED symptoms.

No subject underwent orbital radiation during the Follow-Up Contact Period.

Biomarker evaluation

At Baseline, all XX subjects in the ITT Population ([REDACTED] placebo, [REDACTED] teprotumumab) were positive for TSAb and the majority ([REDACTED] placebo, [REDACTED] teprotumumab)

were positive for TBII. At Weeks 12 and 24, [REDACTED] and [REDACTED] of placebo subjects, respectively, and [REDACTED] and [REDACTED] of teprotumumab subjects, respectively, were positive for TSAAb. At Weeks 12 and 24, [REDACTED] of placebo subjects, respectively, and XXX [REDACTED] of teprotumumab subjects, respectively, were positive for TBII.⁴⁷

A mean reduction in TSAAb was observed at Weeks 12 and 24 in the placebo and teprotumumab groups. The mean reduction and mean percent reduction from Baseline in TSAAb were greater in the teprotumumab group compared with the placebo group at each time point. At Week 24, the mean percentage change (SD) from Baseline in TSAAb was -[REDACTED] in the placebo group and [REDACTED] in the teprotumumab group.⁴⁷

A mean reduction in TBII was observed at Weeks 12 and 24 in the placebo and teprotumumab groups. The mean reduction from Baseline in TBII was greater in the teprotumumab group compared with the placebo group at each time point. At Week 24, the mean change (SD) from Baseline in TBII was -[REDACTED] IU/L in the placebo group and [REDACTED] IU/L in the teprotumumab group. [REDACTED] were negative for thyroid blocking antibody on Day 1 and at Weeks 12 and 24.⁴⁷

Safety evaluation

No trial drug was administered during the Follow-Up Contact Period of the OPTIC study. All exposure and safety data were summarised in the Week 24 and Week 72 CSRs. No additional safety data were collected after the cut-off date for the Week 72 CSR addendum.

B 5. There is an incomplete sentence in B.3.3.1 (“Therefore, is limited compared to the MAIC used in the CEM base-case.”). Please clarify what was intended here.

“Therefore, because of the concerns listed, the use of alternative transition probabilities informed by Douglas et al. (2022) is limited compared to the de novo MAIC used in the CEM base-case.”

Transition probabilities

B 6. Priority question. The company uses observed transition counts for people receiving Teprotumumab between periods to inform transition probabilities in the model and for PSA draws. There is substantial variation in counts for each period and many cells with zero values (and zero variation in the PSA). Please explain why this approach was taken for including transition probabilities in the model versus alternative modelling approaches.

Using observed transition counts from the pooled Phase 2 and OPTIC IPD was considered the most appropriate method for deriving transition probabilities as it produces model outcomes that most accurately reflect the clinical trial data, since these matrices directly capture the patient movement observed in the trial. Due to the low patient numbers in TED, the sample size in the trials was small, resulting in some of the less common transitions in the matrices having zero values. To attempt to mitigate this, data from OPTIC and the Phase 2 trial were pooled to increase the sample size. Due to differences in trial populations, the OPTIC-J and Phase 4 trials were not suitable for pooling. No other suitable data sources were identified to provide any further data, so it was not possible to increase sample size beyond this.

Alternative approaches, such as producing a regression equation based on the trial data, are more complex and require additional assumptions to be made when deriving transitions. In particular, we would have to assume a set functional form across transitions, assuming linearity. This is unlikely to be appropriate based on the proportion of proptosis and diplopia responders over time, which does not follow a linear increase (CS Section B.2.8, Figure 18 and Figure 20). Therefore, these approaches were not used as they are not as transparent and may not predict clinical trial outcomes accurately. Regardless of the method used, there would still be uncertainty arising from small sample size. This is a limitation of the patient numbers in active moderate-to-severe TED being small and the associated difficulties in generating evidence. The NICE manual 2022 notes rare diseases as an area where: "committee may be able to make recommendations accepting a higher degree of uncertainty."⁴⁸

B 7. Priority question. It is noted that clinical outcomes are recorded at 24 weeks for Teprotumumab and at 12 weeks for IVMP or IVMP+MFF and that adjustments need to be made to the probability matrices. The description in B.3.3.1 is not clear. Please provide comprehensive information on these calculations.

As detailed in response to question B2, since the ITC compared endpoints for IVMP and teprotumumab at two different timepoints due to their differing treatment lengths (week 12 and week 24, respectively), to enable the full week 24 teprotumumab data to be used to generate the IVMP treatment effect at week 12, it was assumed that IVMP treatment effect increases twice as fast as teprotumumab, such that IVMP reaches its maximum treatment effect at week 12 and teprotumumab at week 24. Therefore, to derive the IVMP proptosis transition probability matrix for week 1 – 6, the pseudo IPD patient transitions for week 1 – 12 were used, and to derive the IVMP transition probability matrix for week 6 – 12, the pseudo IPD patient transitions for week 12 – 24 were used.

The same assumption was applied to derive the IVMP diplopia transitions, so to generate the IVMP diplopia transition matrix for week 1 – 6, the relative risk was applied to the teprotumumab diplopia transition matrix for week 1 – 12, and to generate the IVMP diplopia transition matrix for week 6 – 12, the relative risk was applied to the teprotumumab diplopia transition matrix for week 12 – 24. For the week 12 – 18 and week 18 – 24 transitions, the model assumes IVMP patients remain in state. This is likely a conservative assumption in favour of IVMP, since it means the maximum IVMP treatment effect is applied for two cycles during which the maximum treatment effect for teprotumumab has not yet been reached.

This adjustment is only applied for the IVMP transitions matrices and not the IVMP+MMF ones, as the ITC outputs for teprotumumab and IVMP+MMF were both recorded at the same timepoint (week 24).

B 8. Priority question. In Section B.3.2.2 it is stated that “The Surgery and Post-surgery transition time points, and the proportion of patients transitioning to the Surgery health state from each of the active disease health states, are informed and validated by UK clinicians due to a lack of data in the

literature.” Please provide more information on the input provided by the UK clinicians and how this was elicited.

As further detailed in our response to question B1, the surgery timepoint of [REDACTED] corresponds to a time period of 3 years and was based on UK clinician feedback incorporating the wait-time for surgery.⁴¹ Patients remain in the surgery state for 30 cycles, reflecting a time period of 3.5 years to complete all surgeries. All (n=4) physicians agreed all surgeries required for an average patient with active TED would be conducted over 3 to 4 years, therefore, an average of 3.5 years was deemed appropriate to use in the model. Clinicians noted this was due to long waiting times between each surgery. At the end of the 30 cycles in the surgery state, all patients transition to a post-surgery health state, where they stay for the remainder of the model time horizon.

Scenario analyses have been conducted to explore the timing of when surgery occurs demonstrates that the associated uncertainty has minimal impact on the ICERs. Changing the cycle at which surgery occurs to cycle 17 (2 years), increases the ICERs IVMP and IVMP+MMF by ~2%, and to cycle 30 decreases the ICERs by <1%. Increasing the duration of recovery from 30 cycles to 39 cycles decreases the ICERs for IVMP and IVMP+MMF by ~2%, whilst decreasing the duration to cycle 17 (2 years) increases the ICERs for IVMP and IVMP+MMF by ~4%.

In terms of the methodology for obtaining clinical expert opinion, four UK expert clinicians were asked to provide the proportion of eligible patients with active TED that require surgery from each health state. The mean value obtained were used in the company model. The proportions obtained are summarised in Table 18 below.⁴¹

Table 18: Proportion of patients with active TED that require surgery

Health states	Proportion of patients that require surgery, mean [range]
No diplopia, small proptosis	5% [0-10%]
No diplopia, large proptosis	38% [37.5-40%]
Intermittent/inconstant diplopia, small proptosis	5% [0-10%]
Intermittent/inconstant diplopia, large proptosis	41% [37.5-50%]
Constant diplopia, small proptosis	44% [37.5-50%]
Constant diplopia, large proptosis	44% [37.5-50%]

Extrapolation

B 9. Priority question. The base-case assumes that patients remain in whatever state they were in at cycle 24. Please provide clinical rationale for this assumption. Please provide all available clinical evidence (including long term follow up from the phase 2 and OPTIC RCTs) about long-term outcomes under teprotumumab and comparators.

The transition probabilities in the model for teprotumumab and comparators correspond to the duration that patients are on treatment. After Week 24, all patients have completed their full treatment courses. Therefore, it is necessary to consider the most clinically plausible approach to reflect patient's symptoms after completing their initial treatment course. Alternative extrapolation approaches were considered. We concluded that average and last observation carried forward (LOCF), were not appropriate as they both extrapolate patient movement whilst on treatment to the off-treatment period for the remainder of the model time horizon.

Further limitations associated with the average approach is related to the relatively short treatment durations (12 and 24 weeks) and the increase in the proportion of patients that have responded to treatment over time; the matrices in the on-treatment period were not considered similar enough to average across and would result in an underestimation of the overall treatment benefit received. If LOCF was used, it would continuously reapply the maximum treatment benefit observed in the last matrix (cycle 3-4) for the remainder of the time horizon (48 years), which is not a plausible representation of long-term patient movement. NICE DSU TSD 17 supports this justification, whereby it states that the LOCF method is not recommended due to several limitations including assuming that future values will be the same as the last observed value, which may not reflect the clinical trend.⁴⁹ This causes inherent biases to estimates if there are differences between the number of observations carried forward for different treatment groups.

Based on the data available, remain in state was considered the most plausible extrapolation option. After completion of their first treatment, it is plausible that most

patients that have responded to treatment would experience a stabilisation of their symptoms. Furthermore, as patients move into the inactive disease phase of TED (typically 1-3 years after diagnosis), inflammation decreases and symptoms stabilise, although persist.

Full details of the long-term outcomes from the Phase 2 and OPTIC RCTs are provided in response to question B4. Details of long-term outcomes for comparators from the clinical SLR are summarised in CS, Document B.2.2 and appendix D. Long-term outcomes for teprotumumab from OPTIC-X, the open-label extension study, are presented in appendix M. As discussed in the CS Section B.3.3.2, due to the small sample size in the OPTIC follow-up period it was not possible to generate robust transition probabilities using this data, so this data is not presented in the model. Furthermore, as the ITC only reported outcomes for IVMP at 12 weeks and IVMP+MMF at 24 weeks, it was not possible to generate robust comparator data beyond Week 24. Therefore, trying to incorporate any longer term data for teprotumumab would be highly uncertain and would not be a robust representation of long-term patient outcomes.

B 10. Priority question. In the model tab 'Clinical Inputs' cell D81 gives another option for extrapolation (i.e. LOCF). This does not appear in the methods. When applied in the model it appears that teprotumumab is more cost-effective vs IVMP and not cost-effective against IVMP+MFF. Please explain why these analyses have been included in the model and not reported in the company submission. And explain the implications of these findings for the model validity and study conclusions.

As described in the response to question B9 above, alternative extrapolation approaches after Week 24 were considered during the model development but LOCF is not an appropriate method. Therefore, results were not presented for LOCF. As described in our response to question B9 above, remain in state was deemed the most appropriate option.^{48, 49}

Health-related quality of life

B 11. Priority question. Utility values were derived from Smith et al. (2023). Please provide more detailed information on the study reported by Smith, including the design, full vignette description, how the TTO exercise was done, the population, and results.

As noted in the CS, due to the limited available literature and no EQ-5D available, a new utility study was conducted specific to active moderate-to-severe TED following NICE's hierarchy of preferred health-related quality of life (HRQoL) methods.

Smith et al. (2023) used the time trade-off (TTO) approach to generate utilities, for six proptosis and diplopia health states that were developed through a mixture of approaches, including interviews with clinicians and patient advocates.⁵⁰ The sample of 111 participants included adult residents (≥ 18 years) who had no conflict of interest (defined as employment in health care or market research). A representative sample was chosen using a general population US proprietary panel identified by a third party recruitment agency. To ensure all respondents matched the study's selection criteria, a population screener was used during recruitment. Furthermore, recruitment quotas were applied to ensure a geographically and demographically representative sample. The main benefit of using the general population over patients with the disease is that this captures views of the general population. Whereas patient valuation may potentially bias study results because patients may adapt to their health state over time and therefore assign higher values to their own health state. These higher values may be associated with patients developing coping mechanisms, allowing for improved functioning in daily activities. Furthermore, ethical concerns regarding patient valuation of health states may arise given the potential for emotional distress provoked by imagining hypothetical situations that they are unable to experience.⁵⁰

Before the TTO, the health states were developed using results from two placebo controlled clinical trials in patients with active, moderate severe TED with differing severities of proptosis and diplopia and interviews with patients with TED.⁵¹⁻⁵³ The health state descriptions were validated through expert TED physician and patient advocate interviews.⁵³ Patient interviews (n=6) were conducted to determine the

important HRQoL aspects. As such, broader domains of HRQoL, such as limitations on daily activities (driving and reading; problems of self-image; reduced social activities and interactions with others; inability to work or reduced productivity; anxiety about the future; and coping mechanism and treatments), were included in the health state descriptions to ensure all relevant HRQoL aspects were captured.

Ten pilot interviews were conducted for linguistic validation, to ensure that the six health states were readily understood by the general public. These were conducted using the same methodology intended for use in the utility elicitation interviews and involved members of the public who fulfilled the same selection criteria. No changes to the health state descriptions were made after the pilot interviews were conducted, concluding that the health state studies conducted were appropriate. Based upon feedback from the pilot interviews, a top line summary of the health state descriptions was developed and shared with participants alongside the full health state descriptions to facilitate an understanding of the differences in severity of the health states before executing the VAS and TTO exercises. Additionally, photos of people with proptosis and images displaying the effects of diplopia were used in the interviews to facilitate understanding and visualisation of the relative values of the health states. The directionality of the TTO scores from the pilot interviews correlated with the most and least severe health states, indicating that the health states descriptions were understood by all participants. The full vignette description can be found in Appendix A.

Utility scores were elicited using TTO methods with a finite 10-year horizon.⁵⁴ Out of 111 participants that completed the TTO interviews (pilot, n=10; main study, n=101), 42% of participants were 55 to 64 years old (n=47), 68% of the population were female (n=75), 81% wore glasses (n=90) and 41% (n=46) self-identified as having received a visual impairment diagnosis, including near or far sightedness (17%, n=19). Participants from the following race and ethnicity groups were included: 4 Asian (3.6%), 11 Black or African American (9.9%), 4 Hispanic (3.6%), and 92 White (82.9%).^{52, 55-57}

To conduct the TTO, the Measurement and Valuation of Health TTO protocol was used, involving the respondent trading off years with a poor QoL for a shorter period of life in full health.⁵⁴ Visual analogue scale (VAS) interviews were conducted, to

value participants own health at the time of analysis, using a scale between 0 (worst health) and 100 (best health). The health state utility values were tested using the Kruskal-Wallis test to determine if a significant difference was present between the values for each health states, using a p-value of 0.05 to determine significance.^{52, 55-}

57

The resulting utilities are summarised in an updated table below (Table 19) from the CS section B.3.4.3 Table 40. As with the utility scores, VAS scores aligned with the severity of health states, with the highest and lowest scores corresponding to the no diplopia, small proptosis (score of 51.71) and the constant diplopia, large proptosis (score of 27.42) states, respectively. While this study was conducted in a US population, the utility values were validated with UK clinicians in 2024, who agreed they were reflective of the quality of life of TED patients in the UK.⁴⁹

Table 19: Summary of utility values from Smith et al. 2023

State	Utility value: mean (SD)	95% confidence interval	Justification
Small Proptosis, No Diplopia	0.60 (0.34)	0.54-0.67	Smith <i>et al.</i> , 2023 ⁵⁸
Large Proptosis, No Diplopia	0.46 (0.32)	0.40-0.52	Smith <i>et al.</i> , 2023 ⁵⁸
Small Proptosis, Intermittent/Inconstant Diplopia	0.52 (0.33)	0.45-0.58	Smith <i>et al.</i> , 2023 ⁵⁸
Large Proptosis, Intermittent/Inconstant Diplopia	0.43 (0.33)	0.36-0.49	Smith <i>et al.</i> , 2023 ⁵⁸
Small Proptosis, Constant Diplopia	0.34 (0.31)	0.29-0.40	Smith <i>et al.</i> , 2023 ⁵⁸
Large Proptosis, Constant Diplopia	0.30 (0.31)	0.24-0.36	Smith <i>et al.</i> , 2023 ⁵⁸

SD, standard deviation.

B 12. Priority question. Please provide some validation, besides the face validity check by the expert panel, for the obtained utility values.

Although the NICE reference case states to use utility values derived from EQ-5D scores,⁵⁹ NICE Decision Support Unit (DSU) 8 and 11 acknowledge there are times when EQ-5D is not appropriate and alternative methods may be used.^{60, 61} NICE DSU acknowledges that EQ-5D is probably not appropriate for assessing specific forms of visual impairment.⁴¹ Existing literature confirms the lack of sensitivity of EQ-

5D in conditions involving visual impairment. EQ-5D was considered to be inferior to disease-specific alternatives (e.g. EQ-5D with vision bolt-on domain in cataracts or general impairment, or IDEEL questionnaire in dry eye).⁶²⁻⁶⁴ TTO is one of the preferred options for obtaining utility values when EQ-5D is not available. As EQ-5D data were not collected in the trial and no published studies reporting utility values for TED patients were identified that could be applied to the model health states, a TTO study was considered the most appropriate option.

To provide additional validation as requested, TTO approaches used and accepted by NICE in submissions for eye related diseases have been identified and considered for their relevance. The submissions considered include ranibizumab (TA155) for the treatment of age-related macular degeneration, aflibercept solution for injection (TA294) for treating wet age-related macular degeneration, voretigene neparvovec (HST11) for treating inherited retinal dystrophies and dexamethasone (TA824) for treating diabetic macular oedema.⁶⁵⁻⁶⁸ It should be noted that while there is some overlap in key symptoms associated with these eye-related conditions – particularly related to vision, there are some key additional symptoms associated with TED that are unique.

In TA155, a Brazier study which derived utility values using TTO direct elicitation was used in the base case. The TTO used health states based on visual acuity in both eyes, a measure of how clearly a person can see objects from given distances. The difference in utility between the lowest and highest visual activity groups for age-related macular degeneration was 0.367, aligning with the 0.3 difference between the ‘Small Proptosis, No Diplopia’ and ‘Large Proptosis, Constant Diplopia’ health states from Smith et al. 2023. The most severe health state reported a utility of 0.497. However, the health states in TA155 were based only on visual acuity, whereas TED patients experience additional negative impacts on QoL beyond visual impairment, which are captured in the Smith et al. 2023 utilities.⁵⁰ TED is unique in that it also includes disfigurement and inflammation from proptosis, orbital pain from inflammation in the eyes, headaches and nausea from constant double vision and irritation and dryness significantly impact a patient's QoL, which has been reflected in the lower utility for the severe health states from Smith et al. 2023, compared with in TA155.⁶¹ In TA294, for treating wet age-related macular degeneration the EAG's

preferred approach was a TTO study by Brown et al. 1999⁶⁹ using health states defined by visual acuity. As detailed above, vision impairment alone does not capture the all the negative impacts to QoL caused by TED.

In HST11 for treating inherited retinal dystrophies, the EAG's preferred assumption for the base case utilities was to use Rentz et al. 2014, a TTO study which assessed utilities for health states defined based on different levels of visual functioning.^{67, 70} The description for the most severe health state, reflects patients that are severely impacted by their vision and unable to perform activities that require being able to see close objects. It is felt that this aligns reasonably with the 'Small Proptosis, Constant Diplopia' state from Smith et al. 2023 given the severity of diplopia symptoms.⁷¹ Rentz et al. reported a utility of 0.343 for this health state, which is similar to the utility of 0.34 from Smith et al. 2023. The utility for the 'Large Proptosis, Constant Diplopia' health state in Smith et al. 2023 is slightly lower (0.3), however, this health state is more severe and also captures additional aspects that have a negative impact on patients' QoL beyond visual impairment.⁷¹ The mildest health state in Rentz et al. 2014 that best aligns with the mildest TED health state, 'Small Proptosis, No Diplopia', has an associated utility of 0.750. This is higher than the utility of 0.6 reported by Smith et al. 2023. Scenario analyses conducted in response to question B13 found that the ICER decreases if a higher utility is assumed for this mildest state, suggesting the current utilities may be underestimating the cost-effectiveness of teprotumumab; further detail is provided in response to question B13.

Additionally, in TA824 for treating diabetic macular oedema,⁶⁸ Czoski-Murray et al. 2009,⁶⁷ a TTO study was used for utilities based on different levels of visual acuity. Utilities ranged from 0.706 for the best visual health state ($\geq 20/40$) to 0.314 for the worst visual acuity health state ($\leq 20/400$). This is similar to the utility range reported in Smith et al. 2023. As detailed above, vision impairment does not capture the all the negative impacts to QoL caused by TED, and as such, utility values would be expected to be lower in TED than for conditions affecting visual acuity alone.

Therefore, while the above examples provide additional validation of the TTO utility values used in the economic model, the examples principally focus on vision loss. As detailed in section B.1.3.1.5 of Document B of the CS, TED is a painful, debilitating

and disfiguring condition that can significantly impact on QoL and physical functioning, psychological and emotional wellbeing, and ability to carry out daily activities including reading, driving and socialising. Some of the symptoms of TED, such as eyelid retraction, proptosis, and strabismus, can cause significant facial disfigurement, challenges in looking straight ahead, and difficulties in closing the eyelids during sleep. The utilities elicited in Smith et al. 2023 are the only suitable source of published utility values and remain the most robust and clinically appropriate to accurately portray all aspects of the disease.

B 13. One of the experts considered the utility of the mildest health state rather low, and suggested that it should be closer to the population average. Please comment on this suggestion.

For those patients who are in the mildest health state, “small proptosis, no diplopia”, the characteristics of the disease include orbital/periocular pain, swelling, and redness. All of which are still associated with a significant quality of life burden and psychosocial distress (Smith et al 2023).⁵⁸ The company has heard from both patients and UK clinicians that the impact of even slight proptosis (up to 3 mm from baseline) can have a significant impact on their perceived appearance, confidence and quality of life.

As discussed in question B 12, Amgen and clinical experts consider the health state utility values to be reflective of patients with active moderate to severe TED, however, in order to facilitate the EAG in their assessment, the following scenario analyses have been explored:

1. Align the HSUV of “small proptosis, no diplopia” to general population norms, while keeping the HSUVs for other health states the same
2. Anchor “small proptosis, no diplopia” to general population norms and apply absolute decrements across the remaining health states
3. Apply a proportionate increase (44%) to all health states such that “small proptosis, no diplopia” is aligned more closely to general population norms

The switch to apply these scenarios is located in ‘Settings G56’

Scenario 1

In Scenario 1, the HSUV for “small proptosis, no diplopia” instead uses age-adjusted utilities using Health Survey for England (HSE) 2014 dataset, as recommended by the DSU.⁷² At cycle 1, patients in the mildest health state are starting with a HSUV of 0.86, decreasing to 0.61 over the modelled time horizon. The HSUVs for all other health states remain as per the base case.

This scenario presents a [REDACTED] in the ICER from [REDACTED] to [REDACTED] for the comparison against IVMP, and [REDACTED] to [REDACTED] for the comparison against IVMP+MMF.

Table 20: Deterministic scenario analysis 1

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Teprotumumab vs comparator) (£/QALY)
Teprotumumab	[REDACTED]	[REDACTED]	-	-	-
IVMP	[REDACTED]	[REDACTED]	[REDACTED]	1.7	[REDACTED]
IVMP+MMF	[REDACTED]	[REDACTED]	[REDACTED]	-1.0	[REDACTED]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Scenario 2

In Scenario 2, the absolute decrements between “small proptosis, no diplopia” and the remaining health states in the company base case setting have been applied to the HSUVs generated for “small proptosis, no diplopia” under Scenario 1. This uses the general population norms for the mildest health state and raises the utility values in the other health states so that the absolute difference between them remains the same as in the base case.

Table 21: Scenario analysis 2 - absolute utility decrements

State	Utility value (base case)	Absolute decrement vs mildest health state	Utility value* (scenario 2)
Small Proptosis, No Diplopia	0.60	-	0.86
Large Proptosis, No Diplopia	0.46	0.14	0.72
Small Proptosis, Intermittent/Inconstant Diplopia	0.52	0.08	0.78

Large Proptosis, Intermittent/Inconstant Diplopia	0.43	0.17	0.69
Small Proptosis, Constant Diplopia	0.34	0.26	0.60
Large Proptosis, Constant Diplopia	0.30	0.30	0.56
Surgery	0.3825	0.22	0.64
Post-surgery	0.5025	0.10	0.76

*At cycle 1

The utility values used over the time horizon for all health states are located in HX7:IF875 in the Markov Trace sheets.

This scenario presents XXXXXX in the ICER.

Table 22: Deterministic scenario analysis 2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Teprotumumab vs comparator) (£/QALY)
Teprotumumab			-	-	-
IVMP				0.8	
IVMP+MMF				0.8	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Scenario 3

In Scenario 3, the proportionate increase between the base case “small proptosis, no diplopia” HSUV of 0.60 and the general population age-adjusted (51.58 years) utility value of 0.86 has been calculated as 44% (Data Store N710). The remaining HSUVs have been inflated by this proportion to provide estimates which align more closely with population-norms.

Table 23: Scenario analysis 3 - absolute utility decrements

State	Utility value (base case)	Utility value* (scenario 3)
Small Proptosis, No Diplopia	0.60	0.86
Large Proptosis, No Diplopia	0.46	0.66
Small Proptosis, Intermittent/Inconstant Diplopia	0.52	0.75
Large Proptosis, Intermittent/Inconstant Diplopia	0.43	0.62
Small Proptosis, Constant Diplopia	0.34	0.49
Large Proptosis, Constant Diplopia	0.30	0.43

Surgery	0.3825	0.55
Post-surgery	0.5025	0.72

*At cycle 1

This scenario presents a [REDACTED] in the ICER from [REDACTED] to [REDACTED] for the comparison against IVMP, and [REDACTED] to XXXX for the comparison against IVMP+MMF.

Table 24: Deterministic scenario analysis 3

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Teprotumumab vs comparator) (£/QALY)
Teprotumumab	[REDACTED]	[REDACTED]	-	-	-
IVMP	[REDACTED]	[REDACTED]	[REDACTED]	1.0	[REDACTED]
IVMP+MMF	[REDACTED]	[REDACTED]	[REDACTED]	1.0	[REDACTED]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B 14. The one vignette provided by Smith in the online appendix appears unusually long, with three pages of descriptors of the health state. Please discuss the impact such long vignette may have on the ability of respondents to perform the TTO exercise, and hence the potential impact on the utility estimates.

During the development of the vignette descriptors, patient interviews (n=6) were conducted to determine the important health-related quality of life (HRQoL) aspects. As such, broader domains of HRQoL, such as limitations on daily activities, (driving and reading; problems of self-image; reduced social activities and interactions with others; inability to work or reduced productivity; anxiety about the future; and coping mechanism and treatments) were included in the health state descriptions to ensure all relevant HRQoL aspects were captured. The description length is also a result of capturing the necessary broader impact on HRQoL from health states defined jointly by two separate endpoints, and in the case of the vignette for the 'Large proptosis, constant diplopia' resulted in the longest description as this is the health state in which patients experience the most symptoms. This approach taken to develop the vignette descriptors follows the recommended approach in the guidance published in 2020 from a NICE-affiliated review group, which states: "Vignettes should include all

important and relevant aspects of health-related quality of life to ensure accuracy and minimise bias.”⁶⁸

The health state descriptions were validated with 3 clinicians experienced in treating active TED and 3 members of a patient advisory council with moderate-to-severe TED to ensure accuracy and relevance.

The full methodology for the vignette study is presented in response to B11 and appendix A. No changes to the health state descriptions were made after the pilot interviews were conducted, concluding that the health state studies conducted were appropriate. The directionality of the TTO scores from the pilot interviews correlated with the most and least severe health states, indicating that the health states descriptions were understood by all participants.^{51-53, 71}

Therefore, given the methodology used to create valid vignette descriptors and validation work, the company believe the vignette descriptors were valid and participants were able to participate in the TTO exercise adequately.

B15. Smith et al. (2023) was performed in the US. Please discuss the generalisability of the results to the UK NHS.

Given that Smith et al. 2023 was conducted in the US, Amgen undertook clinical validation with 4 UK clinical experts to ensure generalisability of the results to the UK setting. The findings from the TTO study were shared, and experts agreed they were reflective of the quality of life seen for moderate-to-severe active TED patients in the UK.

While it is well understood that the valuation method affects the results of vignette studies, the Smith et al. study uses TTO – which is the most commonly used and accepted within the NICE appraisals conducted for England and Wales. As such, the methodology for valuation is expected to have generated utility values that are generalisable and of relevance to England and Wales. Additionally, factors that are most likely to affect population preferences, such as the education and affluence, are similar between the US and the UK, with tertiary education rates of 51% and 58% and GDP per capita of \$78,000 and \$59,000, respectively.^{69, 70} Therefore, this would indicate that the US study is broadly generalisable to the UK. As requested by the

EAG in question B12, further consideration has been provided with respect to further validation of other published utility values, and alternative scenarios varying the utility values are presented in B13.

B16. Please explain why the dimensions and answer categories from the GO-QoL were not used for the TTO exercise? This would have allowed the estimation of utilities for the trial patients.

Although the Graves ophthalmopathy QoL (GO-QoL) questionnaire was measured in the OPTIC trial, the questionnaire has not been mapped previously or correlated with specific TED utility values, as stated in the CS B.3.4.3. However, as described previously in our response to B11 and B14, the methodology for the TTO study was based around using health states informed by patient interviews to ensure that the most important HRQoL implications for TED patients were reflected in the descriptions. This included limitations on daily activities such as driving and reading; problems of self-image; reduced social activities and interactions with others; inability to work or reduced productivity; anxiety about the future; and coping mechanism and treatments.

The HRQoL domains assessed in GO-QoL cover similar limitations on daily living, such as reading, watching TV, engaging in other hobbies, or driving; changes to appearance and associated problems of self-image; and reduced social activities and interactions with others. All of the components captured in the GO-QoL domains were reviewed as part of the TTO vignette health state development.⁵¹ Therefore, although it was not possible to utilise the GO-QoL values from the trial data, the utilities derived from the TTO study are considered to appropriately reflect the HRQoL of each of the model health states.

Probabilistic sensitivity analysis

B17. Priority question. For transition matrices with cell counts of zero, zero is applied in all PSA simulations. Please explore approaches to fully represent uncertainty in cell counts into the PSA.

Transition counts for teprotumumab in the model are varied using the Dirichlet distribution to characterise uncertainty, whereby a gamma-distributed variable is

generated for each transition with shape determined by the observed transition count, and rate and scale equal to 1. As explained in our response to Question B6, due to the rare nature of TED, only a small sample size was available to create the transition probabilities. This resulted in some of the less common transitions in the matrices having a cell count of zero.

Use of an informed prior distribution would help to reduce this uncertainty by providing information on the frequency of transitions observed in clinical practice. The NICE manual notes formal elicitation as an option for informing the associated distribution of a parameter if there is a lack of data.⁴⁸ However, as this approach would require expert elicitation exercises to generate the required data, it would be time intensive and therefore it was unfortunately not feasible to do within the time provided for clarification responses. The company did not consider use of uninformed priors appropriate as due to the small sample size inherent to such a rare disease, any adjustment would have a disproportionately large impact on the transition probabilities, creating bias and a poor fit to the observed data. The NICE manual 2022 notes rare diseases as an area where: "committee may be able to make recommendations accepting a higher degree of uncertainty."⁴⁸

B18. Priority question. For the comparators, transition probabilities calculated by combining teprotumumab cell counts with treatment effects, are then multiplied by 1000 to get cell counts for the comparator arms. These cell counts are then used within the PSA to estimate transition probabilities for each simulation using a Dirichlet distribution. However, multiplying by 1000 leads to very little uncertainty in the resulting transition probabilities for the comparators. Please explore alternative approaches for deriving these numbers in order to reflect the true uncertainty implied by the MAIC.

To reflect the true MAIC uncertainty, the company have updated the model so that the outputs from the MAIC are varied in the PSA according to their standard errors.

With the updated method, the MAIC outputs for the proptosis and diplopia endpoints are varied in the PSA separately using a gamma distribution, based on their respective standard errors from the MAIC. Standard error is used rather than CODA samples as the MAIC was not conducted under a Bayesian framework. The

probabilistic MAIC outputs are then used to derive the comparator transition probabilities used in the PSA. Full calculations for this are presented in the model. IVMP calculations can be found on the following sheets: 'IVMP pseudo IPD', IVMP proptosis TPs', 'IVMP diplopia TPs', 'IVMP combined TPs'; and IVMP + MMF calculations can be found on: 'IVMP+MMF pseudo IPD', 'IVMP+MMF proptosis TPs', 'IVMP+MMF diplopia TPs', 'IVMP+MMF combined TPs'.

PSA results for 10,000 iterations with the updated method are presented in Table 25. Inclusion of the MAIC uncertainty results in a small increase in the probabilistic ICER compared to the base case ICER, of 10.3% and 7.6% for IVMP and IVMP+MMF, respectively. The incremental cost-effectiveness plane is presented in Figure 5 and the cost-effectiveness acceptability curve is presented in Figure 6.

Note that the IPD in the updated model on the 'IVMP pseudo IPD' and 'IVMP+MMF pseudo IPD' sheets have been removed as this is confidential data, however, functionality for all calculations has been left in for transparency.

Table 25: Probabilistic sensitivity analysis results with updated MAIC uncertainty

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Teprotumumab	██████	██████	-	-	-
IVMP	██████	██████	██████	0.7	██████
IVMP+MMF	██████	██████	██████	0.8	██████

Abbreviations: ICER – incremental cost effectiveness ratio; IVMP – Intravenous methylprednisolone; MMF – Mycophenolate mofetil; MAIC – matching adjusted indirect comparison; QALY – quality adjusted life year.

Figure 5: Incremental cost-effectiveness plane

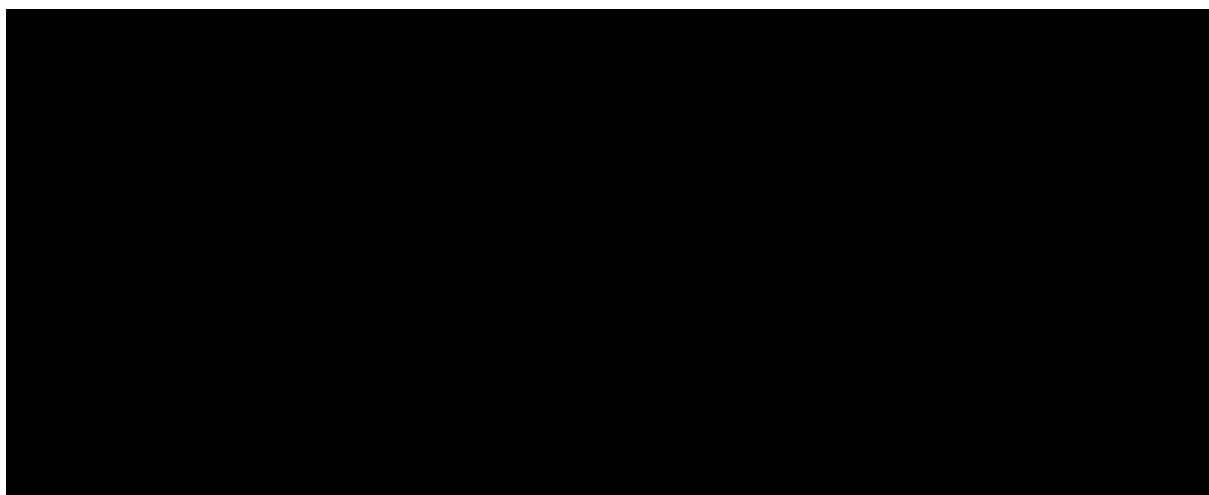
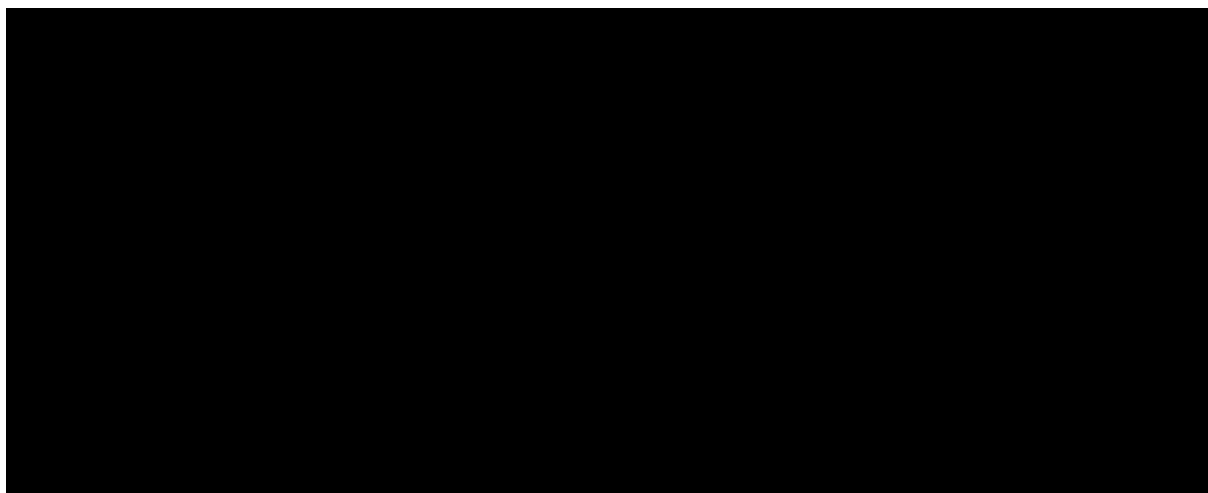


Figure 6: Cost-effectiveness acceptability curve



Abbreviations: IVMP – Intravenous methylprednisolone; MMF – Mycophenolate mofetil.

B19. Priority question. Since cell counts for the comparators are hard coded in the model it is unclear whether and how uncertainty from the treatment effect estimates derived from the MAIC are propagated through the economic model. Please provide a full description of these methods including calculations.

As stated in response to question B3, the model only included mean treatment effect estimates, therefore uncertainty from the MAIC was not accounted for. However, in response to question B18, the company have updated the model so that the outputs from the MAIC are varied in the PSA according to their standard errors to reflect uncertainty. Full calculations for this are presented in the model and further detail on the method is provided in response to question B18.

Discontinuation, compliance and flare

B 20. According to B.3.3.3.1, patients who discontinue treatment remain in the health state they were in when they discontinued treatment. Please explain

why patients who discontinued treatment are not more likely to experience worsening symptoms.

This has been incorrectly described in CS B.3.3.3.1. Instead of “Patients who discontinue treatment no longer accrue primary treatment costs, adverse event costs, or resource use costs, and *remain in the health state they were in* when they discontinue treatment” the text should say “Patients who discontinue treatment no longer accrue primary treatment costs, adverse event costs, or resource use costs, and *remain on the same transition probabilities they were on* when they discontinue treatment”. This means that patients receiving teprotumumab discontinue and will continue to transition with the same transition matrices as teprotumumab treated patients who have not discontinued, up until cycle 4 (week 24) when the remain in state assumption is applied. Therefore, discontinued patients may move around health states after discontinuation.

As discussed in response to question B9, remain in state was considered the most plausible option after 24 weeks based on the data available, so all discontinued patients remain in the state they are in at cycle 4, which is the same assumption as for patients who did not discontinue. Alternative transitions were not applied to discontinued patients as no data from the trial or published literature were available to inform this.

We consider the assumption that discontinued patients remain on the same transition probability matrices as non-discontinued patients to be appropriate since all-cause discontinuation was used to estimate the discontinuation rate in the model, which also includes discontinuation due to adverse events and other reasons not related to lack of therapeutic benefit. It is clinically plausible that patients discontinuing for reasons other than lack of therapeutic benefit could continue to receive a treatment benefit after discontinuation, in line with clinician insights and OPTIC, showing treatment effect from 6 weeks. Patients that do discontinue due to lack of therapeutic benefit are likely non-responders and therefore already in the more severe health states. As the maximum treatment duration in the model is only 24 weeks and the discontinuation rate per cycle was low for all treatments (2.18% for teprotumumab, 1.34% for IVMP, and 1.29% for IVMP+MMF), the total number of

discontinued patients is low and therefore unlikely to have a notable impact on the overall results.

B 21. In section B3.3.3.3 it is noted that disease flares are not included within the economic model. However, they are parameterised (cell AD35 of Clinical Inputs tab). Please explain why these analyses have been included in the model and not reported in the company submission. And explain the implications of these findings for the model validity and study conclusions.

While the model was in development, functionality for a simplified approach for modelling disease flare had been explored but determined to not be appropriate or clinically valid. As such, further details of this approach had not been detailed in the submission.

Under the exploratory analysis, patients that experience a flare move to transition with the average of the placebo arm transition matrices observed in the pooled Phase 2 and OPTIC trials. However, this approach was considered inappropriate for modelling flare for several reasons. Firstly, the placebo efficacy would not accurately reflect the real-world trajectory of flared patients, as in clinical practice these patients would go on to receive a second line of therapy and receive the efficacy and costs associated with that treatment. However, no data on second line treatment efficacy in flared patients, or data on how treatment efficacy might differ based on initial therapy, were available to inform these transitions. Secondly, as noted in the CS, Section B.3.3.3.3, wider evidence around the clinical implications of the flare itself, and treatment of flare, is lacking. Therefore, disease flares are not captured in the model to reduce the level of uncertainty and complexity within the economic analysis. Furthermore, there is no strong evidence to suggest teprotumumab patients have a difference in flare rate compared to either IVMP or IVMP+MMF.

Costs

B 22. Patients are assumed to remain in the surgery state for 30 cycles but the cost of surgery, which is stated to include follow-up surgeries, is given as a

one-off cost (Section B.3.5.1.3). Were costs over the 30 cycle period calculated as present value at [REDACTED] (i.e. discounted)?

The cost of surgery beyond cycle 30 was not discounted to calculate present value costs at [REDACTED], which may have led to the slight overestimation of its cost.

Discounting scenarios were tested, with a discounted surgery price using the standard discount rate of 3.5%, in line with NICE reference case.⁵⁹ The cost was discounted to its present value at cycle 41, which equates to halfway through the surgery follow-up period and to its present value at cycle 56, equating to the end of the surgery follow-up period (given the surgery follow-up period is 30 cycles and patients enter surgery in [REDACTED]). The two different approaches have been tested, to account for subsequent surgeries being able to be received at any timepoint over the surgery follow-up period. Discounting in the middle of the follow-up period is the average timepoint for receiving all surgeries and most represents the true value of surgery cost. Discounting to the end of the follow-up period is to demonstrate the limited sensitivity of surgery cost on the models' outcomes. Discounting surgery cost to its present value halfway through the surgery follow-up period, cycle 41, led to an ICER per QALY for IVMP of [REDACTED], a 0.8% increase from base case, and for IVMP+MMF per QALY of [REDACTED], an 0.3% increase from base case. Discounting to the end of the surgery follow-up period, cycle 56, led to an ICER for IVMP of [REDACTED], a 1.0% increase from base case, and for IVMP+MMF of [REDACTED], an increase on 0.4% from base case.

B 23. In Section B.3.5.1.3 it is stated that “The average number of surgeries that a patient receives by health state and treatment arm was informed by UK clinicians (Table 53)” with more surgeries required for people receiving IVMP or IVMP+MFF than teprotumumab conditional on health state.

a) Please reflect on the validity of the assumption that initial treatment in the first 4 cycles drives the number of surgeries after 26 cycles, rather than the severity of TED at 26 weeks.

As part of clinical expert interviews, clinicians (n=2) validated that the number of surgeries received by patients will differ by treatment arm. Additionally, clear consensus from clinicians was only collected for the average number of surgeries by treatment arm and surgery type. Thus, the average number of surgeries was

assumed to be driven by treatment arm and surgery type (orbital decompression, strabismus or eyelid surgery) in the base case. The values used in the model are shown in Table 26 below.⁴⁹

Clinicians were also questioned on the rates of surgery by health state. All 4 clinicians agreed that around 37.5% patients from each health state are eligible for surgery but two physicians added that the percentage of eligible patients would be higher. The proportions of patients eligible for surgery and receiving surgery therefore already captures the differences in rates of surgery between health states, with the two mildest health states (no diplopia, small proptosis, and intermittent/inconstant diplopia, small proptosis) applying the smallest proportion receiving surgery, due to the mild nature of the disease (5%).

Table 26: Average number of surgeries for patients that receive surgery

Treatment arm	Surgery type	Average number of surgeries used for each health state					
		SPND	LPND	SPID	LPID	SPCD	LPCD
Teprotumumab	Orbital decompression	0.66	0.66	0.66	0.66	0.66	0.66
	Strabismus	0.88	0.88	0.88	0.88	0.88	0.88
	Eyelid surgery	1.00	1.00	1.00	1.00	1.00	1.00
IVMP	Orbital decompression	1.06	1.06	1.06	1.06	1.06	1.06
	Strabismus	1.63	1.63	1.63	1.63	1.63	1.63
	Eyelid surgery	1.50	1.50	1.50	1.50	1.50	1.50
IVMP + MMF	Orbital decompression	1.06	1.06	1.06	1.06	1.06	1.06
	Strabismus	1.63	1.63	1.63	1.63	1.63	1.63
	Eyelid surgery	1.50	1.50	1.50	1.50	1.50	1.50

Abbreviations: IVMP - Intravenous methylprednisolone; LPCD – Large proptosis, constant diplopia; LPID – Large proptosis, intermittent/inconstant diplopia; LPND – Large proptosis, no diplopia; MMF - Mycophenolate mofetil; SPCD – Small proptosis, constant diplopia; SPID – Small proptosis, intermittent/inconstant diplopia; SPND – Small proptosis, no diplopia.

An additional scenario has been conducted, in which the average number of surgeries was dependent on disease severity, rather than treatment arm. Please see question 23 (c) for details of the additional scenario. In summary, this demonstrated a minimal impact on the ICER of <2% impact compared to the base-case ICER for both IVMP and IVMP+MMF.

- b) Please justify why the company opted to make the number of operations depend on initial treatment, rather than the health state, given that only 2 of the 4 experts suggested this.

Please see question 23 (A) for response.

- c) Please provide as a scenario the number of operations being health state dependent instead of treatment dependent.

The company has included an additional scenario where the average number of surgeries per patient was dependent on surgery type and disease severity as opposed to treatment arm.

As data were not available for the number of surgeries being health state dependent, the scenario uses the clinically validated values for IVMP that were originally used for the number of each type of surgery, for all treatment arms. The values for each surgery were then varied by $\pm 20\%$ for the two mildest and two most severe health states. The resulting average number of surgeries per patient are presented below in Table 27.

Table 27: Surgery by type, per health state

Surgeries per patient by health state	Orbital decompression	Strabismus	Eyelid surgery
Small Proptosis, No Diplopia	0.85	1.30	1.20
Large Proptosis, No Diplopia	1.06	1.63	1.50
Small Proptosis, Intermittent/Inconstant Diplopia	0.85	1.30	1.20
Large Proptosis, Intermittent/Inconstant Diplopia	1.06	1.63	1.50
Small Proptosis, Constant Diplopia	1.28	1.95	1.80
Large Proptosis, Constant Diplopia	1.28	1.95	1.80

The scenario generated an ICER per QALY of £[REDACTED] for IVMP, an increase of 1.4% from base-case, and £[REDACTED] for IVMP+MMF, a 1.6% decrease from base-case. Additionally, a scenario was explored where the average number of surgeries was dependent only on the surgery type. The scenario used the average number of surgeries for the middle two health states, 1.06 for orbital decompression, 1.63 for strabismus and 1.50 for eyelid surgery. This scenario generated an ICER of £[REDACTED]

for IVMP, an increase on 1.7% from base-case, and £[REDACTED] for IVMP+MMF, a 1.3% decrease from base-case. The impact on the ICER between the scenario ICERs demonstrate the limited sensitivity to variations in the number of surgeries per patient within the model.

B 24. In Table 53 clarify whether the numbers reported are conditional on moving to the surgical state.

The numbers reported in Table 53 were collected during clinical validation and reflect the average number of surgeries required per patient by treatment arm. The company confirms that the average number of surgeries required is for patients in the surgery health state only and therefore is conditional on moving to the surgery health state.

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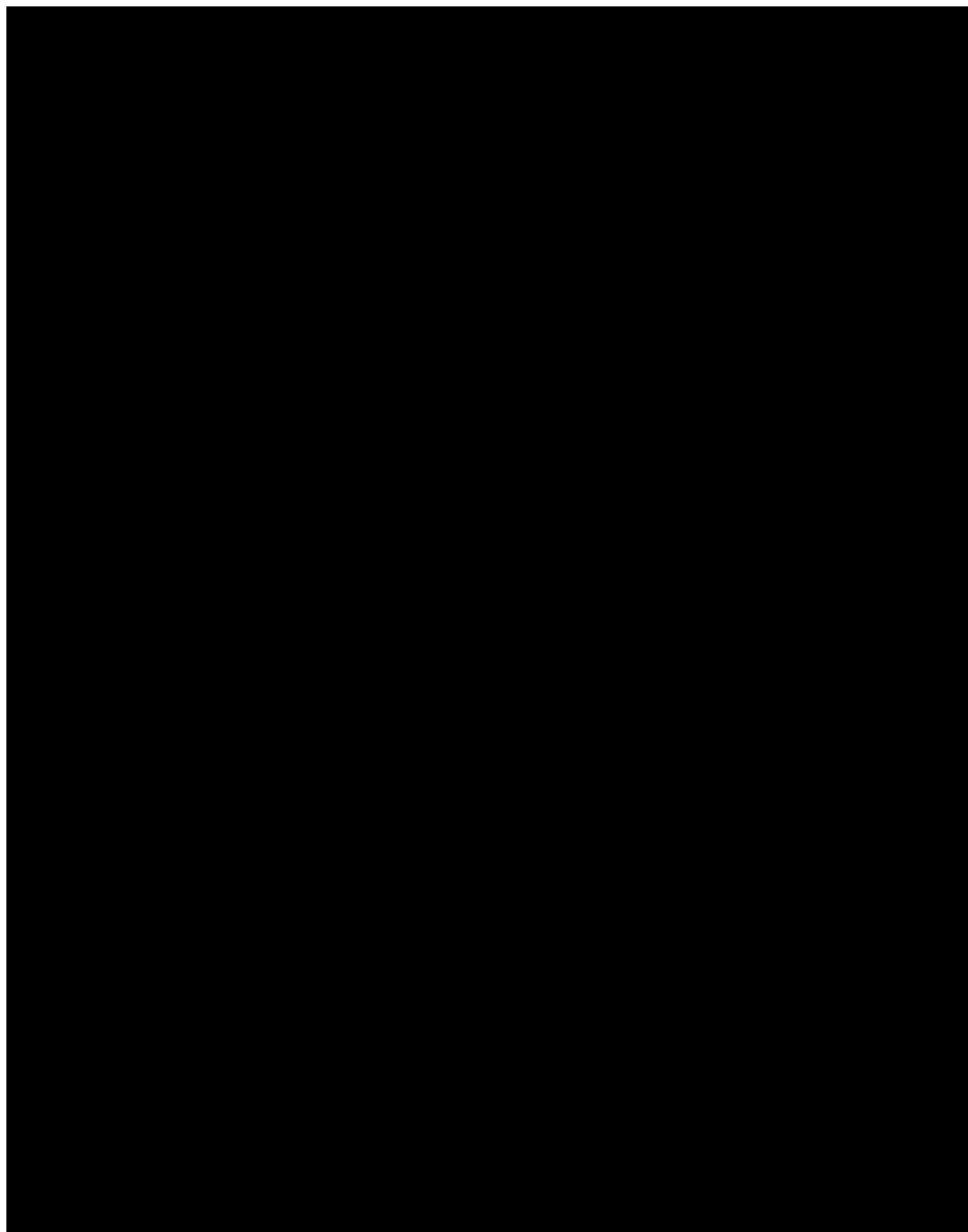
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Appendices

Appendix A

Vignette description



Single Technology Appraisal
Teprotumumab for treating thyroid eye disease [ID6432]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	British Thyroid Foundation
3. Job title or position	CEO
4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Thyroid Foundation (BTF) was established in 1991 and is registered as a charity in England and Wales (No: 1006391) and Scotland (SC046037). The organisation provides information and support to people with thyroid disorders, and helps their families and carers, and the wider population to understand the condition. The BTF is a membership organisation and currently has approximately 3,210 members and 3,300 supporters who we are regularly in touch with. Patients receive peer support through our volunteer-run telephone helpline, as well as through the resources provided on the BTF website (http://www.btf-thyroid.org/) and online support forums. The majority of the BTF's funding comes from membership subscriptions, donations, community fundraising and grants from Trusts and Foundations. No pharmaceutical companies are corporate members of the BTF. Within the last two years the BTF received small grants from two pharmaceutical companies, (argenx and Egetis) which have been used to support the work we do to raise awareness and support for patients with Thyroid Eye Disease.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for	No

evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Since it was founded in 1991 the BTF has been supporting people living with TED. We run a telephone helpline, a 'Medical Query Answering Service' and several online forums which help us understand many of the experiences and concerns faced by people living with this disease. In addition, we are a membership organisation so have supported the needs and tailored our services for patients with TED for nearly 35 years. To prepare for this consultation we posted a survey on the BTF website and shared it with members and supporters and through social media. We have had over 56 very detailed responses from people of all ages that reveal the lived experiences of people living with this disease and the issues that are important to them. 91% of the responses were from women, 76% were over 51 years old.

Living with the condition

6. What is it like to live with thyroid eye disease? What do carers experience when caring for someone with the condition?	The impact of TED varies between patients. Some people suffer only from mild symptoms which may not have a significant impact on their daily life. However, the vast majority of the people we hear from, including the respondents to our survey, report that the diagnosis for them has been life-changing and affects every aspect of it. Physical symptoms The commonly reported physical symptoms are as follows: 1. Pain (sometimes severe) in the eyes and around the eyes 2. Red, dry, gritty or watery eyes 3. Retracted eyelids and protruding eyeballs causing facial disfigurement 4. Sight problems, caused by double and blurred vision 5. Regular and recurrent eye infections 6. Sensitivity to bright lights 7. Swollen and puffy face Patients with TED will usually also be managing the symptoms of Graves' disease (GD) which can be difficult to control. The symptoms of GD include: 1. Heart palpitations and tremors 2. Swollen and painful legs due to Graves' dermopathy 3. Anxiety and nervousness <i>"TED for me has been awful. The squeezing pain, throbbing headaches, your eyes are constantly bulging, eyelids retracted and your eyes are constantly bright red and feel you have Bournemouth beach rubbing around inside your eyes and in the eye socket. It truly is a never-ending symptom that ruins your life. You can't read, you can't really go out because it makes you feel hideous and ugly, plus you are in constant pain."</i> <i>"It impacts all areas of life, from intolerant lights in all forms to my inability to read for pleasure now. My partner has to cope with dimmed lighting all the time in the house. I often go to bed excessively early just to be able to avoid the discomfort with sleep."</i> <i>"Double vision affects so many everyday things like walking down steps, watching TV, reading, computer reading, and many more. The stabbing pains from time to time, dry eyes and general aches are difficult to explain."</i> <i>"Even though I use lubricating gels, my eyes are watery all morning which makes it difficult for me to use my mobile to do health and care arrangements."</i>

Mobility and independence

The symptoms of TED can limit a person's **mobility and independence**. Vision changes impact their ability to perform daily tasks. Some told us they had to give up their driving licence as they no longer felt safe to drive, or they had to rely on friends and family members to drive them around. Double vision affects many everyday activities like walking down steps, watching TV, reading, computer work, supermarket shopping (for example the rapid eye movements necessary for looking up and down and around the items on the shelves) and travelling on public transport. It is not uncommon for people with TED to have falls and suffer fractures due to lack of depth awareness and double vision. Young people wrote that they struggled to see the board at school and they had to give up sports activities.

"The biggest impact for me is not driving. As I live alone and I cannot easily get to see family and friends on public transport, I am having to rely on others for lifts. I feel trapped and more socially isolated and dependent on others when I've been independent all my life. Fortunately, I've retired as it would have been difficult for transport to work. Also, I have two dogs and the bus service doesn't accommodate this so I feel very trapped in my local vicinity."

"I had TED when I started Graves' disease when I was 18. This impacted me massively. I had to take two months off work initially due to the thyroid. My A-levels were messed up I just had to accept my life was going to be different and there was little I could do until I was about 34 when I had my lids lowered which made my eyes look less prominent. I also play rugby and my eyes are much more exposed to injury unfortunately as I have no way of covering them. I have lost many contact lenses which are stuck to people's legs in the scrum."

Psychological impact

One of the most devastating impacts of TED is the **psychological impact** that the disease can have on people's wellbeing. Many described embarrassment about the way they looked and anxiety about what people may think of them. Reduced social confidence and activity in turn impacts on their self-esteem and confidence as they became more isolated. The course of the symptoms can come and go but even those for whom the burden of the disease had burnt out reported that they lived with a fear of the symptoms returning and worried about what the future may bring.

"It's had a big negative impact, it's been suggested by my named nurse that talking therapy would help me come to terms with everything. I feel like I might unravel if I had to unpack everything. I try to be positive but catching a sideways glance of your reflection just hits home how damaging TED is. I could be having a great day but a glimpse of my reflection just brings me down. I have a hard stare so I feel people pre-judge me based on the disfigurement. I feel sometimes I have to be upbeat and cheerful for other people."

"I have Graves' disease, am now 87, and am just having another positive antibody phase. My eyes are no longer swollen but I have become fearful of living through it all again."

"When I developed TED I hid myself away I didn't want to socialise as the amount of stares and horrible comments that were made towards me made me feel suicidal."

"I have stopped going to social functions as I see two of everyone and I'm not sure where my eyes are looking."

"The physical appearance of one eye being more protruded than the other ate into my confidence."

"I avoid going to new places or meeting new people because of how I now look. My marriage of 20 years ended partly as a result of Graves' disease."

Work and family life

TED can significantly impact people's ability to work and their productivity. Computer work, bright lighting and reading tasks can be challenging, particularly in the morning when it can take a couple of hours for eyes to stop watering and feel 'settled'. Several described how they lost their job or had to stop working as they were no longer able to carry out their role. Although some employers had been supportive and made reasonable adjustments for their staff, people wrote that they felt 'embarrassed' by their appearance at work and felt they needed to explain their changed appearance to colleagues and clients. People who undertook voluntary work reported they had to stop doing it as they couldn't cope with the fluorescent lighting at their place of work. Those with caring responsibilities are also impacted. Older women described how their vision problems made it more challenging to look after their elderly parents, younger mothers said they felt guilty they couldn't be the mum they wanted to be.

"My family are very supportive but my mum always asks about my health, I feel I'm defined by TED. It's been a lot for my kids, they are young adults but due to related conditions such as Graves' dermopathy & lymphedema it's had a big impact on them seeing me ill."

"I've recently met my daughter's 7-year-old stepson and I've been worried he'd think I look cross because of mild proptosis."

Changed appearance

All but one of the respondents to our survey were women and this reflects the demographic that is affected with thyroid disease. Even after treatments and surgeries many described how their appearance was entirely changed by their TED diagnosis.

"I feel I always have to explain my weird eyes and serial killer stare."

	<i>"I feel embarrassed at work, needing to explain I'm not on drugs, but sick."</i> <i>"TED has destroyed my life I have been deeply affected by this disease physically I have had some surgeries to improve the effects of TED but I will never look the same."</i> Economic impact Following the original diagnosis patients are usually advised to wait until the active stage of the disease is burnt out before undergoing major treatments. It can be expensive to have to pay for the many treatments and optical equipment that are prescribed and recommended. In addition, the cost of transport to and time taken for multiple medical appointments can take its toll; those who live in rural areas describe sparse availability of public transport. Others spoke of losing their job or being made redundant as they could no longer perform their work adequately. <i>"My eye prescription on my glasses changes constantly which costs a lot of money to get lenses changed."</i> <i>"As I pay for prescriptions the cost of the treatment was high as I was having steroids and the additional medication that comes with it. Drops for pressure, drops for dryness, ointments, supplements to help. These costs added to the stress of the condition."</i> Impact on carers The impact on those who are caring for people with TED can be significant. There can be a greater financial responsibility as the patient can no longer work. In addition, they are likely to have a greater burden as a result of the person suffering vision changes, being less mobile and independent physically, socially and emotionally. This can cause a significant change in the relationship and be a cause of stress and anxiety for each party. <i>"As a family member, I have had to take on additional responsibilities to support my loved one, including helping with daily tasks and providing emotional support."</i>

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is a general feeling that not enough medical professionals are aware of TED and how to treat patients with the condition. We know that a common problem is that symptoms are not picked up early enough, therefore there are late referrals to specialists. Having a timely diagnosis and early treatment is essential so patients worry that the delays and long waiting times will impact adversely on their likely outcomes. There is an urgent need for more experienced specialists and specialist eye clinics throughout the UK. Some report that they had good care but most felt that current treatment and care is a 'postcode lottery'. The psychological impact of the disease is not well understood and there is limited availability to help patients to manage the enormity of these life changing symptoms. The comparator treatments can be beneficial for some patients but many people describe symptoms very challenging symptoms that are ongoing in spite of treatments. <i>"Not getting correct treatment or quick appointments was the most stressful part. I took myself to an optician who referred me as my endocrinologist hadn't told me my chances of developing TED were high, or even a possibility. Trying to get a diagnosis etc has been a struggle and stressful"</i> <i>"It's difficult to access, and there appears to be no joined-up approach. I had symptoms of TED for 14 months before seeing an Oculoplastic Consultant. I had to go through the corneal clinic first where the consultant had no real specialism in TED."</i>
8. Is there an unmet need for patients with this condition?	Yes. Not all patients are referred to the correct specialist care (i.e. ophthalmology and endocrinology) and those who are, often do not get the specialist treatment they need in a timely manner. Many patients get in touch with the BTF for guidance about the referral pathways. Double vision is often residual even after surgical treatment. The change in appearance that occurs is lasting and people have to come to terms with looking different to the people they were before being diagnosed with TED.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients who were aware of the new treatment welcomed the possibility that it could provide more effective and targeted relief for TED symptoms, potentially improving quality of life and reducing the need for ongoing medical interventions. They feel let down that there have been so few effective options to date and therefore are pleased that at least for some patients this may be changing.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Most respondents were worried about what the side effects of the new treatment may be. Several had heard that it can cause deafness. They anticipated that it would be costly and therefore not all patients would be able to access it easily. It will be essential that the most appropriate patients are targeted in order that the maximum benefit is achieved. Another concern is whether the longed-for benefits would last beyond an initial period of weeks or months. And, if did not, would patients have access to additional, follow-up treatments. <i>“After living with this disease for the past four years, I can honestly say no disadvantages come to mind, when all we crave here in the UK, is some help with getting rid of it.”</i>

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are mostly worried that patients won't be diagnosed early enough or referred to specialist clinics in time to be offered this new treatment. In some large centres there are specialist eye clinics but too many patients are never referred to them and are therefore at a disadvantage. Patients who live locations are possibly doubly disadvantaged as they may not have easy access to a specialist eye centre to enable an early diagnosis and their vision symptoms mean they have lost some of their independence to travel to healthcare appointments. We would welcome an increase in training for all HCPs who may come across this disease (dispensing chemists, opticians, GPs, eye and thyroid specialists) so that patients are more likely to be referred to specialist centres and to access the best available treatment and care. Since TED disproportionately affects women consideration should be had to make sure women, including those with caring responsibilities, can easily access this treatment. Patients, not just older ones, commonly have reduced mobility and independence so their transport needs should be taken into account. The social confidence will probably be diminished and they may be isolated.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The physical symptoms of the disease can greatly impact on patients' quality of life, their finances, their independence and their ability to engage socially and economically. • The psychological burden of this disease can be life-changing and should be better recognised and supported. • Improved education and understanding about TED for professionals, patients and employers is essential: it will lead to earlier referrals and better outcomes. • More specialist thyroid eye disease clinics would ensure higher standards of joined-up care and better communication between patients and professionals.

Thank you for your time.

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Single Technology Appraisal
Teprotumumab for treating thyroid eye disease [ID6432]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	British OculoPlastic Surgery Society (BOPSS)
3. Job title or position	Consultant Ophthalmologist and Oculoplastic Surgeon
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	BOPSS is a group of individual members who are all ophthalmologists with a subspecialist interest in oculoplastics (UK and Ireland). Our purpose is to advance education, research and quality of care in oculoplastic surgery (plastic, reconstructive, and aesthetic surgery of the eyelids, the surrounding facial areas, orbits and lacrimal system). Founded in 2000. Charitable organisation funded by members' subscriptions. <i>*Please note that views of our members will overlap largely with those of the Royal College of Ophthalmologists (see separate professional organisation submission for RCOphth) and this has been highlighted in each relevant section. Therefore only additional points are submitted in this document for review*</i>
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No funding from Amgen Limited or comparator products

**5c. Do you have any
direct or indirect links
with, or funding from,
the tobacco industry?**

No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve symptoms, to cure the condition, or prevent worsening or disability.)	<i>See RCOphth Submission</i> Thyroid Eye Disease (TED) is an autoimmune condition, most commonly associated with Graves' disease, which causes inflammation and swelling around the eyes. Symptoms are varied but include painful eyes, swelling, bulging eyes, redness, double vision and loss of vision. Even mild disease can affect visual performance, appearance and psychosocial functioning and severe disease can cause irreversible blindness if untreated. Standard treatment: Treatments for thyroid eye disease have historically aimed to slow/stop progression of disease in order to avoid devastating sight-threatening, disabling or disfiguring consequences. There is no known cure. Surgery is often employed once the disease has been controlled to mitigate/improve the consequences of the disease once stable (usually after 12-18 months of stability). General treatment aims: The ideal treatment for thyroid eye disease would be an agent that could be administered at an early stage, with minimal side-effects either to prevent the disease from occurring or to stop the disease from progressing, but that could also be administered to patients who present later to 'reverse'/improve the physical consequences of swelling/inflammation around the eyes, such that surgery could be minimised or not needed at all. This treatment should be linked to improved quality of life for TED patients. Aims of Teprotumumab Treatment: Teprotumumab (along with other novel agents) was one of the first treatments to show improvement in some aspects of thyroid eye disease (namely proptosis (protruding eyes)). It has also been shown (like other standard treatments – see below) to halt the progression of moderate TED compared to the natural history of the disease, and decrease symptoms such as double vision, pain, redness and swelling.

7. What do you consider a clinically significant treatment response? (For example, a reduction in certain symptoms, or a reduction in disease activity by a certain amount.)	<i>See RCOphth Submission</i> Given the varied symptoms and signs that TED can cause, a clinically significant treatment response can be different in different patients. In all patients, we would look for: -Improvement in quality of life for patients as measured by standardised, specific quality of life tools such as the Graves Orbitopathy Quality of Life Score -Sustained improvement (over a minimum of 6-12 months, but ideally long-term) in symptoms of pain, double vision, swelling, redness, visual loss, visible difference, psychosocial wellbeing and functioning as reported by the patient In addition, a clinically significant treatment response may include: -Stability/Improvement in measurable proptosis (improvement by at least 2mm) -Stability/Improvement in visible signs of thyroid eye disease as evidenced by photographs -Stability/Improvement in visual acuity by at least one Snellen line -Stability/Improvement in range of eye movements by at least 5 degrees in any direction Any one or combination of these would be considered a clinically significant treatment response. In patients with active (changing) disease, the response to treatment should be equal to or more than that which would be expected from current standard treatment (intravenous steroids, immunosuppression or radiotherapy)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	<i>See RCOphth Submission</i> Unmet need for patients: Yes. Current standard treatments (intravenous steroids, immunomodulatory agents, radiotherapy and surgery) are limited in their efficacy, onset of action, duration and/or have a significant side-effect burden for patients. Patients often endure many years of treatment during which time they are unable to function. Despite best available treatment, many patients are left irreversible and persistent consequences. Unmet need for healthcare professionals: Yes. Clinicians are faced with treatments that often have a significant side-effect profile therefore presenting a significant treatment burden in terms of monitoring and managing patients. This puts additional pressure on outpatient follow-up appointments in an already stretched NHS system. With individual patients often needing multiple episodes of rehabilitative surgery, over long periods of time, this also puts pressure on already stretched NHS surgical waiting lists. There is a clear need for targeted effective treatments, with improved safety profiles and more durable responses to reduce the burden on patients, clinicians and NHS services

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	<i>See RCOphth submission</i> Once a patient has reached a multidisciplinary clinic specialising in the treatment of TED, treatment would depend on the phase (activity) and severity of the disease. Mild disease may be observed and treated with conservative methods (symptom relief) with control of risk factors (e.g. smoking, endocrine control) Moderate disease would be treated with the above AND intravenous steroids and/or immunosuppression or radiotherapy Severe sight-threatening disease would be treated with the above and immediate surgery (eg orbital decompression, eyelid closure procedures) to reduce the immediate threat to vision or relieve pressure around the eyes The ability of patients to access specialised multidisciplinary services has however been shown to be variable throughout the UK. A significant amount of work has been done since the Amsterdam Declaration to improve access to specialist services and has been helped by raising awareness through various consensus statements, guidelines and stakeholder group collaborations (EUGOGO – European Group On Graves Orbitopathy – 2021 guidelines, TEAMeD-5, ETA/ATA consensus statements 2022, ITEDS). TED therefore has a strong foundation for multidisciplinary working in the NHS and a vision for standardised equitable treatment, but there is a lack of access to targeted treatment in order to provide best possible care.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	<i>See RCOphth submission</i> The EUGOGO 2021 Guidelines were developed by specialist endocrinologists and ophthalmologists from the UK and Europe and therefore are applicable to the UK population
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	<i>See RCOphth submission</i> Although there exists significant variation in practice across the UK, largely due to limitations of standard treatment, specialists in TED concur that early access to specialised clinics with ophthalmic and endocrine input is fundamental to the successful treatment of the condition. There is also agreement that cessation of smoking

experience is from outside England.)	and stable control of thyroid function are key factors in management. Many BOPSS members have experience of treating TED both in the UK and abroad.
9c. What impact would the technology have on the current pathway of care?	<i>See RCOphth Submission</i>
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	<i>See RCOphth Submission</i> As with current care, teprotumumab will be used on a case-by-case basis individualized to the patient. It will be a particularly useful option where the side-effects of steroid treatment or current immunosuppression modalities are of clinical concern. The side-effects of these treatments should be weighed against the side-effect profile of Teprotumumab (principally hearing impairment and hyperglycaemia, as well as menstrual irregularity).
10a. How does healthcare resource use differ between the technology and current care?	<i>See RCOphth submission</i>
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Teprotumumab should be used in specialist clinics with the multidisciplinary team to administer, monitor and manage any complications of treatment or disease.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	<i>See RCOphth submission</i> Investment will also be required to support the additional cost of the drug itself
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Teprotumumab would be expected to help reduce proptosis and symptoms in the acute phase of the disease, potentially reducing the need for surgery, compared to standard treatment.
11a. Do you expect the technology to increase	<i>See RCOphth submission</i>

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Teprotumumab has been shown to reduce proptosis in some patients which is a common cause of disfigurement and psychosocial distress.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	<i>See RCOphth Submission</i>

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	<i>See RCOphth Submission</i>
14. Will any rules (informal or formal) be used to start or stop treatment with the	<i>See RCOphth Submission</i>

technology? Do these include any additional testing?	It is likely that teprotumumab will be use by specialist clinicians as one of the options for a 2 nd line agent as per EUGOGO guidelines and tailored to the individual patient.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	<i>See RCOphth submission</i>
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	<i>See RCOphth submission</i>
16a. Is the technology a 'step-change' in the management of the condition?	Yes in terms of improvement in disfigurement and visual function – please see point 26
16b. Does the use of the technology address any particular unmet need of the patient population?	<i>See RCOphth submission</i> Please see point 8

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	<i>See RCOphth submission</i>

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	<i>See RCOphth submission</i>
18a. If not, how could the results be extrapolated to the UK setting?	<i>See RCOphth submission</i>
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	<i>See RCOphth submission</i> As per point 7, improved Quality of Life is the most important outcome measure (measured in trials). Durable long-term responses are also key outcomes. Trials on teprotumumab have not currently recorded strict long-term follow-up for all patients. However few trials of standard care have recorded this either.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	<i>See RCOphth submission</i>

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	<i>See RCOphth submission</i> The importance of monitoring for hearing abnormalities has been well documented and from anecdotal experience is a significant one for patients who may already have an existing sensory (sight) problem.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	<i>See RCOphth submission</i>
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE interventional procedures guidance [IPG148]?	<i>See RCOphth submission</i> There are currently ongoing trials looking at biosimilars for thyroid eye disease, since the tocilizumab and teprotumumab trials, and new therapies are likely to emerge in the foreseeable future.
21. How do data on real-world experience compare with the trial data?	<i>See RCOphth submission</i>

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	See RCOphth submission Patients from a lower socio-economic group/area may still have difficulty accessing treatments requiring multiple infusions/hospital visits.
22b. Consider whether these issues are different from issues with current care and why.	<i>See RCOphth submission</i> Currently, standard treatment of intravenous steroid may also require multiple hospital visits however it is easier to administer locally given familiarity of all clinicians with steroid management.

Topic-specific questions

23. If recommended, at what line of treatment would the technology be used? (For example, first line, second line, or both.) What are the key comparators at this line of treatment. Would this be in primary or secondary care?	<i>See RCOphth submission</i>
24. Different population subgroups have been identified and may be explored if evidence allows (subgroups based on disease activity, duration of active symptoms, and severity of proptosis, diplopia and inflammation). What line of treatment would the technology be used at for these subgroups? Would it differ for different subgroups?	<i>See RCOphth submission</i>
25. What measures are used to determine disease activity and severity of thyroid eye disease in UK clinical practice?	<i>See RCOphth submission</i>

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Thyroid Eye Disease is a devastating condition which can not only be blinding but have a profound psycho-socio-economic impact on patients and society • Current standard treatments (steroids, immunosuppression, surgery, radiotherapy) are limited to stabilising the condition and when used, often have significant side-effects, therefore creating a significant treatment burden for patient and clinicians as well as leaving a clear unmet need for more specific, targeted treatment. • Newer agents such are available for patients which have the advantage of fewer side-effects and the opportunity to improve the underlying disease, and marks the first time in the history of the condition that this has been possible. • Teprotumumab was shown in clinical trials to be effective in improving thyroid eye disease with a more acceptable side-effect profile than current standard treatment and the UK is currently 'behind the international curve' in patients' ability to access it • BOPSS members would welcome this appraisal to potentially allow access to Teprotumumab for patients with thyroid eye disease as part of NHS treatment, with the option to extend or revise recommendations in anticipation of other trial treatments currently showing promise, to pave the way for more equitable, cost-effective, 'next generation' step-change treatments for this condition

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**Single Technology Appraisal
Teprotumumab for treating thyroid eye disease [ID6432]
Professional organisation submission**

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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Royal College of Ophthalmologists – Dr Vickie Lee <i>Dr Helen Turner and Professor Bijay Vaidya nominated by the Royal College of Physicians also provided comments on this consultation</i>
3. Job title or position	Consultant Ophthalmic Surgeon
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The RCOphth is a membership organisation that promotes and supports the ophthalmic profession in the UK and overseas. As the voice of our members, we influence national eye health policy for the benefit of patients and the profession of ophthalmology
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	The company is Amgen Limited. The Royal College of Ophthalmologists as not received any funding from the company.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

6. What is the main aim of treatment? (For example, to stop progression, to improve symptoms, to cure the condition, or prevent worsening or disability.)	Thyroid Eye Disease (TED), an autoimmune condition associated with Graves' disease, poses significant challenges due to its debilitating effects on ocular health and quality of life. The most common extra-thyroidal manifestation associated with Graves' hyperthyroidism, TED is characterized by inflammation, proptosis, diplopia, and in 2-5% optic neuropathy and corneal exposure can lead to irreversible visual loss without timely treatment. Even clinically mild cases TED can severely impact visual performance (affecting the ocular surface impairing visual quality), appearance, and psychosocial well-being. The main aim of teprotumumab treatment is to improve symptoms and halt the progression of thyroid eye disease (TED), a condition characterized by inflammation and volume expansion behind the eyes. Teprotumumab, a monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R), addresses the underlying pathophysiology of TED by reducing inflammation, tissue expansion, and fibrosis. Specific Goals of Teprotumumab Treatment: 1 Reduce TED Symptoms: Alleviate proptosis (bulging eyes). Decrease diplopia (double vision). Relieve pain, redness, and swelling. 2 Prevent Progression: Stop further worsening of the disease symptoms above during its active phase. 3 Improve Quality of Life: Enhance visual function and reverse disfigurement and reduce psychological distress associated with TED. While teprotumumab is not considered a "cure" for TED, it has shown significant efficacy in clinical trials in achieving remission and substantial symptom improvement, often preventing long-term disability associated with the condition.

7. What do you consider a clinically significant treatment response? (For example, a reduction in certain symptoms, or a reduction in disease activity by a certain amount.)	A clinically significant outcome should include improvement / reversal visual dysfunction (mainly diplopia/ double vision) and disfigurement caused by TED in terms of the changed oculofacial appearance along with reducing the Pain Redness and Swelling associated with active orbital inflammation 1. Improved Visual Function, Reduction in Diplopia Severity & Improved Eye Alignment: • A noticeable decrease in the frequency or intensity of double vision in the patient's primary field of gaze or other functional gaze positions. • Achieving single vision (fusion) in one or more critical fields of gaze used for daily activities, such as straight-ahead or reading positions. • Measurable improvements in ocular alignment using prism dioptres, or field of monocular ductions demonstrating reduced ocular misalignment. • Reduced or eliminated need for prisms, patching, or compensatory head positioning to manage diplopia. • Reduced eye strain, eye discomfort, or fatigue associated with prolonged double vision. • Enhanced ability to perform daily tasks such as reading, driving, or working, where double vision previously caused difficulty. • Restoration of stereopsis (depth perception), if achievable. Patient-Reported Outcomes: • Significant improvement in patient-reported quality-of-life scores, reflecting less impact of double vision on physical, emotional, and social well-being and subjective improvement in appearance. (specifically using the validated Graves Orbitopathy Quality of Life Score). Durable Response: • Sustained improvements over time without relapse and reduced need for further treatments including surgery, prisms, or pharmacological therapies e.g. botulinum toxin injections to the extraocular muscles. 2. A significant improvement in the reversal of facial disfigurement in a psychosocial context goes beyond the physical correction of appearance and needs to improve psychological well-being of the individual, restoring confidence, reducing stigma, and improving overall quality of life. The reduction of proptosis associated with Teprotumumab which may lead to decreased need for rehabilitative orbital decompression Enhanced Self-Perception and Confidence: • Improved self-esteem and body image as the individual feels more comfortable with their appearance.

	• Reduced feelings of shame, embarrassment, or self-consciousness in social settings. Reduction in Psychological Distress: • Alleviation of anxiety, depression, or stress directly related to the disfigurement. • Improved emotional resilience and coping mechanisms for dealing with residual or perceived imperfections. Improved Social Interactions: • Increased willingness to engage in social activities, including work, school, and personal relationships. • Reduction in perceived or actual social stigma, enabling more positive and natural interactions with others. • Enhanced ability to participate in daily activities without physical or emotional limitations. • Perception of being treated more fairly and equally in social and professional environments e.g. resumption of social engagement and return to work. Improved Quality of Life: • Higher scores on validated quality-of-life and psychosocial well-being measures (specifically using the validated Graves Orbitopathy Quality of Life Score). • Renewed ability to pursue life goals, relationships, and personal aspirations without the barriers imposed by disfigurement. Durable Response: • When treatment is stopped the proptosis and oculo-facial changes do not recur.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?

- While treatments such as **systemic steroids** and **immunosuppressive therapies** as endorsed by the European Group on Graves' Orbitopathy (EUGOGO) remain standard care, there are significant unmet needs in terms of efficacy, safety, and disease modification.

Limitations of Current Treatments

1. Systemic Steroids (e.g., Intravenous Glucocorticoids):

- **Failure to reverse disfigurement:** While steroids reduce inflammation (peri-orbital swelling and redness, conjunctival redness, chemosis) during the active phase of TED, they have limited impact on reversing proptosis.
- **Inadequate Response Rates in double vision** A substantial proportion of patients with significant diplopia either fail to respond adequately or relapse after treatment cessation.
- Systemic steroids may have significant adverse effects.
- Relapse on discontinuation of systemic therapy.

2. Immunosuppressive Agents (e.g., Methotrexate, Azathioprine, or Mycophenolate):

- **Limited Efficacy in TED:** These therapies have shown mixed results in controlling inflammation and do not directly address the fibrotic and remodelling processes that drive the chronic phases of TED.

They are most effective if commenced early in the active phase of the disease.

- **Delayed Onset of Action:** Immunosuppressants often take weeks to months to achieve their effects, which can be suboptimal in a rapidly progressing disease like TED.
- **Side Effect Burden:** Immunosuppressive drugs carry risks of systemic toxicity, increased susceptibility to infections, and potential long-term organ damage. Continual safety monitoring (usually blood tests) is required.

Eligibility limited; some patients who have active inflammatory conditions or already immunocompromised may not be suitable.

3. Lack of Disease Modification:

Both steroids and immunosuppressants target inflammation but do not address the underlying pathophysiology of TED, particularly the activation of orbital fibroblasts and adipogenesis driven by the IGF-1 receptor pathway. This leaves patients vulnerable to ongoing disease progression and irreversible damage, such as persistent diplopia and disfiguring proptosis.

4. Unmet Needs in Long-Term Management:

- Current medical therapies primarily focus on the treatment active inflammatory phase of TED to relieve pain redness and swelling but offer little for managing chronic disease or reversing established structural changes.
- Patients with moderate to severe disease often require rehabilitative surgeries, such as orbital decompression or strabismus correction and eyelid surgery, which carry their own risks and fail to restore normal function or appearance completely. Moreover, they must live with their disfigurement for many years to as the general recommendation is to continue antithyroid drugs until all active treatment for thyroid eye disease is complete.

This leads to significant delay in rehabilitative surgeries to ensure that TED is inactive for several weeks/months before the surgery or definitive management of their thyroid dysfunction (to reach medical quiescence after stopping anti thyrotoxicosis medication or have more definitive treatments such as radio-iodine or thyroidectomy) before becoming eligible to have these rehabilitative surgeries. Some patients (e.g. those with severe proptosis and severe double vision with eyelid retraction) require multiple operations that need to happen in sequence – orbital decompression followed by strabismus surgery followed by eyelid lowering surgery. Many patients have a 3 to 5 year wait living with their disfiguring and disabling disease before accessing effective treatment, particularly in the context of NHS waiting lists. Successful strabismus surgery for double vision usually cannot restore normal single vision in all directions of gaze, usually only in the primary position (looking straight ahead) and reading.

The Need for Novel Therapies The limitations of EUGOGO-endorsed treatments highlight the urgent need for innovative therapies that:

- **Target the Underlying Disease Mechanisms:** A therapy addressing the molecular drivers of TED, such as IGF-1 receptor signalling, can offer disease-modifying potential rather than just symptomatic relief.
- **Provide Durable Benefits:** Long-term resolution of proptosis, diplopia, and inflammation without the need for repeated courses of steroids or adjunctive surgeries.
- **Offer Improved Safety Profiles:** Treatments with fewer systemic side effects, allowing broader applicability and tolerability for patients.

Improve QOL for patients

Earlier visible improvement for patients (avoiding need for disease quiescence)

Addressing this gap requires a shift toward targeted, mechanism-driven therapies capable of halting disease progression, reversing disfigurement, and improving quality of life at TED onset.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In 2017 The British Oculoplastic Surgery Society (BOPSS) that represents oculoplastic surgeons who usually lead TED care in the UK conducted a survey of members' TED practice patterns. This represented a snapshot of TED care in 2017 in the UK ¹ 1. Multidisciplinary Care Deficits: Only 60% of respondents reported working in a multidisciplinary clinic with both ophthalmologists and endocrinologists present. 29% lacked access to a specialist multidisciplinary service for TED management. 2. Variation in Treatment Practices: There was significant inconsistency in the use of treatment modalities across regions, including intravenous steroids, second-line immunosuppression, and orbital radiotherapy. 6% did not use intravenous steroids, and 25% referred patients to another trust for second-line treatments. 3. Limited Screening and Preventative Measures: Only half of the local endocrine services routinely screened for TED. Smoking cessation support, a critical preventative measure, was inconsistently available or documented. 4. Inadequate Quality of Life Assessments: Only 21% of respondents collected patient-reported outcomes or quality-of-life measures, despite their importance in assessing treatment impact. 5. Communication and Collaboration Gaps: Relationships between ophthalmology and endocrinology teams were rated as "good" by only 54%, indicating room for better collaboration. 6. Delays in Diagnosis and Treatment: Geographic disparities and lack of coordinated services led to delays in timely diagnosis and access to appropriate care, often missing the active disease phase when interventions are most effective. Recommendations in the paper were endorsed by all the major stakeholders working in the TED field including TEAMeD, BOPSS, Royal College of Ophthalmologists, The Royal College of Physicians, Society for Endocrinology, British Thyroid Association and the British and Irish Orthoptic Society included.

	1. Implementation of Multidisciplinary Clinics for moderate -severe/ sight threatening disease: Increase access to co-located ophthalmology and endocrinology services, with standardized protocols and shared decision-making. 2. Standardized Screening and Referrals: Adopt universal screening tools and clear referral pathways to identify and manage TED earlier. 3. Improved Patient Support: Provide smoking cessation services, standardized patient education materials, and psychosocial support. 4. Data Collection: Incorporate routine quality-of-life and outcome assessments to improve patient-centred care. 5. Compliance with National Guidelines: Enhance awareness and adherence to the Royal College of Physicians and TEAMeD-5 recommendations². 6. Collaboration Framework: Establish clear communication lines and shared care models between endocrinologists and ophthalmologists, ensuring a seamless patient experience. The study highlighted the need for greater standardization, collaboration, and patient-centred care to address the variability in TED management across the UK. This study predates the publication of the more recent EUGOGO 2021 guidelines and the ETA/ ATA consensus statements in 2022.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The EUGOGO 2021 Guidelines for the Management of Thyroid Eye Disease (TED) and the 2022 Consensus Statement on Thyroid Eye Disease (TED) by the American Thyroid Association (ATA) and European Thyroid Association (ETA) emphasize early detection, multidisciplinary care, and prompt achievement of euthyroidism and stress the importance of quality-of-life assessments, smoking cessation, need for specialist centres and tailored surgical approaches for more severe cases. ³⁴
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Please see Point 9. There is likely significant variation of care across the UK.

9c. What impact would the technology have on the current pathway of care?	Teprotumumab initiation will require a careful patient selection which will require patient access to specialist TED clinics (not all patients have access now). screening and monitoring for side effects like hearing issues, hyperglycaemia (particularly in people with pre-diabetes and diabetes), gastrointestinal disturbances, muscle spasms, and menstrual dysfunction. These potential adverse effects can complicate management for ophthalmologists, as they must coordinate with other specialists, like endocrinologists, otologists / audiologists and gynaecologists, to address and mitigate risks. A multidisciplinary approach to address the complexity of managing these side effects is crucial to ensure patient safety while effectively addressing TED pathology. In addition, there will be a likely impact on primary care and need for liaison as management of diabetes and menstrual abnormalities often resides in general practice.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There will be a number of centres in the UK that already have access to infusion facilities that treat TED patients with intravenous steroids and monitoring procedures for steroid sparing immunosuppression. However, some centres who only use oral steroids will not have the interdisciplinary infra structure to manage the potential side effects of this treatment. The importance of balancing Teprotumumab treatment benefits against the risks of hearing-related AEs and ensuring informed, patient-centred care. Hearing Impairment • Baseline Testing: Audiograms, word recognition tests, and patient-reported assessments before starting treatment. • Ongoing Monitoring: Regular hearing evaluations during treatment. • Management: Collaboration with audiologists and ENT specialists to address symptoms like hearing loss, tinnitus, and Eustachian tube dysfunction. There is a potential need for hearing aids in a minority and ongoing long-term monitoring. Hyperglycemia • Pre-Treatment Screening: Baseline glucose and HbA1c testing to identify risk factors (e.g., prediabetes, diabetes). • During Treatment: Monitor glucose levels before infusions and regularly post-treatment. • MDT approach: Education on nutrition, physical activity, and smoking cessation. • Multidisciplinary management involving endocrinologists for severe or uncontrolled cases and primary care who manage a large proportion of type 2 diabetes. Menstrual irregularity

	Any issues arising may require ultrasound pelvis and gynaecological review (not required with current treatments).
10a. How does healthcare resource use differ between the technology and current care?	Teprotumumab Specialized Administration: Requires a series of eight IV infusions over 24 weeks, administered every three weeks in specialized infusion centres. Monitoring and Side Effects: Requires baseline screening for hearing impairment and monitoring for systemic side effects like hearing impairment, hyperglycaemia, menstrual irregularities, often requiring coordination with specialists outside ophthalmology so will use more healthcare resources in terms of specialized infrastructure, cost, and inter-disciplinary coordination Pregnancy Risk: - Mandatory pregnancy testing for women of childbearing potential due to teratogenic risks. Effective contraception is essential for both males and females - Menstrual irregularities are also very common - Unsuitable for patients with history of hearing issues, optimisation of diabetes treatment may be needed breast feeding /pregnant patients. Patient Education: Educate patients about early signs of adverse effects and flare of thyroid eye disease Current treatment - Intravenous Steroids (IVMP) and second line immunosuppression Standard Administration: Administered in a hospital or clinic setting with weekly visits for 12 weeks. Side Effects: Requires monitoring for well-known adverse effects like glucose intolerance, hypertension, and liver dysfunction but is generally more familiar to clinicians. IVMP has a lower risk profile than oral steroids. Lower Cost: Steroids are significantly cheaper and more accessible than Teprotumumab and cost-effective studies comparing the treatments have not been done., making steroids the standard first-line treatment in many healthcare systems. - Mycophenolate, commonly used in conjunction with IVMP, requires careful monitoring during the treatment period to manage potential risks: Baseline Assessments: - Complete blood count (CBC), liver function tests (LFTs), and renal function tests should be performed prior to starting treatment. Regular Monitoring:

	a. Full blood count and Liver Function tests: Every 2-4 weeks for the first 3 months, then every 1-2 months thereafter. b. Monitor for leukopenia, anaemia, or liver enzyme elevations. 3. Infection Risk: a. Monitor for signs of infections (e.g., fever, sore throat) due to immunosuppression. 4. Pregnancy Risk: a. Mandatory pregnancy testing for women of childbearing potential due to teratogenic risks. Effective contraception is essential. 5. Patient Education: a. Educate patients about early signs of adverse effects (e.g. hearing loss, menstrual dysfunction, symptomatic management of less severe reported adverse events).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology should be used in specialist clinics with interdisciplinary support to monitor for and manage any potential side effects and complications.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1. Access and pathway to multi-disciplinary specialist TED clinics 2. Facility for infusions, specialist nurses 3. Pathway audiology monitoring and interpretation. There are some automated technologies used for audiology 4. Pathway for onward referral to Otology for patients with hearing issues (abnormal audiology / eustachian tube dysfunction issues) 5. MDT pathway for management of hyperglycaemia especially in diabetics and prediabetics 6. Onwards pathways for assessment of persistent menstrual abnormalities after stopping treatment
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Currently we have no treatment to correct disfigurement caused by the proptosis and oculofacial changes in the acute phase of the disease before the TED is stable. The current care of immunosuppression treatment helps with pain and inflammation but is not suitable for patients with only proptosis and no inflammation. The current treatment is not particularly effective in treating double vision.
11a. Do you expect the technology to increase	TED is not a life-threatening disease although a large Danish population study has found that the risk of death by suicide in TED patients is 2.7 times that of the general population and almost twice that of patients with Graves Hyperthyroidism without TED. ⁵

length of life more than current care?	
11b. Do you expect the technology to increase health-related quality of life more than current care?	Teprotumumab can address the disfigurement in responsive TED patients in the acute phase otherwise due the prolonged wait before accessing TED rehabilitation surgery.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	TED patients with significant extraocular muscle enlargement contributing to the proptosis are likely to respond better than patients with predominant fat expansion. Patients with severe diplopia due to extraocular muscle involvement are likely to respond better than with current care.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Teprotumumab needs to be administered in an infusion centre associated with a specialist thyroid eye service who can gauge. There needs to be a clear pathway for multidisciplinary care: Patients need to have audiology monitoring before during and after treatment and a clear pathway for otology referral for those who have hearing issues. Access to diabetic specialist to optimise glycaemic control in patients at risk of hyperglycaemia Access to specialist care for patients with persistent amenorrhea after terminating treatment
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Although teprotumumab has shown to be efficacious in both acute and chronic thyroid eye disease, it appears to be more efficacious in patients with predominantly extraocular muscle expansion and in the acute phase of the disease. Decision to start Teprotumumab can be based on

include any additional testing?	Severity: TED is categorized as mild, moderate-to-severe, or sight-threatening based on symptoms, signs, and impact on quality of life. Activity: Disease activity is assessed using the Clinical Activity Score (CAS), which helps guide treatment decisions. It is recognised as a flawed instrument especially in non-white instruments Quality of Life: The physical and psychosocial impact of TED should be assessed for each patient, as it informs treatment decisions. When formal quantification of quality of life (QOL) is deemed appropriate, Graves' orbitopathy-quality of life (GO-QOL) is the preferred instrument. The clinician should regularly assess the psychosocial impact of concerns about appearance Orbital Imaging to confirm predominant extraocular muscle involvement. Poor response to IVMP at 6 weeks should prompt consideration for treatment withdrawal and evaluation of other therapies. Clinicians should be alert for worsening diplopia or onset of dysthyroid optic neuropathy (DON) that have occurred even while on IVMP therapy. Teprotumumab may be a suitable second line agent here (as recommended in the 2021 EUGOGO guidelines)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There were moderate-to-large improvements with teprotumumab for GO-QOL total scores (19 vs 6, $p < 0.0001$), visual scores (20 vs 7, $p = 0.0003$), and appearance scores (18 vs 6, $p = 0.0003$), respectively, which were maintained during follow-up.⁶ In a longer term follow-up study patients with ± 10-point GO-QoL improvement from baseline at Week 24, 21/ 33 (63.6%; CI [45.12, 79.60]) maintained this response at Week 72.⁷ However, there are emerging studies which raise the concerns about reactivation of TED after completion of a course of Teprotumumab.⁸
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Teprotumumab can simultaneously address inflammation and disfigurement and is more effective in treating double vision than current. There has been no direct comparison trial between intravenous steroids and Teprotumumab. A meta-analysis identified 12 IVMP studies were included in the matching-adjusted indirect comparison (11 for proptosis change [$n = 419$], 4 for diplopia response [$n = 125$], and 2 Teprotumumab [$n = 79$] and placebo [$n = 83$] comparator studies). Treatment with IVMP resulted in a proptosis difference of -0.16 mm (95% CI, -1.55 to 1.22 mm) from baseline to week 12 vs placebo. The proptosis treatment difference between IVMP and Teprotumumab of -2.31 mm (95% CI, -3.45 to -1.17 mm) favoured Teprotumumab. Treatment with IVMP (odds ratio, 2.69; 95% CI, 0.94-7.70) was not favoured over placebo in odds of diplopia response; however, Teprotumumab was favoured over IVMP (odds ratio, 2.32; 95% CI, 1.07-5.03).⁹
16a. Is the technology a 'step-change' in the management of the condition?	Teprotumumab is a step change for treating TED 1 restore/improve visual function – prevent/reverse visual loss & reverse diplopia 2 Reverse disfigurement

16b. Does the use of the technology address any particular unmet need of the patient population?	Rehabilitative surgery to address disfigurement and double vision for moderate-to-severe TED should only be performed when the disease is inactive and euthyroidism has been achieved and maintained (up to 18m-2y after initial presentation). Teprotumumab can be given in an early stage of TED to address inflammation double vision and disfigurement simultaneously. Surgery remains an option in non-responders.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side effects associated with teprotumumab infusions were muscle spasms (25%), nausea (17%), alopecia (13%), fatigue (12%), and diarrhoea (12%). Less frequent side effects included hyperglycaemia, hearing impairment, dysgeusia, headache, and dry skin. ¹⁰ Notably, the initial phase 3 multicentre trial noted 3 of 41 patients reporting amenorrhea in the setting of teprotumumab administration. ¹¹ Subsequent Teprotumumab clinical trials reported a 23% rate of menstrual disorders (including amenorrhea, metrorrhagia, and dysmenorrhea in menstruating female patients). ¹⁰

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trial design Phase 2 & Phase 3 trials of the Teprotumumab vs placebo ie no treatment. The primary and secondary end points are appropriate although very little orbital imaging was used to confirm the change of proptosis measured by exophthalmometry which is known to be subject to variation. Reduction of Clinical Activity score CAS achieved by Teprotumumab is not dissimilar to that with IVMP. Patients with sight threatening TED was excluded from the clinical trials so there is no Level 1 evidence of Teprotumumab for this group of patients. There have been no clinical trials directly comparing the efficacy Teprotumumab to intravenous steroids which is the current standard treatment in the UK.
18a. If not, how could the results be extrapolated to the UK setting?	A study examined matching-adjusted indirect comparison of teprotumumab vs IVMP vs placebo using Deidentified patient-level data from teprotumumab trials and aggregate-level data from literature on the most recommended regimen of IVMP. The main outcome measures were changes in proptosis by millimetre and diplopia response (percentage with 1 grade reduction) from baseline to week 12 in patients receiving IVMP and placebo, and to week 24 in patients receiving teprotumumab. 12 IVMP studies were included in the matching-adjusted indirect comparison (11 for proptosis change [n = 419], 4 for diplopia response [n = 125], and 2 teprotumumab [n = 79] and placebo [n = 83] comparator studies). Treatment with IVMP resulted in a proptosis difference of -0.16 mm (95% CI, -1.55 to 1.22 mm) from baseline to week 12 vs placebo. The proptosis treatment difference between IVMP and teprotumumab of -2.31 mm (95% CI, -3.45 to -1.17 mm) favoured teprotumumab. Treatment with IVMP (odds ratio, 2.69; 95% CI, 0.94-7.70) was not favoured over placebo in odds of diplopia response; however, teprotumumab was favoured over IVMP (odds ratio, 2.32; 95% CI, 1.07-5.03). ⁷

	The authors concluded that teprotumumab, compared with IVMP, is associated with greater improvements in proptosis and may be twice as likely to have a 1 grade or higher reduction in diplopia, randomized trials comparing these 2 treatments would be warranted to determine if 1 treatment is superior to the other to a clinically relevant degree. However, the improvement in QOL was not assessed in this analysis due to insufficient QOL data in the IVMP studies. .
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	In my view, the most important outcome is the improvement in Quality-of-life QOL and the longevity of the treatment response. The first is measured in the trials. In a recent publication looking at longer term effect at one year. The long-term response to teprotumumab as observed 51 weeks after therapy was similar to week 24 results in the controlled clinical trials. Inflammatory and ophthalmic composite outcome improvements were seen in 90% of patients with nearly 70% reporting improvement in diplopia and proptosis. Further, 82% of patients in this analysis did not report additional TED treatment (including surgery) over 99 weeks following the final teprotumumab dose. At week 72, 52/57 (91.2%), 51/57 (89.5%), 35/48 (72.9%), 38/56 (67.9%), and 37/56 (66.1%) of patients were responders for CAS, composite outcome, diplopia, proptosis, and overall response, respectively. The mean reduction in proptosis was 2.68 mm (SD 1.92, n = 56), mean GO-QoL improvement was 15.22 (SE 2.82, n = 56), and disease inactivation (CAS ≤1) was detected in 40/57 (70.2%). Over 99 weeks following teprotumumab therapy, 19/106 (17.9%) patients reported additional TED therapy during formal and extended follow-up. However the trials did not examine patients with more long term TED and the longevity of the response. A small cohort study that only one third of patients had a sustained response on long term follow up. ¹¹
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	One surrogate outcome is the measurement of proptosis as a marker of improvement for orbital disease. The other surrogate marker is Clinical Activity Score as a surrogate outcome for reduction in inflammation. Improvement in diplopia measured by one grade is a surrogate marker that can be misleading as sometimes improvement in movement in the extraocular muscles may change the perception of double vision for better or worse. Using the GOQOL is probably the most reliable indicator as it measures both visual function and appearance perception so if the GOQOL improvement effect is maintained then it bodes well for long term clinical outcome.
18d. Are there any adverse effects that were not apparent in clinical	1 Hearing abnormalities were reported by about 10% of patients receiving teprotumumab in the TED clinical trials but there was no systematic screening/ monitoring for hearing loss in the published trials. IGF-I is involved in cochlear cell differentiation, proliferation, and synapse regeneration. Teprotumumab—which acts to antagonize

trials but have come to light subsequently?	IGF-1 receptors—may disrupt these neuro- trophic signals, leading to downstream pathways of inner ear dysfunction and (SNHL)Sensorineural Hearing Loss Smith et al ¹² studied deidentified claims for ear/labyrinth-related International Classification of Disorders, Tenth Revision codes (KOMODO) were examined in GD patients without TED, and TED patients without/with teprotumumab treatment. Hearing AE incidence/severity was evaluated in teprotumumab clinical trials. Graves' Ophthalmopathy Quality of Life questionnaire (GO-QOL) scores were compared in teprotumumab TED trial patients without/with hearing AEs. The author concluded analyses indicate similar prevalence of hearing claims in patients with GD/TED alone as following teprotumumab treatment. They recommended future analyses of incremental hearing risk from teprotumumab should use a priori study designs accounting for background hearing dysfunction in patients with GD/TED. Wong et al's ¹³ systematic review was performed using standardized methodology noted an important observation was that almost half of patients with hearing loss did not report any symptoms. Meanwhile, about a third of patients without hearing loss did still endorse otologic symptoms. This discordance between subjective symptoms and objective audiometric findings has been noted in the past with teprotumumab. The authors hypothesize this may be explained by changes in hearing thresholds at ultrahigh frequencies (>8 kHz) that are outside the range of testing on standard audiometry. The most reported symptoms during teprotumumab treatment were hearing loss (22%), followed by fullness (18%) and tinnitus (14%) Initial symptom onset occurred after 3.6 infusions Among 97 patients with reported pre- and posttreatment audiometric data, 40 (41%) experienced hearing threshold shifts on pure-tone audiometry meeting criteria for ototoxicity per ASHA guidelines 59% had unilateral hearing loss. The presence of hearing loss at these ultrahigh frequencies may explain why a third of patients without hearing loss on standard audiometry endorsed otologic symptoms. Together, these results suggest a role for extended high-frequency audiometry as part of routine monitoring in patients taking teprotumumab. A reassuring finding was that most patients, regardless of treatment, noted a subjective return to baseline hearing status and resolution of audiovestibular symptoms by about 6 months after last treatment. The reversibility of drug-induced ototoxicity suggests spontaneous recovery in a substantial proportion of affected patients. These findings underscore the importance of further studies to elucidate the underlying disease mechanisms and redefine optimal treatment strategies. McGwin et al ¹⁴ A Large-Scale Analysis and Review of Voluntarily Reported Patient Complaints to the Food and Drug Administration (FDA). A total of 940 teprotumumab-associated adverse events were identified, including 84 hearing-related adverse events. A comparison group of 32,794 nonteprotumumab adverse events was identified with 127 hearing-related adverse events reported. Use of teprotumumab in patients with thyroid conditions was

associated with a nearly 24-fold (proportional reporting ratio [PRR] 23.6, 95% confidence interval [CI]: 18.1–30.8) increased likelihood of any hearing disorder (p value <0.0001). The association was specifically elevated for a variety of deafness conditions (e.g., bilateral deafness [PRR: 41.9; 95% CI: 12.8–136.9]), Eustachian tube disorders (PRR: 34.9; 95% CI: 4.9–247.4), hypoacusis (PRR: 10.1; 95% CI: 7.6–13.3), and tinnitus (PRR: 8.7; 95% CI: 6.2–12.1) the authors encourage the continued utilization of the FAERS system by clinicians who prescribe teprotumumab and all future medications to treat TED to track the progress of such medications, the vigilance in patient selection, and their overall safety track record of this drug and any introduced in the future.

2. Hyperglycemia is a recognized adverse event of teprotumumab, occurring in 10% of patients in the randomized controlled trials. In the long term follow up study Kahaly et al ⁶ reported the four hyperglycemia-related events newly reported during the follow-up, two were hyperglycemia that resolved without medication, one case of glucose intolerance resolved, and one diabetes event occurring in a patient with prediabetes was treated with metformin and was ongoing when the patient discontinued from the study due to a flare. There were two additional hyperglycemia-related events of type 2 diabetes persisting from the treatment period in patients who were prediabetic at baseline. Any other treatment-emergent hyperglycemia-related events resolved during the treatment period. One cohort study from a large US centre found that age, pre-existing diabetes, and Hispanic and Asian race/ethnicity were significant risk factors for hyperglycemia. Among patients with hyperglycemia, 36.4% (8/22) returned to baseline glycaemic status at last follow-up., especially in patients with diabetes. Hyperglycemia may persist after stopping teprotumumab. These findings underscore the importance of guidelines for screening and management of teprotumumab-related hyperglycaemia.¹⁵

3. Menstrual abnormalities Subsequent Teprotumumab clinical trials reported a 23% rate of menstrual disorders (including amenorrhea, metrorrhagia, and dysmenorrhea) in menstruating female patients. One small cohort study the frequency of this menstrual abnormalities (75%) s higher than reported ¹⁶

One study aimed to identify potential safety signals of teprotumumab by analyzing postmarketing safety data from the FDA Adverse Event Reporting System (FAERS) database in 2023. A total of 2158 cases were included in the analysis. Main safety signals identified were ear and labyrinth disorders, reproductive system and breast disorders, metabolism and nutrition disorders, and gastrointestinal disorders. Specifically, autophony (ROR [95% CI] = 4188.34 [1403.29-12500.8]), eyelid retraction (ROR [95% CI] = 2094.17 [850.69-5155.29]), permanent deafness (ROR [95% CI] = 1552.35 [789.07-3053.98]),bilateral deafness (ROR [95% CI] = 73.12 [41.14-129.97]), inflammatory bowel disease (ROR [95% CI] = 23.26 [13.46-40.19]), hyperglycemic hyperosmolar nonketotic syndrome (ROR [95% CI] = 17.75 [5.70-55.28]), and amenorrhea (ROR [95% CI] = 47.98 [36.22-63.54]) showed significant safety signals with teprotumumab.¹⁷

	As a response to these more recently reported AE Amgen has published 2 physicians' guidance for hearing loss and hyperglycemia in the USA.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	• Off-Label Usages and Real-World data: differences in adverse events and efficacy in different patient populations treatment deviations compared to trial settings e.g. using fewer infusions to minimise side effects/ cost or adopting a 'treat and extend model'. Longevity of response and retreatment efficacy. Emerging evidence on efficacy of teprotumumab for treating sight threatening TED as this group was excluded from the clinical trials. • Real world Patient outcomes: Anecdotal or qualitative insights into quality-of-life improvements not covered in standardized trial metrics e.g. resumption of employment, coming off sick leave • Long-Term Safety: Post-marketing surveillance data revealing rare or delayed side effects not identified in trials – hence the need for a registry • Economic and logistical considerations for treatment implementation in different healthcare systems
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE interventional procedures guidance [IPG148]?	Orbital Radiotherapy is the NICE comparator treatment from 2005 There are several RCTs evaluating the therapeutic effect of OR on TED with contradictory findings. A meta-analysis reviewing 18 studies of which 10 were randomised and 8 were cohort studies concluded that OR is efficacious in the treatment of TED and has a greater impact when combined with glucocorticoids ¹⁸ However, a second meta-analysis evaluating 33 RCTs concluded that the efficacy of OR monotherapy is of indeterminate benefit but combining OR with corticosteroids was more efficacious than monotherapy of either alone ¹⁹ Therefore, the evidence base tends to be unclear but there is a tentative understanding that OR with oral corticosteroids is likely effective. CIRTED was a multicentre, double-blind, randomised controlled trial with a 2 × 2 factorial designs done at six centres in the UK. Adults with active moderate-to-severe thyroid eye disease associated with proptosis or ocular motility restriction were recruited to the trial. Patients all received a 24-week course of oral prednisolone (80 mg per day, reduced to 20 mg per day by 6 weeks, 10 mg per day by 15 weeks, and 5 mg per day by 21 weeks) and were randomly assigned via remote computerised randomisation to receive either radiotherapy or sham radiotherapy and azathioprine or placebo in a 2 × 2 factorial design. Randomisation included minimisation to reduce baseline disparities in potential confounding variables between trial interventions. Patients and data analysts were masked to assignment. The primary outcomes were a binary composite clinical outcome score and an ophthalmopathy index at 48 weeks, and a clinical activity score at 12 weeks. The primary analysis was based

on the intention-to-treat allocation, and safety was assessed in all participants. 126 patients were recruited and randomly assigned to groups: 31 patients to radiotherapy plus azathioprine, 31 to sham radiotherapy and azathioprine, 32 to radiotherapy and placebo, and 32 to sham radiotherapy and placebo. Outcome data were available for 103 patients (54 for sham radiotherapy vs 49 for radiotherapy and 53 for placebo vs 50 for azathioprine), of whom 84 completed their allocated treatment of radiotherapy or sham radiotherapy and 57 continued to take azathioprine or placebo up to 48 weeks. There was no interaction between azathioprine and radiotherapy ($p_{\text{interaction}}=0.86$). The adjusted odds ratio (OR) for improvement in the binary clinical composite outcome measure was 2.56 (95% CI 0.98–6.66, $p=0.054$) for azathioprine and 0.89 (0.36–2.23, $p=0.80$) for radiotherapy. In a post-hoc analysis of patients who completed their allocated therapy the OR_{adj} for improvement was 6.83 (1.66–28.1, $p=0.008$) for azathioprine and 1.32 (0.30–4.84, $p=0.67$) for radiotherapy. The ophthalmopathy index, clinical activity score, and numbers of adverse events (161 with azathioprine and 156 with radiotherapy) did not differ between treatment groups. In both groups, the most common adverse events were mild infections. No patients died during the study.

There was an absence of significant improvement in the GOQOL in any of the treatment cohorts. The authors concluded that in patients receiving oral prednisolone for 24 weeks, radiotherapy did not have added benefit. A major limitation of this study was the high rate of patients withdrawing from their allocated treatment. In all study groups, early withdrawals (before 24 weeks) due to disease deterioration occurred as the steroid dose was reduced, and this was not mitigated by orbital radiotherapy.²⁰

Tocilizumab is a monoclonal antibody, directed against interleukin-6 receptors (IL-6R) and is recommended as a second line agent in the EUGOGO guidelines. A small double-blinded RCT²¹ evaluated patients with active moderate-to-severe glucocorticoid resistant TED and a multi-centre observational study²² in patients resistant to conventional therapy that suggests efficacy. The lack of RCTs evaluating the effectiveness of Tocilizumab in steroid naive patients, limits the quality of evidence available to evaluate Tocilizumab's true efficacy. Rituximab, a monoclonal antibody against CD20, is well established in the treatment for a variety of autoimmune diseases. It acts via CD20 receptor expressed on B-Cells, resulting in B-Cell depletion and is recommended as a second line agent in the EUGOGO guidelines.

Two single-centre RCTs have shown conflicting results in the response to treatment with Rituximab. may be due differences in subject recruitment. The Mayo clinic study²³ that did not demonstrate Rituximab efficacy had a cohort that had a significantly longer TED disease duration (mean 30 months), compared to 4.5 months in the Milan study²⁴ that did show significant efficacy. Rituximab maybe more effective in patients with acute inflammatory TED than in more chronic disease. The Milan study was terminated early due to frequent TED

	reactivation in the IVMP arm. In addition, the Rituximab infusion protocol was altered following the first 12 participants The Mayo clinic study concluded prior to reaching the full quota of participants due to challenges faced recruiting patients A 2021 meta-analysis evaluating the use of Rituximab in TED from 2021 evaluated 12 cohort or RCTs (152 patients) and concluded that Rituximab had a rapid and long-lasting impact on the reduction of both CAS and TRAb²⁵. Nevertheless, the small and limited number of RCTs, impacts the ability to effectively evaluate the efficacy of Rituximab in patients with TED. This conclusion was also supported in a 2022 Cochrane review that further larger multi-centre studies are required to ascertain the therapeutic benefit of Rituximab in TED. I co-authored a review examining the current landscape of TED treatments.²⁶
21. How do data on real-world experience compare with the trial data?	Real-world data on teprotumumab largely confirms its efficacy in reducing proptosis, diplopia, and inflammation in thyroid eye disease) as seen in clinical trials. However, real-world studies often report higher frequency of adverse effects, particularly hearing-related issues (up to 81.5% in some cases) and hyperglycemia. These disparities can be attributed to a broader patient population in practice, including those with comorbidities or baseline risks unrestricted by trial inclusion criteria. Monitoring in real-world settings emphasizes multidisciplinary management to balance risks and benefits effectively. Radiologically Teprotumumab appears to significantly reduces orbital fat and muscle volumes so is manifested by a significant reduction in proptosis. Baseline proptosis and muscle volumes are significant predictors of proptosis response.²⁷ A single centre study of 119 patients with post-treatment data (mean follow-up 10.56 months, range: 3.05–25.08), 208 (87.39%) eyes of 110 patients had initial proptosis improvement. Of the 78 patients with multiple follow-up visits, 102 (65.38%) eyes of 59 patients had proptosis regression averaging 12.78% (range: 1.85–58.82%) compared with immediately post-treatment or 2.43 mm (0.5–10.0 mm). Eight (7.84%) eyes had initial documentation of regression more than 1 year after treatment, 40 (39.22%) between 6 months and 1 year, and 54 (52.94%) eyes within 6 months with 25 (46.30%) of these continuing to worsen at subsequent follow-up. Forty (25.64%) eyes of 24 patients had more proptosis at most recent follow-up than before teprotumumab, with an average regression of 1.53mm (0.5–4.0 mm) or 7.74% (1.85–20.69%) of pretreatment proptosis. In comparison, 99 (63.46%) eyes of 54 patients-maintained improvement, with reduction averaging 3.13 mm (0.5–11.0 mm) or 13.19% (1.92–41.67%) of pretreatment proptosis ($p < 0.001$). The authors found that Two-thirds of eyes had regression despite initial teprotumumab response, typically within 1 year of treatment, with ongoing worsening over time. Most patients maintained some proptosis reduction compared with before treatment despite regression,

	although 25% were worse than pretreatment. The occurrence of regression was independent of the pretreatment duration of clinical thyroid eye disease. Overall, compared with pre teprotumumab, there was a greater amount of improvement than regression at most recent follow-up. ²⁸

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Many of the inclusion criteria from the trial can lead to potential equality issues. Proptosis (forward displacement of the eyes) measurements vary by ethnic group due to anatomical differences. Studies report higher normal exophthalmometry readings in individuals of African descent compared to Caucasian and Asian populations. So any criteria to start based on severity of proptosis can be •African populations: Normal upper limits range from 22–24 mm. •Caucasian populations: Normal upper limits are around 20–22 mm. •Asian populations: Normal upper limits are generally lower, around 18–20 mm. The Clinical Activity Score (CAS) for Thyroid Eye Disease (TED) has been critiqued for potential bias, as it heavily relies on visible and palpable signs like redness, swelling, and inflammation. These markers may present differently across skin tones, potentially leading to underdiagnosis or misclassification of disease activity in patients with darker skin. The use of orbital imaging (especially MRI) can mitigate against the underscoring of CAS score in patients in darker skin. The current EUGOGO classification system is geared for immunosuppression so can bias against patients with ‘mild disease’ who have significant QOL impairment. Routine assessment of QOL is essential to close this gap.
22b. Consider whether these issues are different from issues with current care and why.	Currently clinicians have discretion whether patients are likely to benefit from immunosuppression. All the current clinical scoring system is predicated on immunosuppression being the only available treatment, so emphasis is on treating inflammation and treating visual loss rather than reversing disfigurement.

Topic-specific questions

23. If recommended, at what line of treatment would the technology be used? (For example, first line, second line, or both.) What are the key comparators at this line of treatment. Would this be in primary or secondary care?	The treatment should occur in secondary care under a specialist multidisciplinary thyroid eye services with monitoring of hearing issues and optimisation of thyroid and glycaemic control although any long-term hyperglycaemia will also impact on primary care management. Key comparators are • Orbital decompression to reduce proptosis • Extraocular muscle surgery to treat intractable diplopia The technology may be used as • First line treatment in acute moderate- severe TED provided with significant diplopia (Gorman level 2 or 3) and significant proptosis. • Second line treatment in sight threatening disease where immunosuppression/ urgent orbital decompression has failed to halt visual loss or there is intractable diplopia. • First line treatment in chronic TED with significant extraocular muscle enlargement with precarious ocular balance where orbital decompression has a significant risk of worsening diplopia Possibly second line treatment where orbital decompression has failed to achieve a significant reduction in proptosis.
24. Different population subgroups have been identified and may be explored if evidence allows (subgroups based on disease activity, duration of active symptoms, and severity of proptosis, diplopia and inflammation). What line of treatment would the technology be used at for these subgroups? Would it differ for different subgroups?	1.Activity Phase: Most effective in patients with active thyroid eye disease (TED), showing significant reductions in proptosis, diplopia, and inflammation. 2.Duration of TED: Demonstrates benefits even in patients with longer disease durations (chronic TED), though responses may be less impressive compared to early-stage active TED. 3.Baseline Severity: Subgroups with moderate-to-severe TED benefit significantly; however, outcomes for mild cases were not studied in the trials. 4 Possible fat: muscle expansion – appears to be more effective in predominantly muscle expansion types of TED but more radiological studies are needed. 5 Longevity of response and retreatments

25. What measures are used to determine disease activity and severity of thyroid eye disease in UK clinical practice?	The most used instrument to determine disease activity is the clinical activity score (CAS). This grading system is long-established in Europe as the conventional method of assessing disease activity. Devised by Mourits et al²⁹, it is a 7-point (10-point post-presentation) binary scoring system that considers the symptoms and soft tissue signs indicative of anterior orbit inflammation. At presentation, CAS ≥ 3 ($\geq 4/10$ at subsequent clinics) suggests active TED. The severity of disease is usually graded according to the three categories defined by the European Group on Graves' Orbitopathy (EUGOGO): mild, moderate to severe and sight threatening³⁰. based on visual functioning, soft tissue involvement, ocular motility and proptosis. There is no universal consensus on the assessment of TED-induced EOM dysmotility The Gorman scoring system provides a simple and quantifiable method of grading diplopia subjectively³¹. The prominent psychosocial and functional burden of TED can have detrimental consequences on the QOL of patients. The validated Graves' Orbitopathy QOL (GOQOL) questionnaire is a TED-specific HRQOL assessment tool therefore offers value as a primary outcome measurement It consists of two sub scores: visual functioning (VF) and appearance (AP).³²

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	1. Unmet Clinical Need in TED Treatment Current treatments, such as systemic steroids and immunosuppressants, have limitations in efficacy, safety, and disease modification, particularly in addressing structural changes like proptosis and diplopia. Many patients have to live with double vision and disfigurement for many years before accessing suitable rehabilitation surgeries. 2. Goals of the New Technology The primary aims of the technology are to reduce inflammation, alleviate symptoms such as diplopia and proptosis, prevent disease progression, and improve the patient's quality of life, including psychosocial well-being. 3. Potential Benefits and Risks of the Technology It offers the potential for durable remission, disease modification, and reduced need for orbital decompression and strabismus surgeries. However there has been no head-to-head trial with the current standard of care – intravenous methylprednisolone. Also, this technology has complication profile of hearing loss hyperglycaemia menstrual abnormalities, can exacerbate gastrointestinal disorders and teratogenesis. The longevity of the treatment response and the safety and frequency of retreatment is also not established. 4. Importance of Multidisciplinary Care Effective management of TED with this technology requires a multidisciplinary approach involving ophthalmology, endocrinology, audiology, and diabetology for monitoring potential side effects like hyperglycemia and hearing impairment. 5. Real-World Considerations and Innovations The technology represents a step-change in TED management by offering earlier intervention during the active phase and addressing both inflammation and disfigurement, potentially improving outcomes beyond what is achievable with existing therapies.

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Single Technology Appraisal
Teprotumumab for treating thyroid eye disease [ID6432]
NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	Yasmin Stammers
2. Name of organisation	NHS England
3. Job title or position	Head of Internal Medicine

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes ~~or No~~ Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes ~~or No~~ Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? ~~Yes or~~ No An expert in treating the condition for which NICE is considering this technology? ~~Yes or~~ No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ~~Yes or~~ No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England commissions specialised endocrinology, from a small number of specialised centres. Thyroid eye disease is commissioned through specialised ophthalmology commissioning. Although both specialised endocrinology and specialised ophthalmology are to be delegated to ICBs for local commissioning to join up pathways, NHS England remains the accountable commissioner and takes responsibility for the service specification and policies for specialised services, as defined within the Manual of Prescribed Specialised Services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The most commonly used guidelines for managing thyroid eye disease are the EUGOGO guidelines (PMID: 34297684) and the ETA/ATA consensus statement (PMID: 36480280). Both guidelines discuss available data on efficacy, safety and side-effects of teprotumumab but acknowledge that there is no market authorisation for teprotumumab in Europe, only in the US. Data with regards to teprotumumab use in trials continues to accumulate. The drug has been available in the US for 3 years or more. Patient with thyroid eye disease have an unmet need and the NICE appraisal close to the anticipated market authorisation is timely. Thyroid eye disease (TED) is associated with substantial morbidity. TED can be a very disfiguring disease and has huge psychological impacts, including increased suicide rates (PMID: 29084476). It also has huge socio-economic impacts. TED often prevents people from driving owing to double vision leading to loss of employment. Furthermore, disfigurement around the eyes leading to lack of confidence for people in public-facing roles, whether as a receptionist or a teacher, also leads to early loss of employment for many patients with TED. This is a life-changing condition for many people with moderate to severe disease.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway for use of teprotumumab is only in trials with clear inclusion and exclusion criteria and strict protocols. The management of TED is very variable across the NHS. The recommendation is to have joint multidisciplinary clinics with ophthalmologists, endocrinologists, surgeons and specialist nurses and most tertiary/quaternary centres have such clinics but many secondary care settings do not. TED is a heterogeneous disease but first-line treatment for mild disease is with eye drops and selenium; for moderate to severe and active disease treatment is with glucocorticoids and mycophenolate. Other treatments may include azathioprine, tocilizumab, rituximab and radiotherapy. Specialist surgery is usually used in the burnt-out stage for corrective indications but urgent orbital decompression surgery may be needed, especially in cases of dysthyroid optic neuropathy. Notably, specialist surgery is only available in about 15 regional centres. Once patients have inactive “burned-out” disease, follow-up is often in primary care. Patients undergoing surgical interventions have different follow-up to those having medical interventions. Joint multi-disciplinary working is crucial.

8. What impact would the technology have on the current pathway of care?	Teprotumumab is likely to fit as second-line treatment for patients with active disease who have failed methylprednisolone, or have contraindications to it, and have moderate to severe residual exophthalmos/proptosis. Teprotumumab will be prescribed in secondary/tertiary care with follow-up in secondary care. Increased physician and specialist immunosuppression nurse involvement will be needed with more sophisticated immunomodulating therapies becoming available.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Currently used in clinical trials and for compassionate use. Has been mainly used in active disease. Very little use of this in the UK at present.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used as second line treatment in secondary care and will need increased physician involvement and close multi-disciplinary working.
10a. How does healthcare resource use differ between the technology and current care?	This agent has substantial cost but is likely to be of substantial long-term benefit and reduce the need for surgery by reducing proptosis. The health economic impacts also need to take the QoL and socio-economic impacts (effects on employment) into account as described above
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care but specialist thyroid eye clinics in tertiary centres likely to be the main route for prescribing and monitoring

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Specialist training to tertiary centres for assessment starting/stopping rules. Increased physician involvement with and specialist immunosuppression nurse involvement with the use of immunomodulatory agent and potential adverse effects will be needed. All patients will need regular ophthalmology monitoring and investigations.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Well established protocols for inclusion into trials, determination of inadequate response based on ophthalmological response well established. Awareness of side -effects and monitoring has increased with clinical use. The ATA/ETA guidance (PMID: 36480280) contains a clear description of inclusion/exclusion criteria, protocols and side-effects and data from use in the US are accumulating rapidly.
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations or audits have been undertaken in the UK as teprotumumab does not have market authorisation. Data from ongoing trials using teprotumumab as a first line treatment and in established burnt out disease are accumulating. It will be important to establish the duration of response as there is already some evidence that there is disease recrudescence in some patients once teprotumumab is discontinued.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	TED is more common in women (as is Graves' disease which is usually the underlying aetiology). TED is more common in cigarette smokers.
12b. Consider whether these issues are different from issues with current care and why.	These inequalities are well established and recognised.

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Teprotumumab for treating thyroid eye disease [ID6432]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Huiqin Yang, Reviews Manager, KSR Ltd, United Kingdom (UK) Maiwenn Al, Senior Lecturer, Health Technology Assessment (HTA), Erasmus School of Health Policy & Management (ESHPM), EUR, The Netherlands (NL) Seamus Kent, Assistant Professor, HTA, ESHPM, EUR, The NL Marten Poley, Health Economics Researcher, ESHPM & Institute for Medical Technology Assessment (iMTA), EUR, The NL Kevin McDermott, Systematic Reviewer, KSR Ltd, UK Jiongyu Chen, Health Economist/Systematic Reviewer, KSR Ltd, UK Xiaoyu Tian, Systematic Reviewer & Health Economist, KSR Ltd, UK Lisa Stirk, Senior Information Specialist, KSR Ltd, UK Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Correspondence to	Dr Huiqin Yang Kleijnen Systematic Reviews Ltd Unit 6, Escrick Business Park Riccall Road, Escrick York, YO19 6FD United Kingdom
Date completed	19 March 2025

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 17/18/53.

Declared competing interests of the authors: None.

[REDACTED]

[REDACTED]

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This report should be referenced as follows:

Yang H, Al M, Kent S, McDermott K, Chen J, Tian X, Stirk L, Armstrong N. Teprotumumab for treating thyroid eye disease [ID6432]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2025.

Contributions of authors:

Huiqin Yang and Nigel Armstrong acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Seamus Kent and Marten Poley acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott, Jiongyu Chen and Xiaoyu Tian acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse events
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CAS	Clinical activity score
CD	Constant diplopia
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
CiC	Commercial in Confidence
CON	Compressive optic neuropathy
CS	Company submission
CSR	Central serous retinopathy
DARE	Database of Abstracts of Reviews of Effects
DMARD	Disease-modifying antirheumatic drug
DON	Dysthyroid optic neuropathy
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECM	Established clinical management
EQ-5D	European Quality of Life-5 Dimensions
EAG	External Assessment Group
ESHPM	Erasmus School of Health Policy & Management
ESS	Effective sample size
EUGOGO	European Group on Graves Ophthalmology
EUR	Erasmus University Rotterdam
GO-QOL	Graves' ophthalmopathy quality of life
HCRU	Healthcare resource utilisation
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ID	Intermittent/inconstant diplopia
iMTA	Institute for Medical Technology Assessment
IPD	Individual patient data
IV	Intravenous
IVMP	Intravenous methylprednisolone
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KSR	Kleijnen Systematic Reviews Ltd
LOCF	Last observation carried forward
LP	Large proptosis
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
mITT	Modified intention-to-treat
MMF	Mycophenolate mofetil
MMRM	Mixed model for repeated measures
MP	Methylprednisolone
N/A	Not applicable

ND	No diplopia
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NR	Not reported
OLE	Open-label extension
OR	Odds ratio
PAS	Patient Access Scheme
PBO	Placebo
PK	Pharmacokinetic
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RIT	Radioiodine therapy
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SP	Small proptosis
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TA	Technology Appraisal
TBII	Thyrotropin-binding inhibitory immunoglobulins
TEAE	Treatment-emergent adverse event
TED	Thyroid eye disease
TEP	Teprotumumab
TSD	Technical support document
TSH	Thyroid stimulating hormone
TSI	Thyroid-stimulating immunoglobulins
TTO	Time trade-off
UK	United Kingdom
US	United States

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1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Lack of evidence for some comparators at 2 nd line	2.3
2	Lack of adjustment for some important prognostic variables in the MAIC analysis	3.3 and 3.4
3	Sensitivity analyses by using alternative adjustment methods such as simulated treatment comparison were not conducted for the data of base-case MAIC analyses	3.3 and 3.4
4	The EAG disagrees with the company's assumption that patients remain in the same TED state from cycle 4 (24 weeks) to the end of the model	4.2.6
5	The EAG is concerned with the company's approach taken to teprotumumab transition probabilities and state membership over time	4.2.6 and 5.2.1
6	The model is not able to run a meaningful probabilistic sensitivity analysis	5.2.1
EAG = External Assessment Group; MAIC = matching-adjusted indirect comparison; TED = thyroid eye disease		

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the new technology is modelled to affect QALYs by increasing the number of patients in the "no diplopia, small proptosis" health state, which is associated with a better QoL.

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Increasing costs due to treatment acquisition.
- Reducing costs due to surgery.

- Reducing the costs related to routine monitoring and disease management, due to more patients being in a better health state.

The modelling assumptions that have the greatest effect on the ICER are:

- The health state utility values (HSUV) (company one-way sensitivity analysis).
- The assumed level of treatment waning over three years (EAG scenario analysis).

1.3 The decision problem: summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on certain comparators (Table 1.2).

Table 1.2: Key issue 1: Lack of evidence for some comparators at 2nd line

Report Section	2.3
Description of issue and why the EAG has identified it as important	The company seems to make a good case for the comparators in the DP. However, there is uncertainty as to standard of care, particularly at 2 nd line, given that percentage use is based on clinical expert opinion. Also, there is a lack of evidence presented for those comparators other than methylprednisolone at 2 nd line i.e., azathioprine, ciclosporin and orbital radiotherapy, although it does appear that the company SLR was robust enough to demonstrate that it is unlikely that there is evidence that would permit an ITC.
What alternative approach has the EAG suggested?	ITC with all relevant comparators.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Data on the percentage use of each treatment used at 1 st line and 2 nd line in order to validate the values based on company clinical expert opinion. Any evidence that might permit an ITC.
DP = decision problem; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; SLR = systematic literature review	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.3: Key issue 2: Lack of adjustment for some important prognostic variables in the MAIC analysis

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	There was a lack of adjustment for some important prognostic variables in the MAIC analysis. It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables. The duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, intravenous methylprednisolone (IVMP) and IVMP + mycophenolate mofetil (MMF) populations. Therefore, the lack of adjustment for these

Report Sections	3.3 and 3.4
	important prognostic variables in the MAIC analysis may have compromised the validity of results of MAIC analysis.
What alternative approach has the EAG suggested?	All-important prognostic variables should be adjusted for in the MAIC analysis.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that all important prognostic variables should be adjusted for in the MAIC analysis.
EAG = External Assessment Group; MAIC = matching-adjusted indirect comparison TED = thyroid eye disease	

Table 1.4: Key issue 3: Sensitivity analyses by using alternative adjustment methods such as simulated treatment comparison were not conducted for the data of base-case MAIC analyses

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The EAG requested the company to conduct sensitivity analyses by using alternative adjustment methods such as STC instead of a MAIC for the ITC analyses. In responding to the EAG's request, the company stated that due to the timeframe issue, the company was not able to conduct a further STC as a sensitivity analysis during clarification response stage. The EAG considers that, given that the sensitivity analyses by using alternative adjustment methods such as the STC approach were not conducted for the data used in the base-case MAIC analyses, it was unclear whether the results of base-case MAIC analyses were robust.
What alternative approach has the EAG suggested?	Sensitivity analyses by using STC should be conducted for the data used in the base-case MAIC analyses where possible.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that sensitivity analyses by using alternative adjustment methods such as STC should be conducted instead of the base-case MAIC analyses where possible.
EAG = External Assessment Group; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; STC = simulated treatment comparison	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.2 of this report. The EAG's summary and detailed critique can be found in Section 4, the company's cost effectiveness results are presented in Section 5, and the EAG's amendments to the company's model and results are in Section 6. The key issues in the cost effectiveness evidence are discussed below.

Table 1.5: Key issue 4: The EAG disagrees with the company's assumption that patients remain in the same TED state from cycle 4 (24 weeks) to the end of the model

Report Sections	4.2.6 and 6.1

Description of issue and why the EAG has identified it as important	In the company base-case it is assumed that patients remain in the same TED state from 24 weeks (cycle 4) to the end of the model. The 72-week follow-up data provided by the company in response to the clarification letter suggests that the rate of proptosis and diplopia response does reduce between 24 and 72 weeks for people receiving teprotumumab. Differences in state membership at week 24 between treatment arms is the key driver of model outcomes and cost effectiveness.
What alternative approach has the EAG suggested?	The EAG consider various scenarios in which there is some worsening of proptosis and diplopia symptoms at three years. The scenarios represent different levels of shift from small to large proptosis, no diplopia to intermittent/inconstant or constant diplopia, and intermittent/inconstant to constant diplopia. The range is from the company's base-case of no shift to a 30% risk shift at which point state membership is similar to IVMP and IVMP + MMF. While 72-week follow-up data is available, we cannot directly use these estimates due to conformity issues, i.e., outcomes from long-term follow-up do not map directly to TED health states or the ITC outcomes. In addition, modelling scenarios is complex due to the dependency of the model on IPD data from the Phase 2 and Phase 3 OPTIC trials which is not available to the EAG.
What is the expected effect on the cost effectiveness estimates?	Any modelling of worsening in proptosis and/or diplopia response in the teprotumumab arm compared to the comparators will increase the ICER since patients derive fewer benefits in QoL from better proptosis and diplopia outcomes and incur higher healthcare costs.
What additional evidence or analyses might help to resolve this key issue?	Exploring approaches to better representing evidence on 72-week outcomes in the model and performing scenario analyses around treatment waning.
EAG = external assessment group; IPD = individual patient data; ITC = indirect treatment comparison; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; QoL = quality of life; TED = thyroid eye disease	

Table 1.6: Key issue 5: The EAG is concerned with the company's approach taken to teprotumumab transition probabilities and state membership over time

Report Sections	4.2.6 and 5.2.1
Description of issue and why the EAG has identified it as important	The company model transitions every 6-weeks between the TED states for teprotumumab using observed data from the Phase 2 and Phase 3 OPTIC trials. This involves estimating 144 total transitions based on 80 patients and risks overfitting to the trial data. This leads to large variations in the probabilities of particular transitions across model cycles and issues due to small or zero counts for many transitions. This is particularly an issue for the PSA where the company assumed no variation in those transitions with zero counts leading to an underestimation of uncertainty. The estimates of transition probabilities for IVMP and IVMP + MMF are also dependent on the observed transitions for teprotumumab.
What alternative approach has the EAG suggested?	The EAG has done some initial exploration to assess the potential bias created using uninformative priors for cells with zero counts. A full exploration was not possible due to the dependency of the PSA on IPD data from the Phase 2 and Phase 3 OPTIC trials which is not available to the EAG (see Key issue 6).

	Alternative approaches that could be explored by the company include parametric modelling of proptosis and diplopia outcomes over time or modelling transitions directly from 0 to 24 weeks rather than every 6 weeks. The specific transitions within the first 24 weeks have minimal impact on model outcomes except insofar as they impact state membership at 24 weeks which the patients are then assumed to occupy until the end of the model.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Exploring alternative approaches to modelling proptosis and diplopia outcomes that avoid issues of overfitting to the trial data and zero probabilities for many transitions.
EAG = external assessment group; IPD = individual patient data; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; PSA = probabilistic sensitivity analysis; TED = thyroid eye disease	

Table 1.7: Key issue 6: The model is not able to run a meaningful probabilistic sensitivity analysis

Report Section	5.2.1
Description of issue and why the EAG has identified it as important	The model does not allow for PSA analyses that capture the parameter uncertainty correctly.
What alternative approach has the EAG suggested?	A version of the model is required that either includes the teprotumumab IPD or some appropriate alternative, such as synthetic IPD that correctly mimics the parameter uncertainty.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	A model version with IPD teprotumumab or appropriate alternative so that PSAs may be run, especially to explore if noninformative priors for cell counts in the transition matrices lead to a better reflection of uncertainty.
EAG = External Assessment Group; IPD = individual patient data; PSA = probabilistic sensitivity analysis	

1.6 Summary of the EAG's view

The company's base-case deterministic ICERs for teprotumumab compared to intravenous methylprednisolone (IVMP) and IVMP + mycophenolate mofetil (MMF) amounted to [REDACTED] and [REDACTED] per QALY gained, respectively. The company's one-way sensitivity analysis showed that the outcomes are most sensitive to changes in the health state utility values. The probabilistic sensitivity analysis indicated that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that teprotumumab is cost effective was [REDACTED] and [REDACTED], respectively.

Various scenarios explored by the company, either in the main submission or in response to clarification questions by the EAG led to ICERs quite close to the company base-case or slightly more favourable.

An EAG explorative scenario analysis that takes into account some worsening of proptosis and diplopia symptoms after 24 weeks based on the results of the long-term follow-up data shows that the ICERs are highly sensitive to the assumed level of treatment waning. If a small risk shift of 5% is applied the

ICERs increase by approximately 14%, and for a shift of 10% the increase in the ICER is 38%. For the worst-case scenario where treatment effect wanes to the level of IVMP (+/- MMF) after three years, the ICERs are approximately [REDACTED] per QALY gained.

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	People living with moderate-to-severe TED	People living with active moderate-to-severe TED	The company submission focuses on active disease	Active disease seems to be a reasonable qualification to the population. There is, however, an issue with the inclusion of both 1 st and 2 nd line (see Comparators).
Intervention	Teprotumumab	Teprotumumab	Not applicable	The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without teprotumumab which may include: • Corticosteroids - prednisolone - methylprednisolone - triamcinolone • Immunosuppressive agents - mycophenolate - rituximab - tocilizumab - ciclosporin • Orbital radiotherapy • Surgical interventions: eyelid surgery - orbital decompression - strabismus surgery	Established clinical management without teprotumumab which may include: • Corticosteroids - prednisolone - methylprednisolone • Immunosuppressive agents - mycophenolate - ciclosporin - azathioprine • Orbital radiotherapy	Methylprednisolone, with or without mycophenolate, is the main comparator used to treat active, moderate-to-severe TED in UK clinical practice. • Clinical opinion indicates that azathioprine is used in the NHS (usually in combination with IVMP), so it has been suggested as an additional comparator. • Rituximab and tocilizumab are not routinely available in NHS practice and are rarely used as require individual funding requests in most centres. • Triamcinolone is not widely used. • Surgical interventions are not relevant comparators for active, moderate-to-severe TED. They are usually reserved for sight-threatening disease (for which	The company seems to make a good case for the comparators in the decision problem. However, there is uncertainty as to standard of care, particularly at 2 nd line. Also, there is a lack of evidence presented for those comparators other than methylprednisolone at 2 nd line i.e. azathioprine, ciclosporin and orbital radiotherapy, although it does appear that the company systematic literature review was robust enough to demonstrate that it is unlikely that there is evidence that would permit an indirect treatment comparison.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			teprotumumab will not be licensed) or chronic TED only. The evidence base in this submission focuses on the comparison between teprotumumab and methylprednisolone, with or without mycophenolate. The other comparators (azathioprine, ciclosporin, orbital radiotherapy) are used less frequently at second and later lines, and the evidence base for their use is lacking, therefore it has not been possible to do a formal comparison. We instead suggest a conservative assumption that outcomes for teprotumumab versus methylprednisolone (with or without mycophenolate), are generalisable to other comparators (please see Section B.2.12 Interpretation of clinical effectiveness and safety evidence).	
Outcomes	The outcome measures to be considered include: - disease activity - disease severity - proptosis response - diplopia response - adverse effects - HRQoL (including psychosocial impact)	The outcome measures to be considered include: - disease activity - disease severity (note: although the clinical trial programme did not include a specific outcome for severity, it is captured via outcomes such as diplopia and proptosis)	Evidence is not included about the need for rehabilitation surgery or subsequent surgical intervention, as data on these outcomes were not collected in the clinical development programme.	The company justification for the outcomes in the decision problem seems reasonable.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	• duration of treatment response • retreatment • need for rehabilitation surgery • need for subsequent surgical intervention	• proptosis response • diplopia response • adverse effects • HRQoL (including psychosocial impact) • duration of treatment response • retreatment		
Subgroups to be considered	If evidence allows and where appropriate, the following may be considered: Subgroups by disease activity • Active • Inactive Duration of active symptom • More than 1 year • Less than 1 year Severe proptosis Severe diplopia Severe inflammation Treated versus untreated TED	Not included in the CS.	Subgroup analyses have not been included due to insufficient evidence.	The EAG considers that limiting to active disease is reasonable. The EAG have not been able to establish whether there is sufficient evidence for subgroup analyses as none were presented in the CS.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Not included in the CS.	Not included in the CS.	No subgroup analysis was considered in the CE model.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. CEA should include consideration of the benefit in the best and worst seeing eyes' perspective.			
Based on Table 1 of the CS¹ CE = cost effectiveness; CEA = cost-effectiveness analysis; CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; IVMP = intravenous methylprednisolone; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PSS = Personal Social Services; TED = thyroid eye disease; UK = United Kingdom				

2.1 Population

The population defined in the scope is:² People living with moderate-to-severe thyroid eye disease (TED), and the decision problem (DP) populations is:¹ People living with active moderate-to-severe TED. However, the proposed place in the care pathway is either 1st or 2nd line (on no response or deterioration), which the company indicates affects the comparators (see Section 2.3).

EAG comment: The focus on active disease seems reasonable. The effect of line of therapy is discussed in Section 2.3.

2.2 Intervention

The intervention in the scope and the DP are the same i.e., teprotumumab (TEPEZZA®), which is expected to be indicated in the UK [REDACTED].^{1, 2} Teprotumumab is administered by intravenous (IV) infusion. Teprotumumab (500 mg) is formulated as a white to off-white lyophilised powder in a single-dose vial for reconstitution and dilution. The recommended dose of teprotumumab is 10 mg/kg of body weight for the initial dose followed by 20 mg/kg of body weight for seven additional doses given once every 3 weeks as an IV infusion. For the first two infusions, the diluted solution is administered as an IV infusion over at least 90 minutes. If well tolerated, infusions 3 to 8 can be administered over 60 minutes every 3 weeks. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes.

EAG comment: The intervention in the scope and DP are the same, and the dosing regimen in the main Phase 2 trial (NCT01868997) and the Phase 3 OPTIC study was also as in the intended marketing authorisation.

2.3 Comparators

Several comparators as part of established clinical management (ECM) are listed in the NICE scope.² All but surgical interventions are listed in the DP,¹ the reason given by the company being that surgical interventions: *“are usually reserved for sight-threatening disease (for which teprotumumab will not be licensed) or chronic TED only.”* (see Table 2.1). However, the company submission (CS) lacks a formal comparison with any comparator except methylprednisolone, with or without mycophenolate on the basis that: *“The other comparators (azathioprine, ciclosporin, orbital radiotherapy) are used less frequently at second and later lines, and the evidence base for their use is lacking...”* (Table 2.1). Instead, the company provide a brief summary of some evidence to support the claim that: *“the outcomes observed in the clinical studies and in the MAIC versus IVMP and IVMP [intravenous methylprednisolone] + MMF [mycophenolate mofetil] are generalisable to other comparators at second line...”* (p. 125).¹

In the proposed care pathway position, the company suggests the following comparators:¹

- 1st line: IV methylprednisolone +/- mycophenolate
- 2nd line:
 - higher dose of IV methylprednisolone +/- mycophenolate
 - cyclosporin or azathioprine (usually with oral steroids)
 - orbital radiotherapy (usually with IV or oral steroids)

EAG comment: Given the lack of formal comparison, and inadequate evidence to support the claim of ‘generalisability to’, which the EAG interprets as equivalence with all other comparators, the EAG have requested the following in the clarification letter:³

- To provide a list of all treatments currently used in the population in the DP i.e., people living with active moderate-to-severe TED, with percentage use.
- To provide a full systematic review of all clinical effectiveness evidence for all relevant comparators, regardless of frequency of use in the population eligible for teprotumumab.
- To perform indirect treatment comparisons (ITCs) and a cost-effectiveness analysis (CEA) for all of these comparators.

The company responded with a table based on clinical expert opinion (see Table 2.2).

Table 2.2: Interventions used to treat active moderate-to-severe TED in UK clinical practice

Intervention	Percentage use 1L	Percentage use 2L	Company comment
IVMP	████	████	IVMP with or without MMF is mainstay treatment for active moderate-to-severe TED. It is used in almost all patients at 1 st line, and in a large proportion of patients who require a 2 nd line treatment.
IVMP with MMF	████	████	
Orbital radiotherapy (with oral or IV steroids)	████	████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Ciclosporin (with oral or IV steroids)	████	████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Azathioprine (with oral or IV steroids)	████	████	Usually restricted to 2 nd line use after IVMP with or without MMF.
Oral steroids alone	████	████	Usually only used if people are unable to have IV steroids.
Rituximab	████	████	Not available nationally (only via individual funding request) and rarely used. As such we have not proposed rituximab or tocilizumab as comparators for this appraisal.
Tocilizumab	████	████	
Triamcinolone	████	████	Not routinely used in UK clinical practice. As such, we have not proposed triamcinolone as a comparator for this appraisal.

Based on clarification letter response.⁴

1L = 1st line; 2L = 2nd line; IV = intravenous; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; TED = thyroid eye disease; UK = United Kingdom

The company also stated that:⁴

- although triamcinolone is recommended for those contraindicated for IV steroids, UK clinicians prefer oral steroids
- rituximab and tocilizumab “...are only available via individual funding requests, which as per our discussions with UK clinicians, are rarely approved or implemented in clinical practice, owing to the time taken to process such requests.” On this basis they are excluded as comparators.

The company then continue to state that the evidence base for the remaining comparators i.e., orbital radiotherapy (with oral or IV steroids), ciclosporin (with oral or IV steroids), and azathioprine (with oral or IV steroids) is lacking. They then provide an informal summary of some studies for these

comparators, rather than the full systematic literature review (SLR) requested by the EAG, although they state that the studies were included in the SLR from the company submission (CS). In particular, they included:

- one study for azathioprine, CIRTED, which also studied radiotherapy, and is a multicentre, double-blind, randomised controlled trial (RCT) conducted at six centres in the UK in 126 adult patients with active, moderate-to-severe TED. With regards to the choice of CIRTED they state:⁴ “...according to clinical advice received, is considered the best available evidence for radiotherapy and azathioprine.”
- three further studies of radiotherapy were also included:
 - Nicosia et al. (2019)⁵ - retrospective single-arm, 40 patients with moderate-to-severe TED not responsive or resistant to high dose systemic steroids or with severe diplopia.
 - Wu et al. (2015)⁶ – double-blind, self-controlled study of 51 patients in a single hospital outpatient ophthalmology clinic in China (population description not reported).
 - Stoyanova et al. (2023)⁷ – single-arm, 26 patients (population description and location not reported).

However, they concluded that an ITC using these studies was not feasible for the following reasons:⁴

- CIRTED⁸ - does not report appropriate data in terms of diplopia response or change from baseline in proptosis, and instead reports outcomes in the form of a binary composite clinical outcome score
- Nicosia et al. (2019)⁵ - proptosis and diplopia measurements are reported in a three-to-six-month range post radiotherapy, and patients with sight threatening TED included.
- Wu et al. (2015)⁶ - does not specify the timepoints when proptosis scores were collected, nor does it provide any data on diplopia.
- Stoyanova et al. (2023)⁷ – “...single-arm design and had a small sample size, which would lead to uncertain comparative effectiveness estimates...”

In the absence of an ITC, the company conducted three scenarios, one for each comparator (radiotherapy, ciclosporin, and azathioprine), each in combination with intravenous methylprednisolone (IVMP) +/- mycophenolate mofetil (MMF), at 2nd line, assuming efficacy to be that of IVMP +/- MMF at 1st line.

The EAG has checked the SLR reported in Appendix D,⁹ and concluded that the eligibility criteria were appropriate to locate studies of the three comparators at 2nd line i.e., radiotherapy, ciclosporin and azathioprine, and that no studies were reported to have been excluded that could have provided data for an ITC. Therefore, it does appear that an ITC was not feasible for these three treatments. It also appears reasonable to believe that an assumption of efficacy at 2nd line of each comparator in combination with IVMP +/- MMF equal to IVMP +/- MMF at 1st line is conservative. Nevertheless, the uncertainty due to the proportion of patients receiving each treatment being based only on clinical expert opinion, and the lack of evidence on efficacy does imply a key issue, regardless of the difficulty in resolving it.

2.4 Outcomes

All outcomes in the NICE scope were included in the DP except need for surgery of some kind, which the company stated was not an outcome in their trials.

EAG comment: No major concerns.

2.5 Other relevant factors

None.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed an SLR to identify and summarise the available RCT and other relevant evidence relating to the efficacy and safety of teprotumumab and other treatments in patients with moderate-to-severe TED.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.¹ The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.¹⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SLR conducted to identify relevant clinical evidence on the efficacy and safety of teprotumumab and other treatments for TED.⁹ Searches were conducted in June 2023 and updated in September 2024.

EAG comment:

- Searches were undertaken to identify clinical evidence on the efficacy and safety of teprotumumab and other treatments for TED. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 4, 9}
- The following databases were searched from inception on 9 June 2023: Embase, MEDLINE, the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE). Update searches were conducted on 11 September 2024.
- Four key conference proceedings were manually searched for the last four years (where available). Four clinical trials registries were searched in May 2023, and updated in September 2024. Seventeen HTA sources were searched in September 2024 with no date limit. Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked.
- The database searches for the clinical effectiveness SLR combined a facet for TED with a facet containing search terms for teprotumumab and its comparators. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Animal-only studies were excluded, and no date limit was applied.
- Search results were limited to studies published only in English. The EAG was concerned that limiting the MEDLINE, Embase and CENTRAL searches to English language may have introduced potential language bias. Current best practice states that 'To reduce the risk of introducing bias, searches should not be restricted by language'.¹¹
- All searches were well-structured, transparent and reproducible. Full details of the update searches were not originally included in the CS, but were provided in response to clarification.⁴
- All clinical effectiveness searches contained a good range of search terms, synonyms and subject headings. Study design filters, where used, were not referenced, so it was unclear whether the filters used were published objectively-derived filters. The filters contained a combination of subject heading terms and free text terms however, and the EAG deemed them to be adequate.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.1.

Table 3.1: PICOS eligibility criteria used in the search strategy

PICOS	Inclusion	Exclusion
Population	Patients with moderate-to-severe active TED Patients with chronic or acute TED Patients with active or inactive TED Patients with inflammatory or non-inflammatory TED Patients with CON or DON	Disease other than TED Non-human Healthy volunteers
Interventions	Approved in the US as a treatment for TED Teprotumumab Recommended in guidelines/off-label use <i>Immunomodulators:</i> Glucocorticoids (oral or IV, alone or in combination) Betamethasone Doxycycline Methylprednisone <i>Conventional DMARDs:</i> Mycophenolate Cyclosporin Azathioprine <i>Other – surgery/radiotherapy:</i> Orbital radiotherapy Orbital surgery (decompression [including 2-wall vs 3-wall vs 4-wall vs fat decompression], strabismus, eyelid surgery [blepharoplasty]) Orbital surgery with pharmacological interventions <i>Monoclonal antibodies:</i> Tocilizumab Rituximab Investigational compounds <i>Monoclonal antibodies:</i> Batoclimab Secukinumab Vunakizumab (SHR-1314) Infliximab Adalimumab VRDN-002 Efgartigimod VRDN-001 VB421 K1-70 <i>Other – pharmacologic:</i> Atorvastatin Bimatoprost Sirolimus (Rapamycin)	Studies not including at least one of the interventions listed in the inclusion criteria

PICOS	Inclusion	Exclusion
	Selenium <i>Immunomodulators:</i> Antithymocyte globulin ATX-GD-59 <i>T-cell co-stimulatory treatments:</i> Aflibercept Etanercept <i>Kinase inhibitors:</i> Linstinib	
Comparators	Any included intervention Any non-included intervention	None
Outcomes	<i>Efficacy:</i> Overall response Proptosis response CAS response Change from baseline in proptosis Diplopia response Strabismus Extraocular motility Flare Recurrent disease Other clinical outcomes <i>Safety:</i> Treatment-related grade 3 or 4 AEs Any grade 3 or 4 AEs SAEs Other safety outcomes <i>HRQoL and PROs:</i> Disease-related HRQoL outcomes (GO-QOL, TED-QoL)	No restrictions
Study design	RCTs, single-arm, non-RCTs Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	Non-human, pre-clinical studies Reviews, Editorials, Notes, Comments, Letters Case reports/case series
Language restrictions	English language only	Full-text articles not published in English
Timeframe	2013 to present	Published prior to 2013
Based on Table 7, CS. ¹ AE = adverse events; CAS = clinical activity score; CON = compressive optic neuropathy; DMARDs = disease-modifying antirheumatic drugs; DON = dysthyroid optic neuropathy; GO-QOL = Graves' ophthalmopathy quality of life; HRQoL = health-related quality of life; IV = intravenous; MAIC = matching-adjusted indirect comparison; PRO = patient-reported outcome; RCT = randomised controlled trial; SAE = serious adverse event; TED = thyroid eye disease; TED-QoL = thyroid eye disease quality of life; US = United States		

3.1.3 Critique of data extraction and data screening

The CS provides well described detail on the process of screening and data extraction.⁹ It is confirmed by the company that two reviewers independently screened all titles and abstracts and that

disagreements were then resolved by the involvement of a third independent reviewer. All articles obtained for full-text screening were then screened by two independent reviewers, and any discrepancies in their decisions were resolved by a third, independent reviewer. Data extraction was also conducted by two independent reviewers and independently checked by a third, senior reviewer. In the event of inconsistency, a consensus-based discussion or a third reviewer was consulted to make the final decision.

EAG comment: This is well reported by the company in a clear format and informs that screening and data extraction was conducted in the optimal way to minimise likelihood of error and bias. Screening and data extraction was performed by two independent reviewers, and the involvement of a third reviewer, when necessary.

3.1.4 Quality assessment

It was not clear how quality appraisals were conducted. While data screening and data extraction were conducted in the optimal manner, there is a lack of information in the submission to describe how quality appraisals were performed. We asked the company to provide additional information and in their response to clarification they stated that:⁴ *“For the clinical SLR, risk of bias (RoB) assessment was carried out according to Version 2 of the Cochrane risk-of-bias tool for randomised trials. This is the most up-to-date version of the Cochrane risk-of-bias tool designed, validated for RCTs, and recommended by the Cochrane Handbook. RoB was carried out by one reviewer.”*

EAG comment: Given that the company have stated that one reviewer carried out the assessment and that they do not confirm if a second reviewer checked the initial appraisal, it must be assumed that the likelihood of error and potential bias is increased.

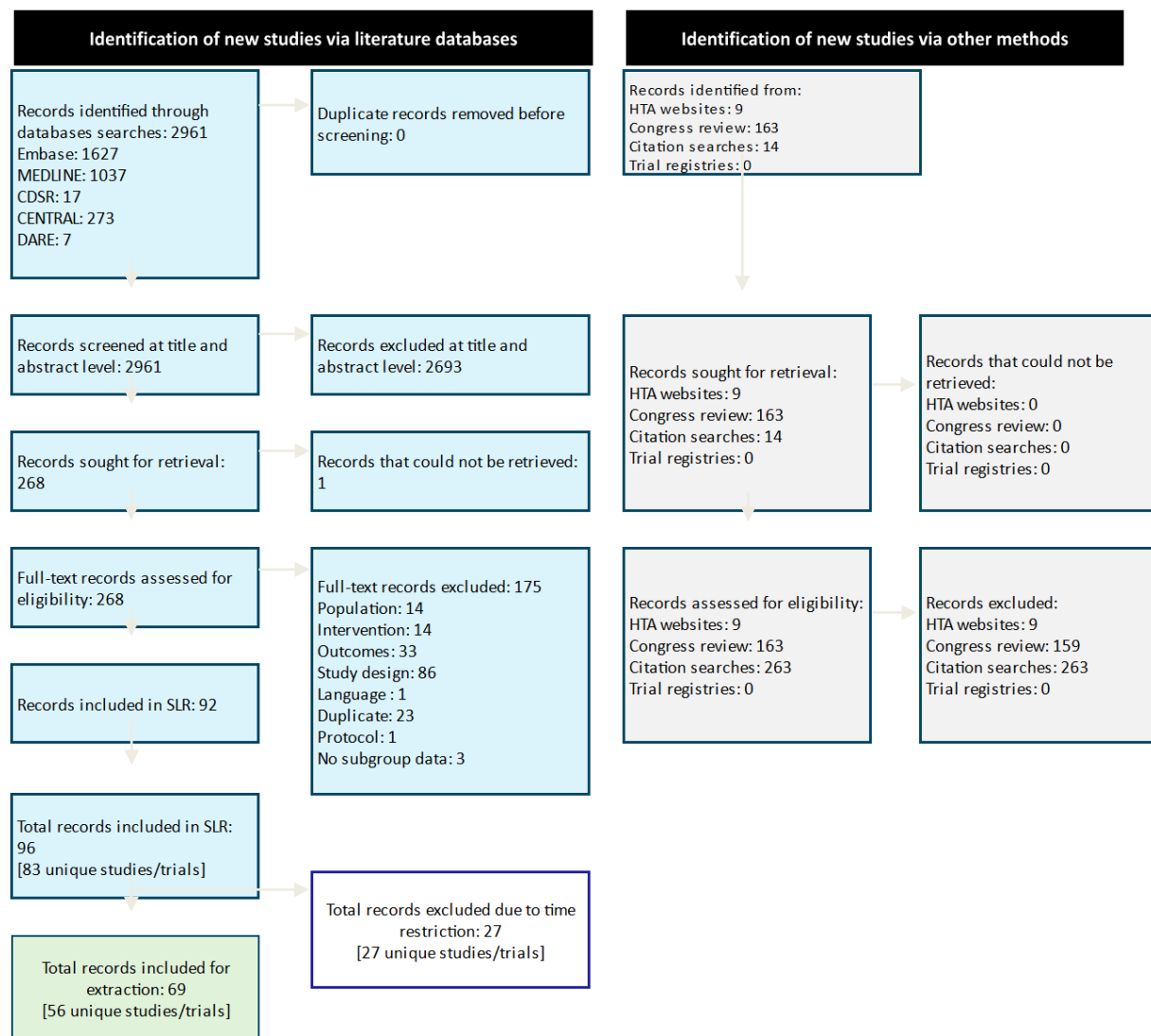
3.1.5 Evidence synthesis

In the absence of a head-to-head trial comparing teprotumumab with other comparators, matching-adjusted indirect comparison (MAIC) analysis was conducted to determine the relative efficacy in patients with moderate-to-severe TED. Details are provided in Sections 3.3 and 3.4 for the ITC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

A total of 2,961 records were identified by both combined searches which were screened at the title and abstract level against the inclusion and exclusion criteria. Of these 268 were then included for full-text screening. After full-text screening, 92 reports met the review inclusion criteria. There were 163 reports identified through congress searches, 14 through bibliographic searches, and nine reports through HTA sources. After assessing the records against the PICOS criteria, four from methods other than database searches were deemed eligible. A total of 96 reports from 83 unique studies were included in the SLR. Following the addition of date restrictions to include studies published after 2013, a further 69 reports from 56 unique studies were included. Figure 3.1 below contains the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for study identification.

Figure 3.1: PRISMA Diagram – Clinical Efficacy SLR

Based on Figure 9, CS.¹

Records with duplicated information were not extracted.

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; DARE = Database of Abstract of Reviews of Effects; HTA = Health Technology Assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

3.2.2 Details of included trials

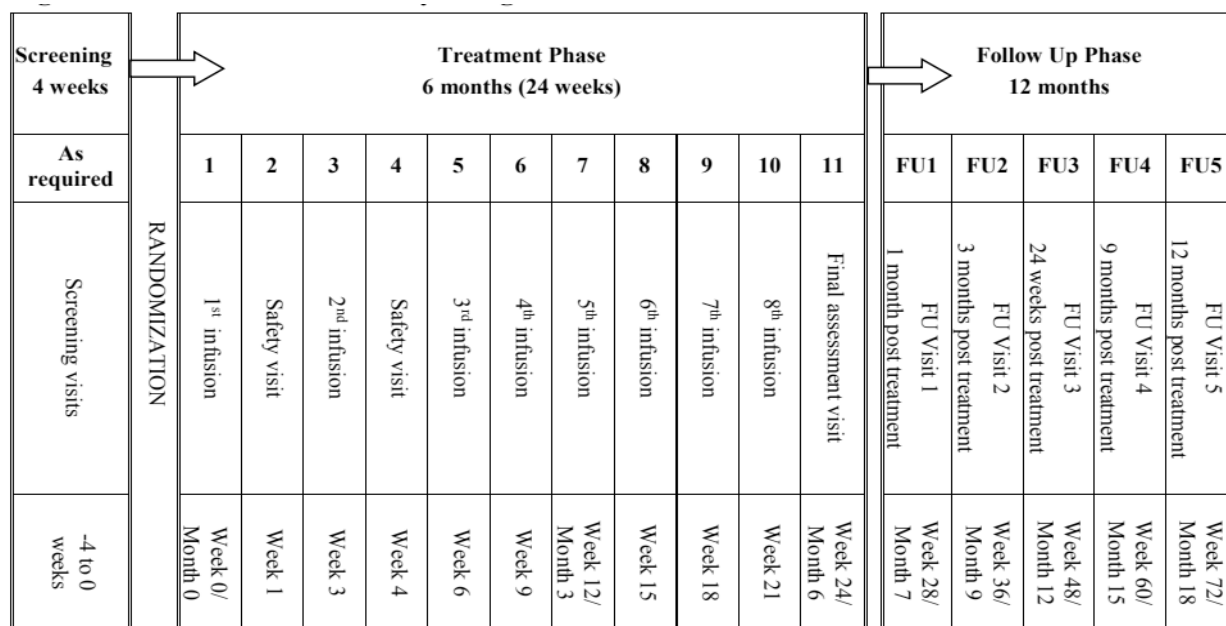
3.2.2.1 The Phase 2 trial (NCT01868997)

This as a multicentre (15 sites in US and Europe), randomised, double-blind, placebo-controlled, two-arm study which ran from July 2013 to February 2017 to evaluate the efficacy, safety, and tolerability of teprotumumab (investigational name: HZN-001) in patients with acute, moderate-to-severe TED.¹ Eighty-eight patients were enrolled^{12, 13} and randomised in a 1:1 ratio to receive either teprotumumab or placebo. Patients received eight IV infusions (once every 3 weeks), over 6 months with an initial dose of 10 mg per kg of body weight, followed by 20 mg per kg for the remaining seven infusions.¹ Key inclusion criteria included ages from 18 to 75 years, diagnosis of ophthalmopathy within 9 months from the onset of symptoms, had a clinical activity score (CAS) of four or more on a seven-point scale

(with a score of ≥ 3 indicating acute thyroid-associated ophthalmopathy) in the more severely affected (study) eye, had not previously received surgical or medical treatment for TED (with the exception of local supportive measures and oral steroids if the cumulative dose was <1000 mg methylprednisolone or equivalent) and did not require immediate surgical ophthalmological intervention.

The trial consisted of a screening phase of 4 weeks (± 2 weeks) with no treatment; a double-blinded treatment phase of 24 weeks; and a follow-up phase of 48 weeks with no additional treatment during at least the first 12 weeks (see Figure 3.2).

Figure 3.2: Schematic of Phase 2 RCT design



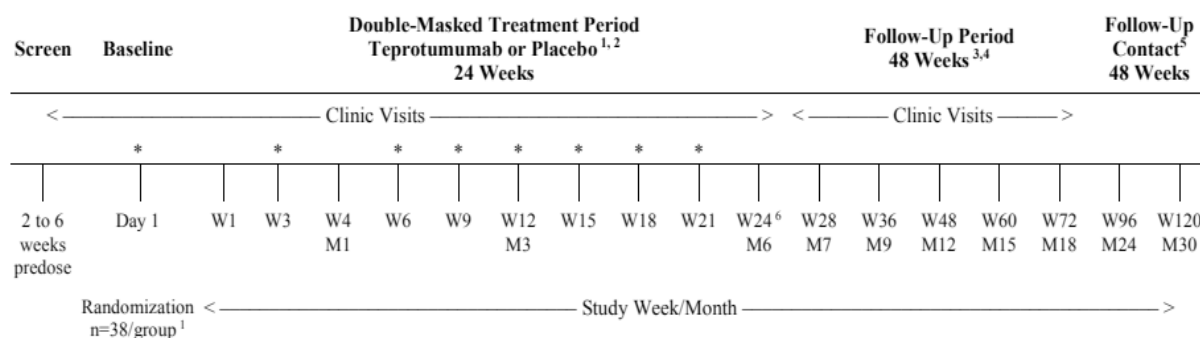
Based on Figure 10, CS.¹

CS = company submission; FU = follow-up; RCT = randomised controlled trial

3.2.2.2 OPTIC trial (NCT03298867)

This was a Phase 3, randomised, double-blind, placebo-controlled, multicentre trial to investigate the efficacy, tolerability, and safety of teprotumumab in the treatment of subjects with moderate-to-severe acute TED¹. Participants were screened for the study within 2 to 6 weeks prior to the Baseline (Day 1) Visit and if included, randomised on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive eight infusions of teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining seven infusions) or placebo. All subjects entered a 24-week double-blind treatment period, during which the study drug was infused on Day 1 (Baseline) and weeks 3, 6, 9, 12, 15, 18 and 21 (with a final visit at Week 24).¹

At Week 24, participants who were proptosis non-responders (study eye had <2 mm decrease in proptosis) were eligible to enter the open-label extension (OLE) study, OPTIC-X. Proptosis responders, as well as non-responders who chose not to enrol in the OLE study, entered a follow-up period of up to 48 weeks, during which study drug was not administered.¹ A schematic of the OPTIC trial design is presented at Figure 3.3.

Figure 3.3: Schematic of OPTIC study design

Based on Figure 11, CS.¹

* Infusion of study drug.

CS = company submission; M = month; OLE = open-label extension; q3W = every three weeks; TED = thyroid eye disease; W = week

1. Subjects were randomised in a 1:1 ratio (stratified by tobacco use status) to receive: a. Teprotumumab 20 mg/kg (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining seven infusions); or b. Placebo (placebo q3W for all eight infusions).

2. Visit windows were ± 1 day for weeks 1 and 4, ± 3 days for weeks 3, 6, 9, 12, 15, 18 and 21, and ± 7 days for Week 24.

3. Subjects who were proptosis responders or non-responders who do not elect to participate in the OLE study entered a follow-up period. Subjects who were responders at Week 24 but relapse during the follow-up period may have enrolled in the OLE study if they met the criteria defined in Section 9.3.4 of the clinical study report.

4. Visit windows of ± 7 days.

5. Subjects who completed the week 72 visit were contacted via phone or email by research staff to enquire if any treatment for TED had been received since last study contact.

6. Subjects who were proptosis non-responders at Week 24 of the double-masked treatment period were offered the option to enter an OLE study.

Given the inclusion of the two principal sources of evidence, the CS contained a tabulated summary of the trial characteristics which provides a helpful and informative overview of the important aspects of the study methodologies.¹ These details are included in Table 3.2 below.

Table 3.2: Comparative methodology of the Phase 2 and Phase 3 Optic RCTs

Study ID/name	Phase 2	Phase 3 (OPTIC)
Clinicaltrials.gov ID	NCT01868997	NCT03298867
Study design	Phase 2, multicentre, double-blind, randomised, placebo-controlled trial	Phase 3, multicentre, double-blind, randomised, placebo-controlled trial
Duration	Each trial consisted of 3 phases: a screening phase of 4 weeks duration (± 2 weeks) a double-blind treatment phase of 24 weeks a follow-up phase of 48 weeks	
Location(s)	The trial was conducted at 15 sites, including 11 sites in the United States and 4 sites in Europe	The trial was conducted at 13 sites, including 8 sites in the United States and 5 sites in Europe (Germany, Italy)
Eligibility criteria for participants	Key inclusion criteria Aged 18-75 years (inclusive)	Key inclusion criteria Aged 18-80 years (inclusive)

Study ID/name	Phase 2	Phase 3 (OPTIC)
	Clinical diagnosis of Graves' disease associated with TED with a CAS ≥ 4 (on the 7-point version of the scale) for the most severely affected eye Ophthalmopathy diagnosis fewer than 9 months from onset of TED as determined by patient records No previous medical or surgical therapy for TED, excluding local supportive measures and oral glucocorticoids (a cumulative dose of ≤ 1 g of methylprednisolone or equivalent, with a 6-week washout period) Key exclusion criteria Patients with optic neuropathy, severe ocular surface damage Improvement in CAS of ≥ 2 points between screening and baseline Treatment with oral or IV steroids or any other immunosuppressive agent for any indication in the previous 3 months. Topical steroids for dermatological conditions were not excluded Any treatment with any investigational agent for any condition in the past 60 days or during the trial. Previous orbital irradiation or any previous treatment with rituximab	Clinical diagnosis of Graves' disease associated with acute TED with a CAS ≥ 4 for the most severely affected eye at screening and baseline. Having ocular symptoms fewer than 9 months before the baseline assessment Key exclusion criteria Decreasing visual acuity or a visual-field or colour vision defect from optic nerve involvement within the previous 6 months Previous orbital irradiation or surgery for TED Previous glucocorticoid use (cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED) Previous treatment with rituximab or tocilizumab
Treatment group(s)^a	1:1 randomisation to teprotumumab (n=42) or placebo (n=45)	1:1 randomisation to teprotumumab (n=41) or placebo (n=42)
Dosing regimen	Patients received a total of eight IV infusions: 10 mg per kilogram of body weight for one initial infusion, followed by 20 mg per kilogram of body weight for seven subsequent infusions (one every 3 weeks for 21 weeks)	
Permitted and disallowed concomitant medication	No prior or concomitant medication or other surgical or medical therapy were permitted for the treatment of TED with the exception of simple analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory therapies). Supportive treatment for AEs was permitted throughout the study at the discretion of the investigator with the exception of oral and systemic corticosteroids. Corticosteroids (IV dexamethasone up to a maximum dose of 20 mg) could only be administered as part of a premedication regimen for patients experiencing infusion	

Study ID/name	Phase 2	Phase 3 (OPTIC)
	associated events. The use of any immunosuppressant i.e., rituximab, tacrolimus, etc., for treatment of any condition was also excluded.	
Primary outcomes (including scoring methods and timings of assessments)	A reduction in overall CAS ≥ 2 points and a reduction in proptosis ≥ 2 mm in the study eye (composite endpoints) in the absence of a corresponding amount of worsening in the non-study eye at week 24	Proptosis response (defined as a reduction in proptosis of ≥ 2 mm from baseline in the study eye without a corresponding increase of ≥ 2 mm in the fellow eye) at week 24
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints included^{13, 14}: reduction of proptosis: assessed by the Hertel exophthalmometer for each eye reduction of CAS: consisted of seven components, with each component being scored as present (one) or absent (zero). The score is the sum of components. A change of two points was considered to be clinically relevant subjective diplopia: based on Gorman Grading of diplopia which categorises patients to four grades. A change of 1 grade was considered to be clinically relevant. The change in GO-QOL score: a change of six points from the range of 0 to 100 points in one or both visual-function and appearance subscales was considered to be clinically important for less invasive treatment safety: assessed by the incidence of AEs, SAEs, and withdrawals due to AEs, ECGs, vital signs, physical and ophthalmic examination, and laboratory parameters (haematology, biochemistry, and urinalysis).	Overall response: defined as a reduction of ≥ 2 points in the CAS plus a reduction in proptosis of ≥ 2 mm without a corresponding increase (of ≥ 2 points or ≥ 2 mm) in the fellow eye. Percentage of subjects with a CAS of 0 or 1 (no or minimal inflammatory symptoms). Mean change in proptosis. Diplopia response: defined as a reduction in diplopia of ≥ 1 grade from baseline. Mean change in overall score on the GO-QOL. Safety^b
Other outcomes used in the economic model/specified in the scope	N/A	N/A
Statistical Analysis	A sample size of 84 was required to have at least 80% power to detect a between-group difference if 42 patients per trial group had data that could be evaluated. All statistical tests were 2-sided and performed at the 5% significance level. No interim data analysis was performed.	A sample size of 38 participants per trial group was estimated to provide 90% power to detect a 39 percentage-point difference between arms at a two-sided alpha level of 0.05 and allow for a rate of discontinuation of 16% All efficacy analyses were performed in all patients who

Study ID/name	Phase 2	Phase 3 (OPTIC)
	The analysis of efficacy was performed in all randomised patients who received at least 1 infusion (i.e., ITT population). Safety analyses were conducted in participants who received teprotumumab or placebo The primary analysis was a logistic regression model with the intervention group as model effect and smoking as a covariate. Patients who did not have week 24 data for any reasons were considered to have treatment failure. Results of a stratified Cochran–Mantel–Haenszel chi-square test, with smoking status as the stratification factor, enabled confirmation of the logistic analysis results. For assessment of the secondary endpoints, a mixed model of repeated measurements was fit to the individual change from baseline with the use of the PROC MIXED procedure in SAS software. Each baseline score (including smoking status, intervention group, time, time according to intervention, and time according to baseline interaction) was incorporated into the analysis. Responses in the non-study eye were assessed with the use of identical analyses Further details of the statistical analysis and analysis sets are provided in Section B.2.4 ‘Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence’.	underwent randomisation (i.e., ITT population) Analyses to evaluate the sensitivity of the ITT analyses were performed in all patients who underwent randomisation, received ≥ 1 infusion, had at least one postbaseline value, and completed the treatment period (i.e., per-protocol population)

Based on table 10, CS.¹

^a 88 patients underwent randomisation, of these, 87 patients had at least 1 infusion and were considered the ITT population

^b Safety was monitored during the Phase 3 trial especially for the AEs of special interest, including anaphylaxis, infusion related reactions, hyperglycaemia, muscle spasms, diarrhoea, and hearing impairment

AE = adverse event; CAS = clinical activity score; CS = company submission; ECG = electrocardiogram; GO-QOL = Graves’ ophthalmopathy-specific quality-of-life questionnaire; ITT = intention-to-treat; IV = intravenous; N/A = not applicable; RCT = randomised controlled trial; SAE = serious adverse event; TED = thyroid eye disease

3.2.2.3 External validity

The Phase 2 trial included only 10 participants that were UK based, and the company did not provide sufficient evidence or documented clinical opinion to support the argument that this trial population would be generalisable to the population in England and Wales, or to adequately describe the clinical population in England and Wales (see Section 3.2.4). The OPTIC trial did not contain any UK based

participants. The justification from the company about the relevance of this population to the UK was provided in the response to clarification⁴ and is described elsewhere in this report (Section 3.2.4). The EAG does not consider there to have been sufficient arguments made for the generalisability of these populations to the UK. Additionally, the EAG raised concerns regarding the comparator medications and lack of formal comparison, uncertainty as to standard of care, particularly at 2nd line, the proportions of patients likely to be receiving said treatments, and inadequate evidence essentially based on clinical opinion to support the claim of ‘generalisability to’ (see Section 2.3).

EAG comment: The EAG remains unconvinced by the insufficient evidence and undocumented clinical opinion in regard to the relevant population, comparator medications and proportions of patients. We highlight the need for appropriate auditable evidence.

3.2.3 Statistical analysis

This section includes an overview of the statistical aspects of the included studies and describes the methods and approaches as reported in the CS.¹

3.2.3.1 Phase 2 trial

At the baseline visit (week 0), patients who met all inclusion and exclusion criteria were randomly assigned to receive teprotumumab or placebo in a 24-week intervention phase of the trial. In total, 112 patients were screened, and 88 patients were eligible for randomisation. Of these patients, 45 patients in the placebo group and 42 patients in the teprotumumab group had at least one infusion of teprotumumab or placebo and were considered as the intention-to-treat (ITT) population. One patient who was randomly assigned to teprotumumab was excluded from the ITT population after withdrawing consent before the drug was administered due to difficulty with blood draws. Figure 3.4 provides an overview of flow through the trial.

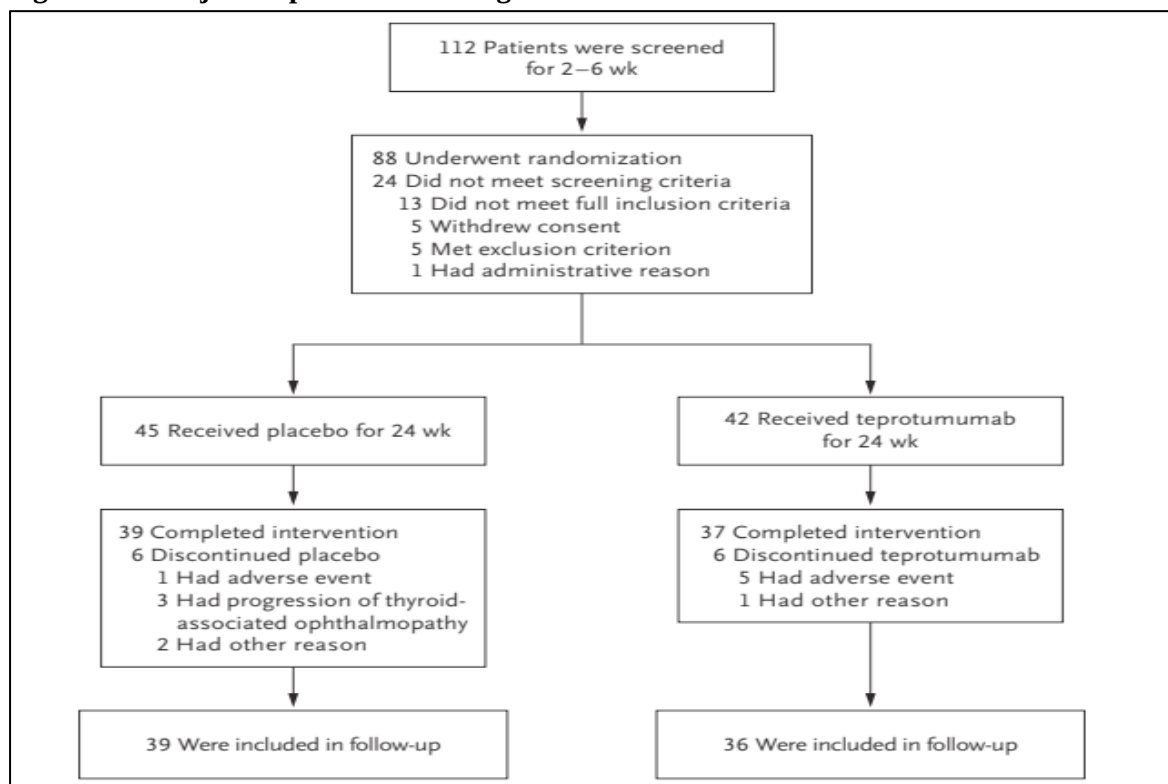
The CS summarises the approach as follows:¹

- *A screening phase of 4 weeks ($\pm$ 2 weeks) with no treatment. Subjects attended the clinic once or twice, or as required, during the screening period.*
- *A double-blind treatment phase of 24 weeks. Subjects attended clinic visits at Week 0 (Baseline visit, 1st infusion), Weeks 1 and 3 (2nd infusion), 4 and 6 (3rd infusion), 9 (4th infusion), 12 (5th infusion), 15 (6th infusion), 18 (7th infusion), 21 (8th infusion), and 24 (final assessment visit). Research staff telephoned subjects focusing on safety and tolerability aspects the day after infusion for the 1st and 2nd infusions, and thereafter as required. Research staff also contacted subjects who experienced an infusion-related event the day after the infusion.*
- *A follow-up phase of 48 weeks with no additional treatment during at least the first 12 weeks. Subjects attended clinic visits at Week 28, 36, 48, 60, and 72.*

The CS clarifies that: “Subjects underwent eligibility assessments during screening. Eligible subjects who satisfied study entry criteria were randomly assigned to the double-masked treatment phase in a 1:1 ratio to receive a starting dose of 10 mg/kg of teprotumumab or placebo once every 3 weeks (q3W) intravenously. At Week 3, the dose was escalated to 20 mg/kg IV q3W. Following dose escalation, subjects continued at this dose level for all subsequent infusions. In the case of an intolerable adverse event (AE), subjects were to be withdrawn from the study. During the 24-week active treatment period, subjects were evaluated at clinic visits every 3 weeks and, if appropriate, by telephone contact by

research staff. Measurements for efficacy, tolerability, safety, biomarkers, and pharmacokinetics were performed according to the assessment schedule”.¹

Figure 3.4: Subject disposition flow diagram – Phase 2 RCT



Based on Figure 2, CS appendices.⁹

CS = company submission; RCT = randomised controlled trial; wk = week

All statistical tests were 2-sided and were performed at the 5% significance level except where otherwise noted. Baseline was defined as the last pre-dose measurement unless otherwise specified. Change from baseline was the measurement at each time point minus baseline. Continuous endpoint summaries included the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Categorical endpoint summaries included the frequency and percentage of subjects in each category. In general, the denominator for the percentage calculation was based upon the total number of subjects in the study population for each treatment, unless otherwise specified.¹

Primary and secondary endpoints were tested in a hierarchical stepwise fashion, comparing teprotumumab versus placebo. If the primary efficacy analysis achieved significance at the 0.05 alpha level, then the secondary endpoints were evaluated for significance at the same level in the following order 1) Graves’ ophthalmopathy-specific quality-of-life questionnaire (GO-QOL) - overall score; 2) proptosis; 3) CAS; 4) GO-QOL - visual functioning score; and 5) GO-QOL - appearance score. Testing was to continue in numbered order until the first nonsignificant p-value was encountered, at which time formal statistical testing would cease.¹

3.2.3.2 Phase 3 trial

Patients were screened 2 to 6 weeks prior to the baseline (Day 1) visit. Eligible participants were randomised in a 1:1 ratio (stratified by tobacco use status) to receive either eight infusions of

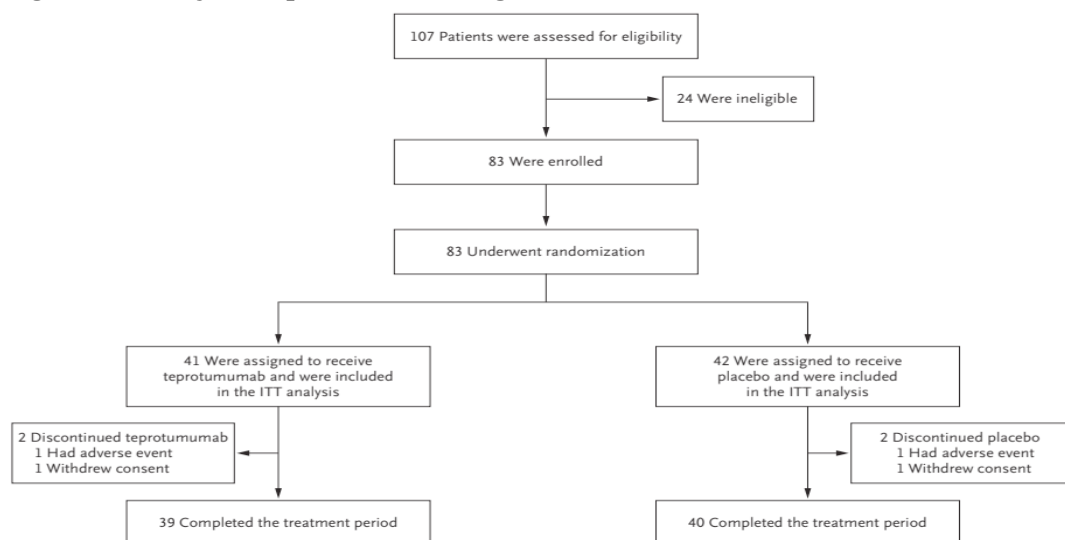
teprotumumab (10 mg/kg for the first infusion and 20 mg/kg for the remaining seven infusions) or placebo.

All participants entered a 24-week double-blind treatment period, during which study drug was infused on Day 1 and weeks 3, 6, 9, 12, 15, 18 and 21. Week 24 was the final visit.¹

At the end of week 24, patients who were proptosis non-responders were eligible to enter an OLE study (OPTIC-X). Proptosis responders, as well as non-responders who chose not to enrol in the OLE study, entered a follow-up period, during which study drug was not administered. Clinic visits were scheduled for weeks 28, 36, 48, 60 and 72 (months 7, 9, 12, 15 and 18) during the follow-up period. Subjects who were responders at week 24 but who met the re-treatment criteria due to a relapse during the follow-up period could also enrol in the OLE study.¹

Those patients who completed the week 72 visit were contacted 6 and 12 months later to enquire if any treatment for TED had been received since last study contact. If yes, the subject was questioned regarding type of treatment and outcome/response. The treatment-free follow-up period was completed with final study contact (week 120) or earlier if the subject withdrew prematurely.¹

Figure 3.5: Subject disposition flow diagram – Phase 2 RCT



Based on Figure 3, CS appendices⁹

CS = company submission; ITT, intention-to-treat; RCT = randomised controlled trial

The ITT population was used for all analyses of efficacy endpoints and included all subjects randomised to treatment. The modified intention-to-treat (mITT) population and the per protocol (PP) population were used to evaluate sensitivity of the primary efficacy analysis. The safety population was used for all analyses of safety endpoints and included all subjects who received at least one dose of study drug. The pharmacokinetic (PK) population included all subjects who received at least one dose of study drug and had at least one quantifiable PK serum concentration measurement.¹

3.2.3.3 Statistical comparison

The company tabulated a comparative summary of the statistical aspects of the two included trials. This is detailed in Table 3.3 below.

Table 3.3: Statistical summary for the Phase 2 and OPTIC trials

Trial no. (acronym)	Phase 2	OPTIC
Hypothesis objective	The primary objective was to investigate the efficacy, safety, and tolerability of teprotumumab administered every 3 weeks for 6 months, in comparison to placebo, in the treatment of subjects suffering from active TED.	The overall objective of the study was to investigate the efficacy, tolerability and safety of teprotumumab (HZN-001), administered every 3 weeks (q3W) for 24 weeks, in comparison to placebo, in the treatment of subjects with moderate-to-severe active TED. The null hypothesis tested for the primary efficacy endpoint was that teprotumumab and placebo achieved equal proportions of proptosis responders at Week 24. The corresponding alternative hypothesis was that teprotumumab achieved an unequal proportion of proptosis responders at Week 24 compared to placebo. The primary efficacy endpoint was achieved if the null hypothesis was rejected at the 0.05 alpha level in favour of teprotumumab.
Statistical analysis – efficacy analysis	To control for overall Type 1 error, the primary and secondary endpoints were tested in a hierarchical stepwise fashion, comparing teprotumumab versus placebo. If the primary efficacy analysis achieved significance at the 0.05 alpha level, then the secondary endpoints were evaluated for significance at the same level in the following order 1) GO-QOL - overall score; 2) Proptosis; 3) CAS; 4) GO-QOL - visual functioning score; and 5) GO-QOL- appearance score. Testing was to continue in numbered order until the first nonsignificant p-value was encountered, at which time formal statistical testing would cease.	For prespecified primary and secondary outcome measures, teprotumumab was tested against placebo at the 0.05 significance level only if the test statistic was statistically significantly in favour of teprotumumab for the outcome measure preceding it in the hierarchical order. Main analyses were performed on the study eye when appropriate.
Statistical analysis – primary efficacy analysis	The primary result of the primary endpoint was based on the ITT population using a logistic regression model with treatment group as the model effect and smoking status as a covariate. The same analysis was performed using the mITT population (if different from the ITT population) and the PP population to evaluate sensitivity.	The primary analysis of the proptosis responder endpoint 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 randomisation, tobacco use (non-user, user). Estimates from the two strata were combined using Cochran-Mantel-Haenszel weights. The test statistic was calculated by dividing the stratified difference by the standard error. A two-sided p-value

Trial no. (acronym)	Phase 2	OPTIC
		was calculated assuming that the test statistic was distributed as a standard normal random variable under the null hypothesis. The primary efficacy analysis was repeated for the mITT and PP populations as sensitivity analyses. 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. 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). Sensitivity analyses were conducted using the primary analysis method to evaluate the impact of missing data. Time to proptosis response was characterised by Kaplan-Meier estimates and the treatment group difference was assessed by the log-rank test stratified by tobacco use status (non-user, user)
Statistical analysis – secondary efficacy analysis	The secondary efficacy endpoints included quality of life scores (GO-QOL), proptosis, and CAS. For each secondary endpoint, an MMRM was fit to the individual change from baseline scores, incorporating the baseline score, smoking status, treatment group, time, time by treatment, and time by baseline score interaction.	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. Secondary efficacy endpoints of change in proptosis and change in GO-QOL transformed overall score were analysed with a 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 unstructured variance covariance matrix was used.
Sample size, power calculation	Planned enrolment for the study was approximately 84 subjects (42 per treatment group). 88 subjects were enrolled. All statistical tests were 2-	Planned enrolment for the study was 76 subjects (38 per treatment group). All statistical tests were 2-sided and

Trial no. (acronym)	Phase 2	OPTIC
	sided and were performed at the 5% significance level except where otherwise noted.	were performed at the 5% significance level except where otherwise noted.
Data management, patient withdrawals	Subjects who dropped out of the study were encouraged to return at 24 weeks for an evaluation, which was used in the ITT analysis. Dropout subjects who did not return for the week 24 assessment, or subjects missing the week 24 evaluation, were considered treatment failures for the primary efficacy analysis.	Subjects missing the week 24 evaluation were considered treatment failures (non-responders) for the primary analysis. Further, subjects who prematurely discontinued study drug dosing prior to week 21 during the double-blind treatment period were analysed as treatment failures (non-responders), unless an assessment at week 24 was available.
Based on table 15, CS. ¹ CAS = clinical activity score; CS = company submission; GO-QOL = Graves' ophthalmopathy quality of life; ITT, intention-to-treat; MMRM = mixed model for repeated measures; TED = thyroid eye disease		

EAG comment: The statistical methods for the Phase 2 and OPTIC trials appear to be satisfactory.

3.2.4 Baseline characteristics

The baseline characteristics of the Phase 2 safety population was provided in the CS¹ and summarised in Table 3.4 below.

The CS states that baseline demographic and disease characteristics were mostly well-balanced between treatment arms and highlights that participants were stratified by smoking status, a known risk factor for TED. The company acknowledges that there were more smokers in the placebo group than the teprotumumab group. The EAG identified that there were additional differences at the >5% level which are noteworthy.

There were more females in the placebo group than in the intervention group (81.8% versus 65.1%). The time since initiation of treatment for thyroid disease was also longer in the placebo group than in the intervention group (15 months (3-189) versus 8 months (1-134)). Treatment numbers with antithyroid drug also differed between groups with more patients in the placebo group (45% versus 35%) as did treatment with levothyroxine with more patients in the intervention group than the placebo group (60% versus 52%). The adjustment of medication at trial entry also differed between groups with regards to levothyroxine, with more patients in the intervention group being affected (19% versus 11%). Levels of free triiodothyronine and free thyroxine also differed. Those who were euthyroid at baseline and through intervention phase were increased in the intervention group (46% versus 30%) while there were more patients with values occasionally outside normal range during intervention phase in the placebo group (57% versus 42%).

With regards to the Phase 3 trial the CS provides the baseline characteristics of the ITT population. Stating that demographic characteristics at baseline were generally comparable between the placebo and teprotumumab group.¹ There were more females (73.8% placebo and 70.7% teprotumumab) than males in both groups but no obvious differences at the >5% level were identifiable between groups according to the data presented in Table 12 of the CS.¹ The CS states that ‘*With respect to geographic distribution, slightly more than half of the subjects in both treatment groups were enrolled at sites in the U.S. (52.4% placebo and 53.7% teprotumumab), with the remainder enrolled at sites in*

Europe (Germany and Italy). In both the placebo and teprotumumab groups, more than half of the subjects had never used tobacco (59.5% and 56.1%, respectively).¹

It is apparent that Table 12 in the CS which presents the baseline data does not contain all the data to which the company refer. There are no data included on geographical distribution, or for prior use of sulphur-containing imidazole derivatives, or thyroid hormones for treatment of hypothyroidism for instance. Yet these are described in the text. Additionally, some of the data described in the text does not fully align with what are presented in the table. The company describe the data on smoking distribution for example as having ‘similar proportions of subjects in the placebo and teprotumumab groups in the user (21.4% and 22.0%, respectively) and non-user strata (78.6% and 78.0%, respectively).’ On reviewing the data in the table, the distribution of smokers in the placebo group is 81%. Additionally, the company write that ‘The time since diagnosis of Graves’ disease (median: 0.9 years placebo and 1.0 years teprotumumab) and the time since diagnosis of TED (median: 6.8 months placebo and 6.3 months teprotumumab) were similar between the groups.’ However, in the table it is mean values which are reported and are therefore different.

Table 3.4 below summarises the characteristics of patients at baseline (safety population) in the Phase 2 trial.

Table 3.4: Baseline characteristics (Safety Population) - Phase 2

Characteristics	Placebo (n=44)	Teprotumumab (n=43)
Age (years) – means (SD)	54.2 (12.98)	51.6 (10.67)
Female gender – no. of patients (%)	36 (81.8)	28 (65.1)
Time since initiation of treatment for thyroid disease (months) – median (range) ^a	15 (3-189)	8 (1-134)
Duration of eye symptoms or signs (months) – means (SD)	5.2 (2.3)	4.7 (2.1)
Duration of Graves’ disease (months) – median (range)	10.8 (1.2-299.0)	10.7 (1.2-228.0)
Race – no. of patients (%)		
White	38 (86.4)	37 (86.0)
Asian	2 (4.5)	1 (2.3)
Black	4 (9.1)	4 (9.3)
Current treatment for thyroid disease – no. of patients (%)		
Antithyroid drug ^b	20 (45)	15 (35)
Levothyroxine	23 (52)	26 (60)
Thyroid extract	3 (7)	1 (2)
Adjustment of medication at trial entry – no. of patients (%)		
Levothyroxine	5 (11)	8 (19)
Antithyroid drug	7 (16)	5 (12)
Smoking status – no. of patients (%)^c		
Non-smoker	26 (59)	32 (74)
Smoker	18 (41)	11 (26)

Characteristics	Placebo (n=44)	Teprotumumab (n=43)
Biochemical status		
TBII (% level of inhibition) – means (SD)	48.7 (25.4)	51.6 (26.9)
TSI (% level of stimulation) – means (SD)	435.1 (105.2)	422.9 (118.1)
Mean thyroid hormone levels (pmol/L) – means (SD)^d		
Free triiodothyronine	4.9 (1.7)	4.8 (1.4)
Free thyroxine	16.3 (3.6)	16.3 (4.8)
Levels of free triiodothyronine and free thyroxine – no. of patients (%)		
Euthyroid at baseline and through intervention phase	13 (30)	20 (46)
Values occasionally outside normal range during intervention phase	25 (57)	18 (42)
Sustained out-of-range values during intervention phase	6 (14)	5 (12)
Based on Table 11, CS.¹ ^a Data shown are for 10 patients in the placebo group and 10 patients in the teprotumumab group. ^b The antithyroid drugs were carbimazole, methimazole, and propylthiouracil ^c Data for smoking status were based on patients who were current smokers at the time of the screening visit. Patients were stratified at randomisation according to smoking status to balance the trial groups with respect to this known risk factor for thyroid-associated ophthalmopathy. However, there were imbalances in randomisation blocks and discrepancies between patients who were randomly assigned to an intervention as non-smokers at week 0 and those recorded as being smokers in their case-report forms. Data from the case-report forms were considered to be more accurate and were used to define smoking status at baseline. ^d The normal ranges of free triiodothyronine are 2.3 to 4.2 pg/mL (3.5 to 6.5 pmol/L), and of free thyroxine, 0.9 to 1.8 ng/dL (11.6 to 23.2 pmol/L). CS = company submission; ng/dL = nanograms per decilitre; pg/mL = picograms per millilitre; pmol/L = picomoles per litre; SD = standard deviation; TBII = thyrotropin-binding inhibitory immunoglobulins; TSI = thyroid-stimulating immunoglobulins		

The EAG queried the generalisability of this population to a relevant clinical population in England and Wales and we requested that the company provide further information to justify this. Additionally, we asked the company to provide the baseline data of any participants who were UK based. In their response to clarification, the company stated that ‘No UK-based patients were enrolled in the Phase 3 OPTIC study. A total of [REDACTED] UK patients ([REDACTED] of all study subjects) were enrolled in the Phase 2 RCT’ and provided baseline characteristics of these participants (see Table 3.5) from the ITT population.⁴ The company also reinforced their view that there was a generalisability to the UK clinical population and stated that ‘subjects enrolled in the two pivotal trials are expected to be representative of the TED patients who would be treated with teprotumumab in clinical practice’. To support this assertion the company made several arguments,⁴ including that:

- ‘all study subjects were adults, had received a diagnosis of Graves’ disease and had active thyroid eye disease of moderate to severe severity at baseline’
- ‘A high proportion of Caucasian or Western subjects, and UK clinicians have advised the submitting company that the baseline characteristics, demographics and previous medical histories of the study subjects are broadly representative of the TED patients they would treat in clinical practice’
- ‘the generalisability of assumptions around the patient weight used in the model was also raised as an area for further clarification. The model uses the average baseline weight from all patients in the pooled analysis (78.07 kg). The mean weight of the UK patients specifically from the pooled analysis was similar (77.65 kg). UK clinicians indicate that this is a

reasonable estimate for the average weight of a TED patient in the NHS although some clinicians felt that their patient population has a lower average weight given that these patients are predominantly female and with recent onset hyperthyroidism, one of the key symptoms of which is weight loss'

The company provided details of the [REDACTED] patients in the Phase 2 ITT population¹⁵ and these limited data can be found in Table 3.5 below. Additional data was provided including age category, ethnicity, weight, childbearing potential and time since diagnosis of TED, however the EAG have extracted and tabulated only information in the table below to reflect the characteristics that were reported in Table 3.5.

Table 3.5: Phase 2 UK based ITT population

Characteristics	Placebo UK based ([REDACTED])	Teprotumumab ([REDACTED])
Age (years) – means (SD)	[REDACTED]	[REDACTED]
Female gender – no. of patients (%)	[REDACTED]	[REDACTED]
Time since initiation of treatment for thyroid disease (months) – median (range) ^a	Not provided by company	Not provided by company
Duration of eye symptoms or signs (months) – means (SD)	Not provided by company	Not provided by company
Duration of Graves' disease (months) – median (range)	Not provided by company	Not provided by company
Race – no. of patients (%)		
White	[REDACTED]	[REDACTED]
Asian	[REDACTED]	[REDACTED]
Black	[REDACTED]	[REDACTED]
Current treatment for thyroid disease – no. of patients (%)		
Antithyroid drug ^b	Not provided by company	Not provided by company
Levothyroxine	Not provided by company	Not provided by company
Thyroid extract	Not provided by company	Not provided by company
Adjustment of medication at trial entry – no. of patients (%)		
Levothyroxine	Not provided by company	Not provided by company
Antithyroid drug	Not provided by company	Not provided by company
Smoking status – no. of patients (%)^c		
Non-smoker	[REDACTED]	[REDACTED]
Smoker	[REDACTED]	[REDACTED]
Biochemical status		
TBII (% level of inhibition) – means (SD)	Not provided by company	Not provided by company
TSI (% level of stimulation) – means (SD)	Not provided by company	Not provided by company
Mean thyroid hormone levels (pmol/L) – means (SD)^d		
Free triiodothyronine	[REDACTED]	[REDACTED]
Free thyroxine	[REDACTED]	[REDACTED]

Characteristics	Placebo UK based (■)	Teprotumumab (■)
Levels of free triiodothyronine and free thyroxine – no. of patients (%)		
Euthyroid at baseline and through intervention phase	Not provided by company	Not provided by company
Values occasionally outside normal range during intervention phase	Not provided by company	Not provided by company
Sustained out-of-range values during intervention phase	Not provided by company	Not provided by company
Based on data provided in response to clarification ⁴ ITT = intention-to-treat; ng/dL = nanograms per decilitre; pg/mL = picograms per millilitre; pmol/L = picomoles per litre; SD = standard deviation; TBII = thyrotropin-binding inhibitory immunoglobulins; TSI = thyroid-stimulating immunoglobulins		

EAG comment: The EAG has concerns about the evidence to support relevance of these populations to the relevant clinical populations in England and Wales. We note principally the minimal involvement of patients based in the UK in the Phase 2 trial and no UK based patients in the OPTIC trial. We also highlight the responses of the company when we asked them to provide data for the characteristics of the patients as would be treated in clinical practice in England and Wales. The EAG does not consider that the company response provided sufficient evidence to provide reassurance. No data was provided on any basic characteristics of this population in the UK, but rather the company stated that ‘...Caucasian or Western subjects, and UK clinicians have advised the submitting company that the baseline characteristics, demographics and previous medical histories of the study subjects are broadly representative of the TED patients they would treat in clinical practice’. It is unclear what ‘broadly representative’ means in these circumstances, and it is equally unclear as to how ‘Caucasian or western subjects’ represent an appropriate or authoritative source of advice on representativeness of trial population data. Additionally, the company stated that ‘The mean weight of the UK patients specifically from the pooled analysis was similar (77.65 kg). UK clinicians indicate that this is a reasonable estimate for the average weight of a TED patient in the NHS although some clinicians felt that their patient population has a lower average weight’. Again, the company provided no data or documentation to support these statements and claims made by UK clinicians, which is made even more important when there is a disagreement between clinicians as in this case, and no reference is provided in the company response to clarification where such clinical advice can be accessed.⁴

Typically, where clinical opinion from experienced clinicians is cited as a source of evidence the EAG would expect to see information on the expertise of the clinicians, minutes of committee meetings, statements, or any preliminary or audit data to support the claim. This information has not been provided alongside the response to clarification and therefore the EAG cannot accept that there is a generalisability to the UK based population. The EAG reviewed the document provide by the company in the initial submission entitled ‘clinical expert opinion’¹⁶ but no mention of these claims could be located in this particular document. We emphasise that we are not disputing the generalisability but rather highlighting that there has been no evidence to support it.

The EAG also makes the point of discordancy between the presentation of baseline data table, the accompanying text and some of the values described. It is important that a CS can present an approach that is evidence supported, and that this evidence is included within the CS along with appropriate summaries and citation of references. In this case the EAG feels that the company have not adequately completed this which adds to the concerns noted above.

3.2.5 Risk of bias assessment

The company stated that they conducted appraisals of the relevant studies according to Version 2 of the Cochrane risk-of-bias tool for randomised trials. This is the most up-to-date version of the Cochrane risk-of-bias tool designed, validated for RCTs, and recommended by the Cochrane Handbook. The results of the appraisals are included in section B.2.5 of CS.¹ A summary of the appraisals are detailed below in Table 3.6.

EAG comment: The company has confirmed that only one reviewer conducted appraisals. Therefore, it must be assumed that these appraisals were not checked by a second reviewer and the likelihood of error and/or bias is increased. While the EAG emphasises that this does not mean that there is any actual increased error or bias, it would be good practice to ensure that the risks are diminished by having a second reviewer conduct a duplicate appraisal or a check of the initial appraisal.

Table 3.6: Quality assessment results for RCTs

	Phase 2	Phase 3 OPTIC
Was randomisation carried out appropriately?	Yes. Trial subjects were randomly assigned in the double-blinded intervention phase to either of the two intervention groups in a 1:1 ratio in blocks of two, stratified within each clinical centre according to smoking status using an interactive Web-response system.	Yes. Trial subjects were randomly assigned in a 1:1 ratio to receive IV infusions of either teprotumumab or placebo.
Was the concealment of treatment allocation adequate?	Yes. An interactive Web-response system was used to allocate trial subjects to treatment.	Yes. Randomisation was performed with the use of an interactive Web-response system, administered by Bioclinica eClinical Solutions, a contract research organisation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, the baseline demographic and disease characteristics were similar and mostly well-balanced between treatment arms. Trial participants were stratified by smoking status, a known risk factor for TED. However, there were more smokers in the placebo group than the teprotumumab group, resulting in an imbalance between treatment groups. The potential imbalance in smoking status was adjusted for by including smoking as a covariate.	Yes, the baseline demographic and disease characteristics were similar and mostly well-balanced between treatment arms. Trial participant randomisation was stratified by tobacco use status at Baseline, with similar proportions of subjects in the placebo and teprotumumab groups in the user and non-user strata.

	Phase 2	Phase 3 OPTIC
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. The study subjects and study investigators were blind to treatment allocation. Study pharmacists who were aware of the trial-group assignments prepared the masked/blinded infusion. The on-site principal investigators of the study could identify the participant's intervention only in the case of an emergency.	Yes. The study participants, investigators and trial-site personnel (excluding the formulating pharmacists) were unaware of the trial-group assignments and remained unaware through the follow-up data analysis and completion of the trial-site close-out visit.
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances in drop-outs.	There were no unexpected imbalances in drop-outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of evaluating the efficacy and safety of teprotumumab and placebo as a treatment for TED.	No. All outcomes were related to the clinical goals of evaluating the efficacy and safety of teprotumumab and placebo as a treatment for TED.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	An ITT analysis was included. The ITT population, which included all randomly-assigned participants who received at least one infusion, was used to analyse the primary and secondary efficacy outcomes. The safety population, which included all participants who received either placebo or teprotumumab, was used for all safety analyses. Methods used to account for missing data were appropriate.	An ITT analysis was included. The ITT population, which included all randomly-assigned participants who received at least one infusion, was used to analyse the primary and secondary efficacy outcomes. The safety population, which included all participants who received either placebo or teprotumumab, was used for all safety analyses. Methods used to account for missing data were appropriate.
Based on table 16, CS. ¹ CS = company submission; ITT = intention to treat; RCT = randomised control trial; TED = thyroid eye disease		

3.2.6 Clinical effectiveness results of the relevant studies

3.2.6.1 Phase 2 NCT01868997

3.2.6.1.1 Primary efficacy outcome

The company stated that “early and consistent efficacy of teprotumumab over placebo, with a greater proportion of patients responding in the teprotumumab group than in the placebo group from Week 6 through the study treatment phase ($p < 0.001$ at each time point).”¹ Further details can be found in Table 3.7.

The company also reported that “The teprotumumab group had a significantly shorter time to the first response than the placebo group with the mean time to first response of 11.2 weeks (standard deviation [SD]: ± 6.6) vs 18.7 weeks (SD: ± 7.6) for teprotumumab vs placebo ($p < 0.001$).”¹

Table 3.7: Overall response rate in study and non-study eye (ITT population) – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)	Difference (95% CI)^a
Response in study eye – no. of patients (%)			
Week 6	18 (42.9)	2 (4.4)	40.0 (24.2-56.3)
Week 12	23 (54.8)	2 (4.4)	49.0 (32.4-65.6)
Week 18	30 (71.4)	2 (4.4)	65.8 (50.2-81.3)
Week 24	29 (69.1)	9 (20.0)	48.9 (30.2-67.6)
Response in non-study eye – no. of patients (%)			
Week 6	8 (19.1)	2 (4.4)	14.7 (1.3-28.1)
Week 12	13 (31.0)	1 (2.2)	29.6 (14.6-44.6)
Week 18	17 (40.5)	1 (2.2)	38.4 (22.7-54.1)
Week 24	22 (52.4)	6 (13.3)	38.9 (20.6-57.3)
Based on Table 17 of the CS ¹ ^a Difference and its corresponding 95% CI is based on a weighted average of the difference within each randomisation stratum (tobacco user, tobacco non-use) using Cochran–Mantel–Haenszel weights. CI = confidence interval; CS = company submission; ITT = intention-to-treat			

3.2.6.1.2 Secondary efficacy outcomes

As the company stated, a summary of the secondary efficacy outcomes from OPTIC was presented in Table 3.8.

Based on the Table, the company stated that “Patients who received teprotumumab had reductions in proptosis, the CAS, and subjective diplopia that were clinically meaningful and statistically significant compared to patients who received placebo ($p \leq 0.001$ for all comparisons with placebo).”¹

Table 3.8: Results of secondary efficacy endpoints (ITT population) – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)	P-Value
Proptosis (mm) – means (SE)			
Baseline	23.38 (3.16)	23.10 (2.93)	
Change from baseline overall post-baseline time points up to Week 24 ^a	-2.46 (0.20)	-0.15 (0.19)	<0.001
Clinical activity score – means (SD)^b			
Baseline	5.1 (0.97)	5.2 (0.74)	
Change from baseline overall post-baseline time points up to Week 24 ^a	-3.43 (0.18)	-1.85 (0.17)	<0.001
Subjective diplopia^c			
Baseline diplopia according to grade – no. of patients (%)			
No diplopia	4 (10)	14 (31)	
Intermittent	16 (38)	19 (42)	
Inconstant	7 (17)	8 (18)	
Constant	15 (35)	4 (9)	

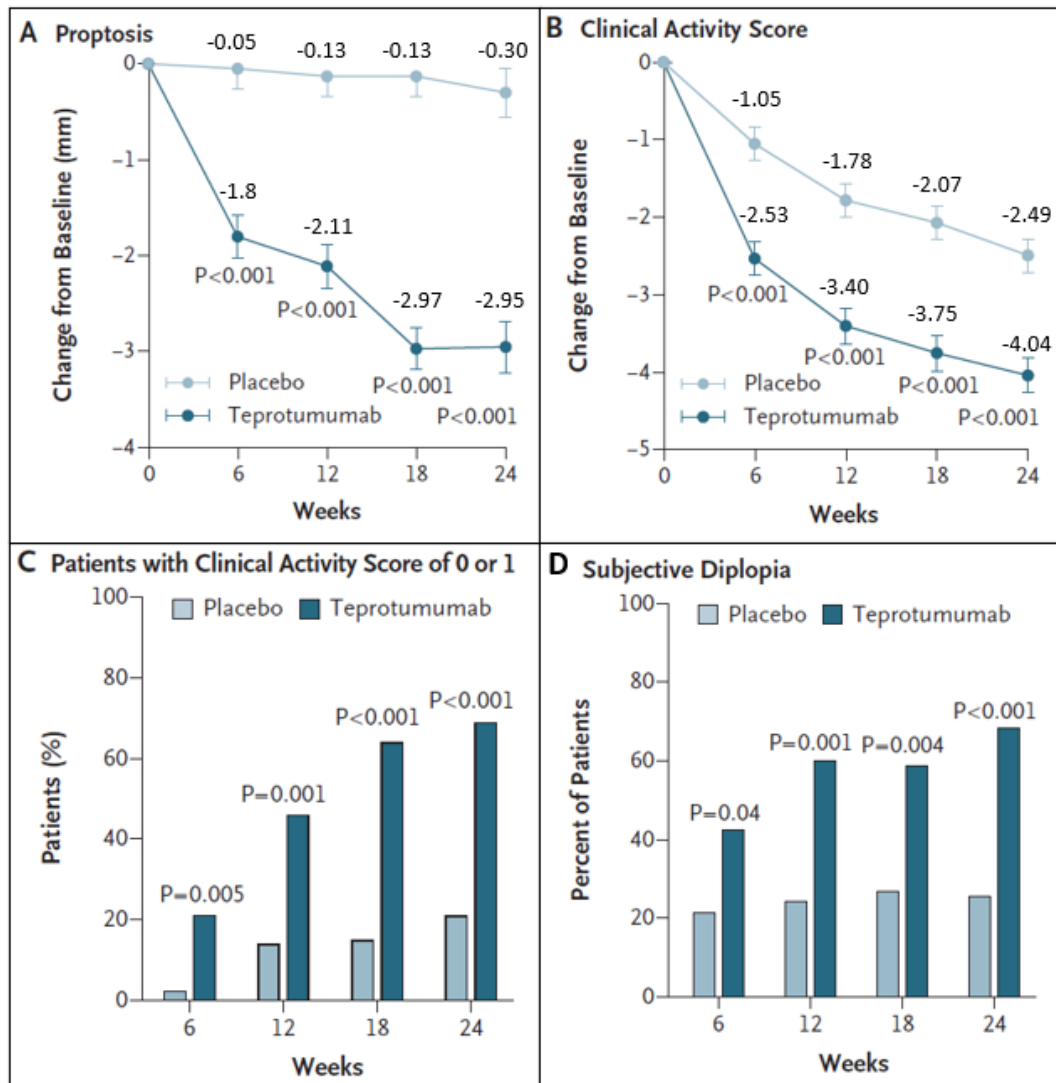
	Teprotumumab (n=42)	Placebo (n=45)	P-Value
Odds ratio (95% CI): 3.78 (1.68-8.54) ^d			0.001
Week 24 diplopia according to grade – no. of patients (%)			
No diplopia	21 (50)	18 (40)	
Intermittent	4 (10)	8 (18)	
Inconstant	9 (21)	7 (16)	
Constant	4 (10)	6 (13)	
Response	26/38 (68)	10/39 (26)	<0.001
Based on Table 18 of the CS¹ ^a Secondary endpoints were analysed with the use of a mixed model of repeated-measurements with smoking as a covariate. Any apparent discrepancies between the tabulated mixed model of repeated-measurements calculations for change from baseline and data plotted are because tabulated data are an average difference between the trial groups overall post-baseline time points up to Week 24. ^b The CAS comprised 7 components. Scores range from 0 to 7, and a change of 2 points is considered clinically relevant. ^c Subjective diplopia was assessed on the basis of 4 grades, and a change of 1 grade or more is considered to be clinically relevant. A response in patients with diplopia was defined as a decrease of 1 grade or more. The chi-square test was used to compare data from patients who had a response with data from those who did not at Week 24. ^d The estimated OR shown was calculated with the use of logistic regression for cumulative logits. This imbalance should be viewed in light of the large number of characteristics assessed at baseline. A sensitivity post hoc logistic-regression analysis of the Week 24 response, which included adjustment for baseline smoking status, sex, study eye, and diplopia, did not show a substantial difference from the primary analysis (adjusted OR, 8.16; p<0.001). CI = confidence interval; CAS = clinical activity score; CS = company submission; ITT = intention-to-treat; OR = odds ratio; SD = standard deviation; SE = standard error			

3.2.6.1.2.1 Reduction in proptosis

The company illustrated that “at Weeks 6, 12, 18, and 24, patients treated with teprotumumab experienced a significantly greater reduction in proptosis from baseline compared to those on placebo ($p<0.001$ for all comparisons).”¹ Further details can be found in Figure 3.5 A.

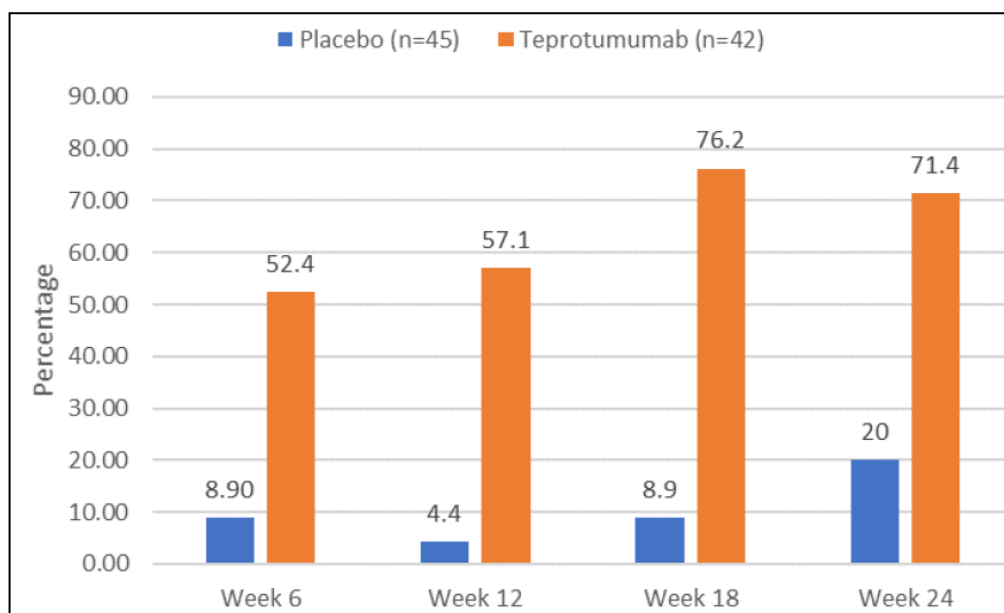
The company also reported the details of proptosis responders for Week 6, 12, 18, 24 and the details of proptosis response results graded by the reduction in mm, which can be found in Figure 3.6 and Table 3.9.

Figure 3.5: Secondary efficacy assessment from Week 0 to Week 24 – Phase 2



Based on Figure 12 of the CS¹

CS = company submission

Figure 3.6: Proptosis responders (percent of patients with a decrease ≥ 2 mm from baseline) – Phase 2

Based on Figure 13 of the CS¹

p < 0.001 for comparisons at all time-points

CS = company submission

Table 3.9: Proptosis graded response at Week 24 – Phase 2

	Teprotumumab (n=42)	Placebo (n=45)
Graded response – no. of patients (%)^a		
High response	23 (54.8)	4 (8.9)
≥4 mm reduction	17 (40.5)	0 (0)
Response	7 (16.7)	5 (11.1)
Low response	8 (19)	8 (17.8)
No response	0 (0)	22 (48.9)
Missing	4 (9.5)	6 (13.3)

Based on Table 19 of the CS¹

^a A high response indicates a reduction in proptosis of ≥ 3 mm from baseline. A response indicates a reduction in proptosis of 2 to < 3 mm from baseline. A low response indicates a reduction in proptosis of 1 to < 2 mm from baseline. No response indicates a reduction in proptosis of < 1 mm from baseline

CS = company submission

3.2.6.1.2.2 Reduction in the clinical activity score

The company reported that “Significant reductions in the CAS were observed at Weeks 6, 12, 18, and 24 in the teprotumumab group compared to the placebo group ($p < 0.001$ for all comparisons).”¹ Further details can be found in Figure 3.5 B.

3.2.6.1.2.3 Subjective diplopia response rates

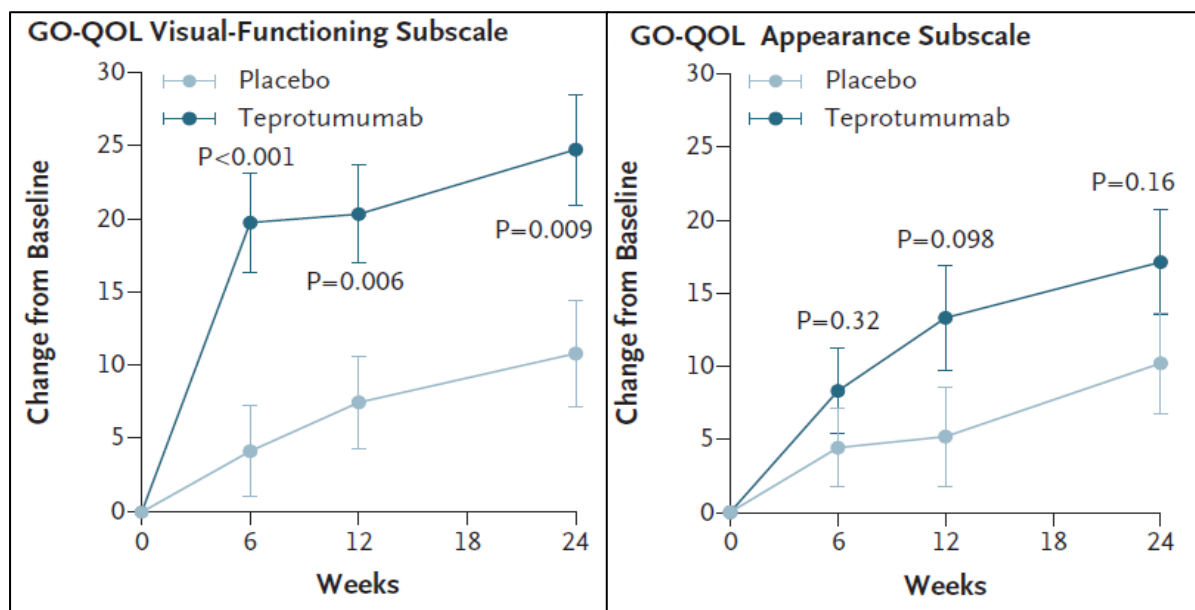
The company reported that “Subjective diplopia response rates were also higher in the teprotumumab group compared to the placebo group ($p \leq 0.001$ for all placebo comparisons).”¹ Further details can be found in Figure 3.5 D.

3.2.6.1.2.4 Change in GO-QOL

The company reported that “The phase 2 trial demonstrated that for acute, moderate-to-severe TED, teprotumumab resulted in a significant increase in the GO-QOL visual-functioning score across all time points, ranging from [REDACTED] to [REDACTED] points higher than the placebo group.”¹

The company also stated that “While a consistent trend toward improvement on the GO-QOL appearance subscale was observed in the teprotumumab group, statistical significance in the difference over the placebo group was not reached.”¹ Further details can be found in Figure 3.7.

Figure 3.7: GO-QOL scores from Week 0 to Week 24 – Phase 2



Based on Figure 14 of CS¹
CS = company submission

3.2.6.2 Phase 3 OPTIC

As the company stated, a summary of the primary and secondary efficacy outcomes from OPTIC was presented in Table 3.10.

Table 3.10: Summary of primary and secondary efficacy outcomes (ITT Population) – OPTIC

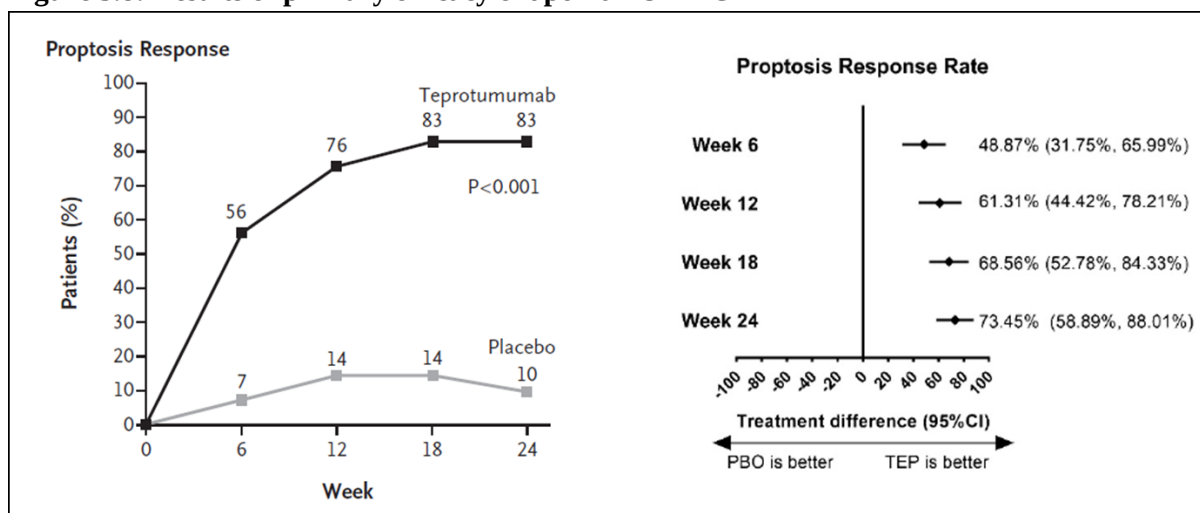
	Teprotumumab (n=41)	Placebo (n=42)	Difference (95% CI)	P value
Primary outcome of proptosis response at wk 24				
In the ITT population - % of patients (number/total number)	83 (34/41)	10 (4/42)	73 (59 to 88)	<0.001
In the PP population - % of patients (number/total number)	88 (29/33)	12 (4/34)	76 (61 to 92)	<0.001
Secondary outcomes in the ITT population				
Overall response at wk 24 - % of patients (number/total number)	78 (32/41)	7 (3/42)	71 (56 to 86)	<0.001

	Teprotumumab (n=41)	Placebo (n=42)	Difference (95% CI)	P value
Clinical activity score of 0 or 1 at wk 24 - % of patients (number/total number)	59 (24/41)	21 (9/42)	36 (17 to 55)	<0.001
Mean change in proptosis from baseline to wk 24 - mm	-2.82±0.19	-0.54±0.19	-2.28 (-2.77 to -1.80)	<0.001
Diplopia response at wk 24 - % of patients (number/total number with diplopia at baseline)	68 (19/28)	29 (8/28)	39 (16 to 63)	0.001
Mean change in GO-QOL score from baseline at wk 24	13.79±2.07	4.43±2.10	9.36 (4.08 to 14.64)	<0.001
Based on Table 20 of CS ¹ CI = confidence interval; CAS = clinical activity score; CS = company submission; GO-QOL = Graves' Ophthalmopathy Quality of Life; ITT = intention-to-treat; mm = millimetre; PP = per protocol; wk = week				

3.2.6.2.1 Primary efficacy outcome

The company stated that “the teprotumumab group consistently demonstrated a higher response rate across all timepoints compared to the placebo group”.¹ Further details can be found in Figure 3.8.

Figure 3.8: Results of primary efficacy endpoint – OPTIC



Based on Figure 15 of CS¹

The p-value for the between-group differences at week 24 was adjusted for multiplicity.

CI = confidence interval; CS = company submission; PBO = placebo; TEP = teprotumumab

3.2.6.2.2 Secondary efficacy outcomes

3.2.6.2.2.1 Overall response

The company reported that “a significantly greater proportion of patients responding to teprotumumab than to placebo”.¹ Further details can be found in Figure 3.9 A.

3.2.6.2.2.2 Proportion of patients with a CAS of 0 or 1

The company stated that “*the teprotumumab group also showed an increase in patients with a CAS of 0 or 1 throughout the treatment period, significantly surpassing the placebo group at all trial visits*”.¹ Further details can be found in Figure 3.9 B.

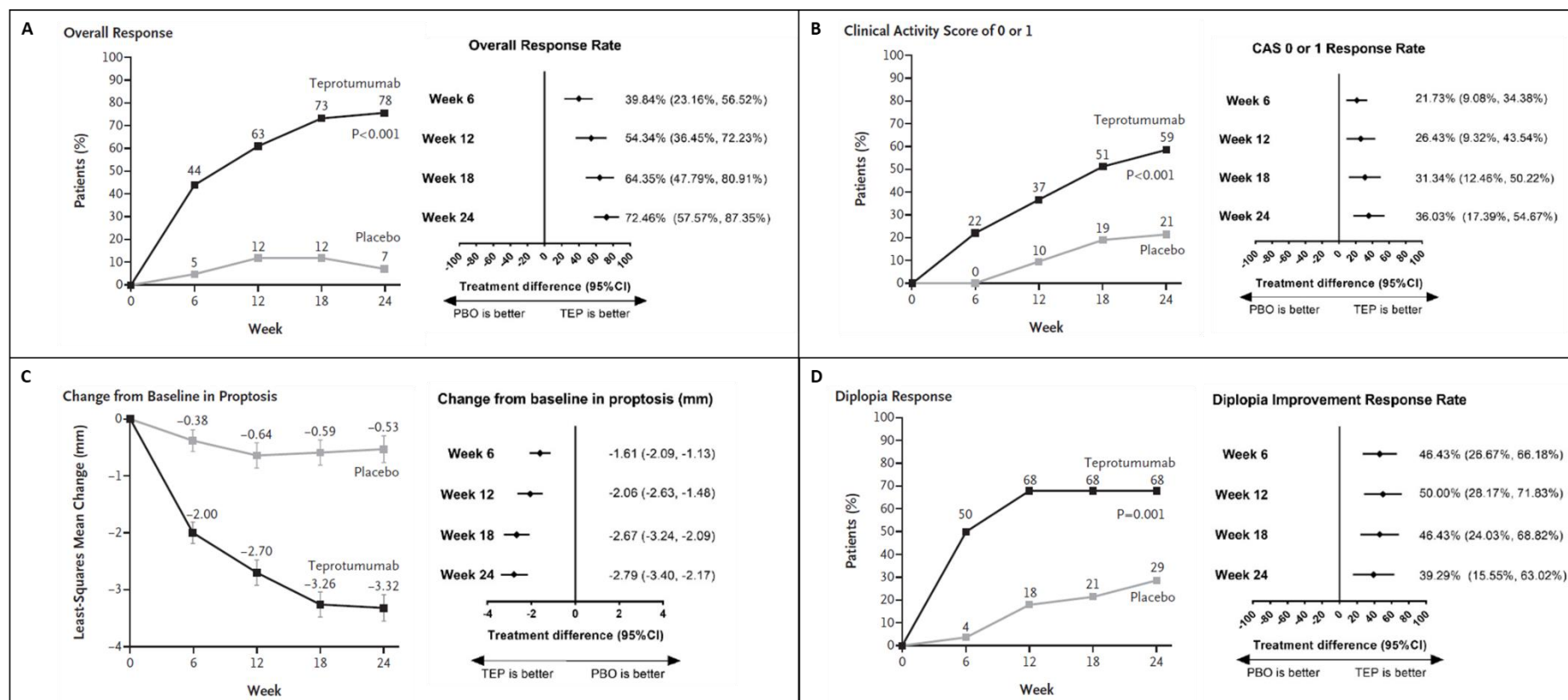
3.2.6.2.2.3 Change in proptosis

The company reported that “*the teprotumumab group consistently demonstrated a significantly greater mean change in proptosis from baseline compared to the placebo group at all time points*”.¹ Further details can be found in Figure 3.9 C.

3.2.6.2.2.4 Diplopia response

The company reported that “*Among the 28 patients having diplopia at Baseline in each group, the teprotumumab group demonstrated a significantly higher diplopia response (reduction of ≥ 1 grade) at the first visit and subsequent visits compared to the placebo group*”.¹ Further details can be found in Figure 3.9 D.

Figure 3.9: Results of secondary efficacy endpoint – OPTIC

Based on Figure 16 of CS¹

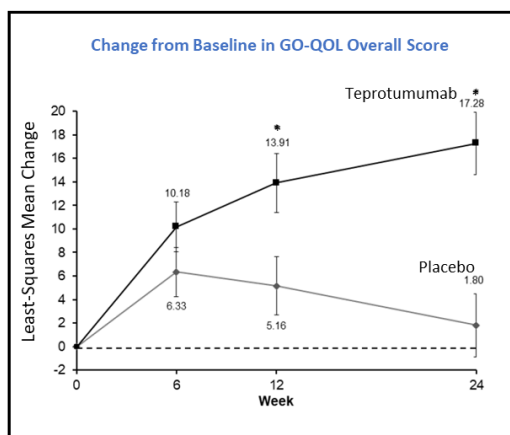
CI = confidence interval; CAS = clinical activity score; CS = company submission; PBO = placebo; TEP = teprotumumab

3.2.6.2.2.4 Change in GO-QOL

The company stated that “patients who received teprotumumab had a better overall score on the GO-QOL compared to those who received placebo”.¹

The company also reported that “scores on the visual and appearance subscales were also significantly better with teprotumumab than with placebo at Week 24”.¹ Further details can be found in Figure 3.10.

Figure 3.10: GO-QOL scores from Week 0 to Week 24 – OPTIC



Based on Figure 17 of CS¹

*p≤0.010; ** p≤0.05

CS = company submission; GO-QOL = Graves' ophthalmopathy-specific quality-of-life

3.2.6.3 Pooled analysis from Phase 2 and Phase 3 OPTIC

The company also conducted a pooled analysis examined integrated data and follow-up data from the two studies (Phase 2 and Phase 3 OPTIC) to assess the consistency of the results across teprotumumab clinical programs for the treatment of acute TED.

3.2.7 Subgroup analysis

In the pooled analysis, the company assessed the trial data for the primary and secondary outcomes by pre-specified patient subgroups: tobacco use; age <65 years or older; sex; time to diagnosis; CAS score 4 or 5, or 6 or 7; and thyrotropin binding inhibiting immunoglobulin (TBII) concentration <10 IU/L or ≥10 IU/L versus placebo.¹

3.2.8 Adverse events

Teprotumumab has been evaluated for its safety profile in patients with TED through multiple clinical trials, including Phase 2, OPTIC, and the extended OPTIC-X study. Overall, the drug is well tolerated, with most adverse events (AEs) being mild to moderate in severity. The rate of TEAEs in the teprotumumab group across these studies ranged from 74% to 85%, compared to 69% to 80% in the placebo group across the Phase 2, OPTIC and Phase 4 (chronic TED only) studies. The most frequently reported AEs included muscle spasms, alopecia, nausea, diarrhoea, dry skin, dysgeusia, and hearing impairment. Serious adverse events (SAEs) were uncommon, with an incidence of 2.4% to 12% in the teprotumumab group, compared to 2% to 5% in the placebo group. No deaths or anaphylactic reactions were observed in any of the pivotal trials. The reported AEs were generally temporary and manageable, rarely leading to treatment discontinuation.

3.2.8.1 Phase 2

Table 3.11: Adverse events and serious adverse events (safety population, ≥5% of patients) – Phase 2

	Teprotumumab (n=43) ^a	Placebo (n=44)
AE during intervention – no. of patients (%)^b		
Nausea	8 (18.6)	4 (9.1)
Muscle spasms	8 (18.6)	2 (4.5)
Diarrhoea	6 (14.0)	2 (4.5)
Hyperglycaemia	5 (11.6)	2 (4.5)
Alopecia	3 (7.0)	2 (4.5)
Dry skin	3 (7.0)	0
Dysgeusia	3 (7.0)	0
Headache	3 (7.0)	2 (4.5)
Paresthesia	3 (7.0)	0
Hearing impairment	3 (7.0)	0
Weight loss	3 (7.0)	0
Any AE during intervention	32 (74.4)	32 (72.7)
SAE – no. of patients (%)^c		
Optic neuropathy ^d	0	1 (2.3)
Diarrhoea	1 (2.3)	0
Inflammatory bowel disease	1 (2.3)	0
Escherichia sepsis ^e	1 (2.3)	0
Hashimoto's encephalopathy	1 (2.3)	0
Urinary retention	1 (2.3)	0

	Teprotumumab (n=43)^a	Placebo (n=44)
Any SAE	5 (11.6)	1 (2.3)
Based on Table 28 of CS.¹ ^a One patient in the placebo group received a single dose of teprotumumab in error at week 15. That patient is included here in the teprotumumab group. ^b AEs of any cause were defined as those that occurred between the administration of the first dose and 30 days after the administration of the final dose. Listed AEs that emerged during the intervention phase are those that occurred in more than 5% of patients in the teprotumumab group and that occurred in greater numbers in the teprotumumab group than in the placebo group. Patients may have had more than one AE. ^c Listed are all SAEs reported in the trial, including any AE involving hospitalisation. In the teprotumumab group, four patients discontinued the intervention because of the following SAEs: diarrhoea that occurred after six infusions, inflammatory bowel disease after seven, Escherichia coli sepsis after three, and Hashimoto's encephalopathy after six. ^d A total of three patients in the placebo group withdrew from the trial because of worsening eye symptoms or a lack of response. One case of dysthyroid optic neuropathy designated by an investigator as a SAE occurred 3 days after the week 24 evaluation. ^e This patient was the only one whose intervention was unmasked during the course of the trial. AE = adverse event; CS = company submission; ITT = intention-to-treat, SAE = serious adverse event		

The Phase 2 trial demonstrated a similar AE rate between the teprotumumab and placebo groups, with nausea and muscle spasms being the most common AEs. Hyperglycaemia was observed as a treatment-related AE, although it was mild and intermittent in non-diabetic patients. In diabetic patients, some cases reached moderate-to-severe levels but were effectively managed through medication adjustments. Serious AEs were more frequent in the teprotumumab group, with a few cases of diarrhoea, inflammatory bowel disease, Escherichia coli sepsis, and Hashimoto's encephalopathy, although none resulted in fatalities.

3.2.8.2 OPTIC

Table 3.12: Adverse events and serious adverse events (ITT population, $\geq 5\%$ of patients)^a – OPTIC

	Teprotumumab (n=41)	Placebo (n=42)
AE during intervention – no. of patients (%)		
Muscle spasms	13 (31.7)	4 (9.5)
Alopecia	8 (19.5)	5 (11.9)
Nausea	6 (14.6)	4 (9.5)
Fatigue	5 (12.2)	1 (2.4)
Diarrhoea	4 (9.8)	5 (11.9)
Headache	4 (9.8)	4 (9.5)
Dry skin	4 (9.8)	0
Dysgeusia	4 (9.8)	0
Stomatitis	3 (7.3)	1 (2.4)
Amenorrhoea	3 (7.3)	0
Dizziness	3 (7.3)	0
Cough	2 (4.9)	3 (7.1)
Upper abdominal pain	2 (4.9)	3 (7.1)
Influenza	1 (2.4)	3 (7.1)

	Teprotumumab (n=41)	Placebo (n=42)
Any adverse events	35 (85.4)	29 (69.0)
SAE during intervention – no. of patients (%)		
Infusion reaction	1 (2.4)	0
Pneumothorax	1 (2.4)	0
Visual-field defect	0	1 (2.4)
Any SAE	2 (4.9)	1 (2.4)
Based on Table 29 of CS. ¹		
^a Shown are the AEs that occurred in 5% or more of patients in either study group within 21 days after the final dose of the trial drug or placebo.		
AE = adverse event; CS = company submission; ITT = intention-to-treat, SAE = serious adverse event		

In the OPTIC trial, a similar safety profile was observed, with muscle spasms, alopecia, nausea, and fatigue being the most frequently reported AEs. Potential infusion-related reactions were reported in both treatment and placebo groups, but none led to treatment discontinuation except for one case. Hyperglycaemia remained a rare but manageable side effect. Hearing impairment, which was identified as a potential safety concern, was reported in five patients in the teprotumumab group, but all cases resolved over time. The rate of SAEs remained low, with only two cases reported in the teprotumumab group, including pneumothorax and an infusion reaction, and one case in the placebo group related to visual field impairment requiring surgery.

3.2.8.3 Pooled Analysis from Phase 2 and Phase 3 OPTIC

Table 3.13: Adverse events and serious adverse events (≥5% of patients) – pooled analysis

	Teprotumumab (n=84)	Teprotumumab related ^a (n=84)	Placebo (n=86)
Summary of adverse events in double-masked study period – no. of patients (%)			
AEs	67 (80)	47 (56)	60 (70)
SAEs	7 (8)	3 (4) ^b	1 (1)
Deaths	0	0	0
AE occurring in ≥5% of patients in the double-masked study period – no. of patients (%)			
Muscle spasms	21 (25)	16 (19)	6 (7)
Nausea	14 (17)	8 (10)	8 (9)
Alopecia	11 (13)	8 (10)	7 (8)
Diarrhoea	10 (12)	7 (8)	7 (8)
Fatigue	10 (12)	3 (4)	6 (7)
Hyperglycaemia	8 (10)	7 (8)	1 (1)
Hearing impairment	8 (10)	4 (5)	0
Dysgeusia	7 (8)	4 (5)	0
Headache	7 (8)	5 (6)	6 (7)
Dry skin	7 (8)	4 (5)	0
Rash	5 (6)	3 (4)	5 (5)
Based on Table 30 of CS. ¹			
^a Probably or possibly related to teprotumumab as assessed by investigator.			

	Teprotumumab (n=84)	Teprotumumab related ^a (n=84)	Placebo (n=86)
^b The SAEs reported by investigator as teprotumumab-related or possibly related: infusion-related reaction, diarrhoea, and Hashimoto's encephalopathy AE = adverse event; CS = company submission; ITT = intention-to-treat, SAE = serious adverse event			

A pooled analysis of Phase 2 and OPTIC trials confirmed that most AEs were mild to moderate, with a slightly higher occurrence in the teprotumumab group compared to placebo. The most commonly reported AEs were muscle spasms (25%), nausea (17%), alopecia (13%), diarrhoea (12%), and fatigue (12%). Serious AEs were rare, occurring in 8% of teprotumumab patients compared to 1% of placebo patients, with infusion-related reactions, diarrhoea, and Hashimoto's encephalopathy being identified as possibly related to the drug. Importantly, no deaths were reported.

3.2.8.4 Cumulative safety experience

Table 3.14: Summary of safety concerns at the beginning of the Periodic Benefit-Risk Evaluation Reporting Period

Risk category	Safety concern
Important identified risks	Infusion reactions (hypersensitivity) Hyperglycaemia Exacerbation of Inflammatory Bowel Disease Hearing Impairment
Important potential risks	New Onset of Inflammatory Bowel Disease
Missing information	None
Based on Table 31 of CS. ¹ CS = company submission	

Long-term safety data from post-marketing surveillance and extended studies reaffirm the overall tolerability of teprotumumab. Since its market approval in 2020, cumulative patient exposure has exceeded 10,565 patient-years. One of the most significant safety concerns identified post-approval is hearing impairment, which has been added to the "Warnings and Precautions" section of United States (US) prescribing information. A total of 943 cases of hearing impairment were reported, with 77.4% classified as non-serious and 22.6% as serious AEs. Among reported cases, tinnitus (40%) and hypoacusis (31%) were the most common symptoms. However, a retrospective study indicated that 20% of untreated TED patients also had hearing loss, suggesting that baseline audiometric testing should be considered for proper risk assessment. Other important safety concerns include infusion reactions (555 cases), hyperglycaemia (533 cases), and inflammatory bowel disease exacerbation (16 cases). Despite these risks, the overall benefit-risk profile of teprotumumab remains favourable for its approved indication, as no significant safety concerns have emerged that would warrant a reassessment of its use.

3.2.8.5 Safety conclusions

In conclusion, teprotumumab demonstrates a generally well-tolerated safety profile in TED patients. While AEs are common, the majority are mild or moderate and can be effectively managed. Serious AEs are infrequent, and no deaths or severe allergic reactions have been reported. Hearing impairment, hyperglycaemia, and infusion reactions remain the primary safety concerns, but

available evidence suggests they are mostly reversible or manageable. Based on both clinical trials and post-marketing data, teprotumumab's benefit-risk balance continues to support its use in the approved indications.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company performed the ITC based on the data of RCTs (Phase 2, and OPTIC) comparing teprotumumab with placebo. The current standard of care for moderate-to-severe TED in the active phase is a cumulative dosage of 4.5 g to 5.0 g of IVMP administered over 12 weeks, with or without mycophenolate.¹ The company performed the ITC by using MAIC methodology to estimate relative treatment effects between the three interventions.¹

For the ITC, an unanchored MAIC was performed to estimate the treatment effect of teprotumumab relative to IVMP and teprotumumab relative to IVMP + MMF in patients with acute moderate-to-severe TED.¹

Unanchored matching-adjusted methodology was chosen as the clinical trials identified in the feasibility assessment were not connected by a common comparator.¹

The company made the following statements:

- *‘A literature review was conducted to identify existing published literature assessing the most commonly recommended dose of IVMP among patients with moderate to severe active TED.*
- *The primary MAIC analysis set consisted of pooled IPD from the Phase 2 and OPTIC trials for teprotumumab, together with reported data from eight identified studies for IVMP. As both diplopia and proptosis response are needed to derive the transition probabilities in the economic analyses, two outcomes for the ITC were reported: mean difference in change from baseline proptosis score (mm), reflective of the continuous nature of the endpoint, and odds ratio (OR) for diplopia response (defined as reduction in diplopia of ≥ 1 grade), reflective of the binary nature of the endpoint. The outcomes were considered at week 12 for IVMP and week 24 for teprotumumab, to align with the end of their standard treatment periods.’*

In terms of treatment effect modifiers, the company made the following statement:

- *‘Treatment effect modifiers and prognostic variables were identified both from a previous ITC comparing teprotumumab with IVMP (Douglas et al., 2022) and an Amgen clinical expert, and then were further validated with three external key opinion leaders.¹⁵ Covariate selection for base-case and scenario analyses was based on the order of importance determined by clinical opinion and on the availability of data from the IVMP studies. Based on the availability of data, the ranking of importance of baseline*

characteristics, and the ESS considerations, the covariates that were considered in the base-case MAIC analyses were:

- *proportion of smokers [mean, %]*
- *baseline diplopia [mean, %]*
- *baseline proptosis [mean, mm]*
- *RIT [mean, %].¹*

The company further stated that for the IVMP + MMF comparison, only three of the most important factors identified by clinical experts were included in the MAIC, which were based on availability of baseline characteristics reported in the IVMP + MMF study and the effective sample size (ESS) threshold of >30. These factors were proportion of smokers, baseline diplopia, and baseline proptosis.¹

For each outcome for teprotumumab versus IVMP and teprotumumab versus IVMP + MMF, the company performed a number of scenario analyses. Sensitivity analyses were also performed to assess the impact of covariate selection and outliers.¹

Table 3.15 presents a summary of the sensitivity and scenario analyses.

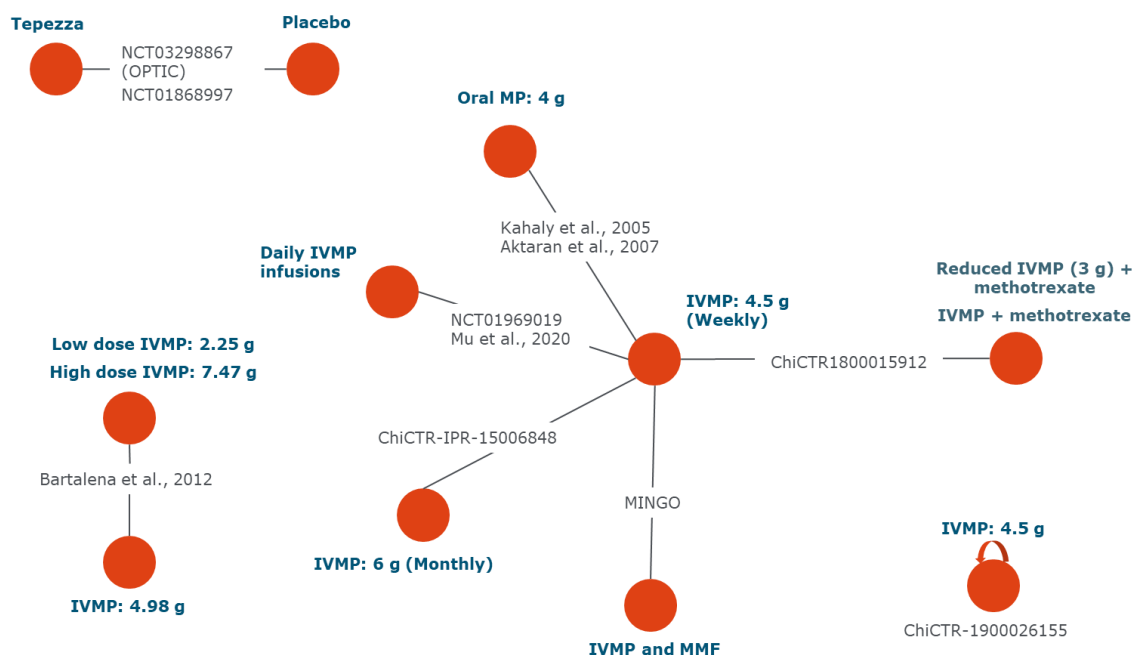
Table 3.15: MAIC base-case and scenario analyses

		Studies	Covariates	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Teprotumumab versus IVMP	Base-case	Only RCTs	Smoking Baseline diplopia Baseline proptosis RIT	Smoking Baseline diplopia Baseline proptosis	Smoking Baseline diplopia	Excluding patients with outlier weights
	Scenario 1	Europe and North America (RCTs and non-RCTs)	Smoking Baseline diplopia Baseline proptosis RIT	-	-	
	Scenario 2	RCTs and RWEs	Smoking Baseline diplopia Baseline proptosis RIT	-	-	
	Scenario 3	OPTIC only	Smoking Baseline diplopia	-	-	

		Studies	Covariates	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
			Baseline proptosis RIT			
Teprotumumab versus IVMP + MMF	Base-case	Only RCTs	Smoking Baseline diplopia Baseline proptosis	Smoking Baseline diplopia	Excluding patients with outlier weights	
	Scenario 1	OPTIC only	Smoking Baseline diplopia Baseline proptosis	-	-	
Based on Table 22 of CS. ¹ IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; MMF = mycophenolate mofetil; RCT = randomised controlled trial; RIT = radioiodine therapy; RWE = real world evidence						

The network of evidence for ITCs comparing IVMP, IVMP + MMF and teprotumumab is presented in Figure 3.11.

Figure 3.11: Set of clinical trials evidence based on the included studies after feasibility assessment



Based on Figure 28 of CS.¹

CS = company submission; g = grams; IV = intravenous; kg, = kilograms; mg = milligrams; MMF = mycophenolate mofetil; MP = methylprednisolone

Table 3.16 presents studies forming the evidence base for the base-case MAIC.

Table 3.16: Summary of baseline characteristics across the evidence base

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
IVMP													
He <i>et al.</i> , (2017). (ChiCTR-IPR-15006848)	Phase NR, RCT	18	41.20	44.44	22.20	NR	17.20	Absent: 6 (33.30) Intermittent: 2 (11.10) Constant: 6 (33.30) Constant: 5 (22.20)	NR	33.30	NR	NR	NR
Kahaly <i>et al.</i> , (2018). ((MINGO) EUDRAC T2008-002123-93)	Phase NR, RCT	81 (73 at week 12)	50.60	20.99	51.00	8.50 months	NR	52 (64.00)	0.52 mIU/L	20.00	NR	NR	NR
Zhu <i>et al.</i> , (2014).	Phase 4, RCT	39	45.30	38.46	13.51	NR	21.66	Absent: 11 (28.21) Intermittent: 6 (15.38)	0.41 μ IU/L	10.26	NR	NR	FT3: 4.42 pmol/L FT4: 13.43 pmol/L

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline n (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
								Inconstant: 15 (38.56) Constant: 7 (17.95)					
Shen <i>et al.</i> , (2022)	Phase NR, RCT	30	46.50	30.00	0.00	NR	22.30	Absent: 9 (30.00) Intermittent: 3 (10.00) Inconstant: 7 (23.30) Constant: 11 (36.70)	NR	20.00	NR	3.30	FT3: 4.70 (4.10-5.30) FT4: 12.60 (10.60-13.80)
Mu <i>et al.</i> (2020).	Phase NR, RCT	46	35.20	60.87	34.80	12.64 months	17.25	16 (34.80)	0.26	NR	NR	NR	FT3: 12.39 pmol/L FT4: 31.08 pmol/L
Aktaran <i>et al.</i> , (2007).	Phase NR, RCT	25	44.30	44.00	40.00	NR	22.20	Constant: 2(18.00) Inconstant: 4 (36.00)	1.90 (1.30) μ U/mL	NR	NR	NR	FT3: 2.70 $\pm$ 1.90 ng/dL FT4: 1.50 $\pm$ 0.30 ng/dL

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline n (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
								Intermittent: 5 (45.00)					
Bartalena <i>et al.</i> (2012).	Phase NR, RCT	54	50.00	42.59	54.00	12.40 months	22.20	Constant: 9 (17.00) Intermittent: 20 (37.00) Intermittent: 11 (20.00) Absent: 14 (26.00)	1.10 mIU/L	9.00	NR	NR	NR
Kahaly <i>et al.</i> (2005).	Phase NR, RCT	35	52.00	28.57	60.00	4 months	NR	Constant: 23 (66.00) Intermittent: 3 (9.00) Intermittent: 0 (0)	NR	NR	NR	NR	NR
IVMP + MMF													
Kahaly <i>et al.</i> (2018)	Phase NR, RCT	83	52.10	27.00	53.00	9 months	21.09	Constant: 13 (16.00) Intermittent: 23 (28.50)	0.72 mIU/L	18	NR	NR	FT3: NR FT4: NR

Study (trial name)	Study design	Number of patients	Mean age (years)	Male (%)	Smoking (%)	Mean duration of TED symptoms	Mean baseline proptosis (mm)	Diplopia at baseline n (%)	Mean TSH levels [Range] or (SD)	RIT %	Cholesterol levels (mg/dL)	Diabetes	Thyroid function
								Intermittent: 19 (23.50)					
Teprotumumab													
Smith <i>et al.</i> (2017). (NCT01868997)	Phase 2, RCT	41	51.60	35.00	26.00	NR	23.40	Absent: 4 (10.00) Intermittent: 16 (38.00) Intermittent: 7 (17.00) Constant: 15 (35.00)	NR	NR*	NR	NR	FT3: 4.80 (1.40) pmol/L FT4: 16.30 (4.80) pmol/L
Douglas <i>et al.</i> (2020). (NCT03298867 (OPTIC))	Phase 3, RCT	42	51.60	29.00	9.00	6.20 months	22.62	68.29 (NR)	1.75 mIU/L	NR*	NR	NR	FT3: 5.10 pmol FT4: 6.46 pmol/L

Based on Table 23 of CS.¹
CS = company submission; dL = decilitres; FT3 = free triiodothyronine; FT4 = free thyroxine; IV = intravenous; L = litres; mg = milligrammes; mIU = milli-international units; mm = millimetres; MMF = mycophenolate mofetil; MP = methylprednisolone; mU = milli-units; µU = micro-units; n = number; NR = not reported; pmol = picomoles per litre; RCT = randomised controlled trial; RIT = radioiodine therapy; SD = standard deviation; TED = thyroid eye disease; TSH = thyroid stimulating hormone; TSI = thyroid-stimulating immunoglobulin

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Base-case results of change from baseline proptosis outcome: teprotumumab versus IVMP

The base-case analysis of change from baseline (CFB) proptosis outcome for the comparison of teprotumumab versus IVMP were based on the data from seven IVMP RCT studies and the pooled individual patient data (IPD) from the two teprotumumab trials NCT01868997 and NCT03298867. The studies were matched on the basis of four covariates: smoking, baseline diplopia, baseline proptosis and radioiodine therapy (RIT).¹

Figure 3.12 presents the distribution of the weights for the base-case analysis. The rescaled weights ranged from [REDACTED] to [REDACTED], with the median skewed towards [REDACTED] ([REDACTED]). One patient was assigned a much larger weight of [REDACTED] compared to other weights from other patients. It should be noted that a considerable number of individuals were assigned a weight of less than 1 ([REDACTED]). This suggested that these individuals contributed little to the overall treatment effect, which resulted in a reduction in the ESS from [REDACTED] to [REDACTED].¹

Figure 3.12: Histogram of rescaled weights - base-case (teprotumumab versus IVMP)



Based on Figure 29 of CS.¹

CS = company submission; IVMP = intravenous methylprednisolone

The results showed that teprotumumab was associated with a statistically significantly greater mean difference (MD) change from baseline in proptosis compared with IVMP (MD in CFB: [REDACTED] mm [95% CI: [REDACTED]]) (see Table 3.17).¹

Table 3.17: Base-case MAIC results for mean change from baseline proptosis (teprotumumab versus IVMP)

	ESS	Mean change from baseline proptosis difference (teprotumumab versus IVMP) (SE)	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis, RIT)				
Adjusted results	████	████████	████	████
Unadjusted results	N/A	████████	████	████
Based on Table 25 of CS. ¹ CI = confidence interval; CS = company submission; ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; mm = millimetres; N/A = not applicable; RIT = radioiodine therapy; SE = standard error				

3.4.2 Base-case results of CFB proptosis outcome: teprotumumab versus IVMP + MMF

The base-case analysis of CFB proptosis outcome for the comparison of teprotumumab versus IVMP + MMF was based on the data from one IVMP + MMF RCT study and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. The studies were matched on the basis of three covariates: smoking, baseline diplopia, and baseline proptosis.¹

Figure 3.13 presents the distribution of the weights for the base-case analysis. The rescaled weights ranged from █████ to █████, with the median skewed towards █ (████). It should be noted that one patient was assigned a much larger weight of █████ compared to other weights from other individuals. A large number of individuals were assigned a weight of than 1 (████). This suggested that they contributed little to the overall treatment effect, which resulted in a reduction in the ESS from XX to █████.¹

Figure 3.13: Histogram of rescaled weights - base-case (teprotumumab versus IVMP + MMF)

Based on Figure 30 of CS.¹

CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil

The results showed that teprotumumab was associated with a statistically significantly greater mean difference change from baseline in proptosis compared with IVMP + MMF (MD in CFB: [REDACTED] [95% CI: [REDACTED]]).¹

Table 3.18: Base-case MAIC results for mean change from baseline proptosis (teprotumumab versus IVMP + MMF)

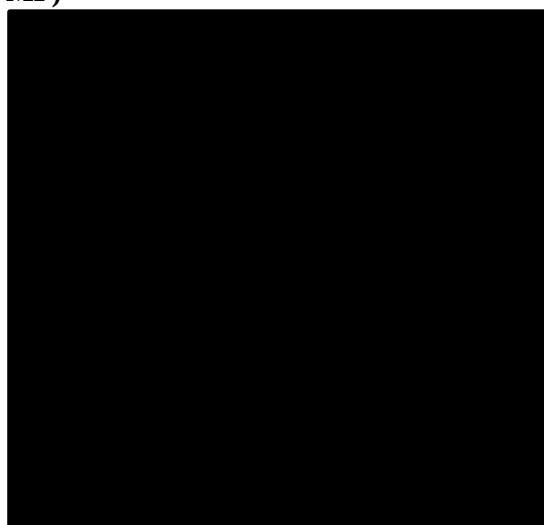
	ESS	Mean change from baseline proptosis difference (teprotumumab vs IVMP + MMF) (SE)	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis)				
Adjusted results	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Unadjusted results	N/A	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 26 of CS. ¹ CI = confidence interval; CS = company submission; ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; mm = millimetres; MMF = mycophenolate mofetil; N/A = not applicable; SE = standard error				

3.4.3 Base-case results of teprotumumab versus IVMP: diplopia response rate outcome

The base-case analysis of teprotumumab versus IVMP for the diplopia response rate outcome were based on the data of four IVMP studies and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. The included studies were matched on the basis of smoking, baseline diplopia, baseline proptosis and RIT.¹

Figure 3.14 presents the distribution of rescaled weights. The rescaled weights ranged from [REDACTED] to [REDACTED], with the median skewed towards [REDACTED] ([REDACTED]). It should be noted that three patients had noticeably larger weights indicating a greater influence on the overall treatment effect. By applying these weights to the dataset, it resulted in reduction of ESS from [REDACTED] to [REDACTED].¹

Figure 3.14: Histograms of rescaled weights for the diplopia response rate MAIC - base-case (teprotumumab versus IVMP)



Based on Figure 31 of CS.¹

CS = company submission; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison

Table 3.19 presents a summary of the analysis. The results showed that the odds of diplopia response for patients treated with teprotumumab were over three times higher than those treated with IVMP. The results were statistically significant (OR: [REDACTED] [95% CI: [REDACTED]]).¹

Table 3.19: Base-case diplopia response rate MAIC results – adjusted results (teprotumumab versus IVMP)

	ESS	OR	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Unadjusted results	N/A	[REDACTED]	[REDACTED]	[REDACTED]
Based on Table 27 of CS. ¹ CI = confidence interval; CS = company submission; ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; mm = millimetres; N/A = not applicable; OR = odds ratio; RIT = radioiodine therapy; SE = standard error				

3.4.4 Additional data

The EAG asked to company to provide mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm (IVMP; IVMP + MMF) before and after matching where appropriate. The EAG also asked the company to provide the standardised mean difference for the comparison of the intervention arm and the comparator arm after matching where appropriate. The company provided the following data in responding to the EAG's request.

In the base-case analysis for the proptosis outcome, the included studies were matched on four covariates (smokers, baseline diplopia, baseline proptosis, and RIT). Table 3.20 presents the ESS and covariates after matching. For ease of comparison, the means before matching are also included in the table.⁴

Table 3.20: Covariates after matching for studies included for the proptosis outcome (teprotumumab versus IVMP)

	Teprotumumab baseline characteristics		IVMP baseline characteristics
	Before MAIC	After MAIC – 4 covariate adjustment	
ESS	n=83	n=31.40	n=282
Smoker (%)	24.10	30.51	30.51
Baseline diplopia (%)	79.52	51.48	51.48
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	20.74 (2.97)	20.74 (2.89)
RIT (%)	7.23	14.38	14.38
Based on Table 7 of company clarification response. ⁴ ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; mm = millimetres; n = number; RIT = radioiodine therapy; SD = standard deviation			

In the base-case for teprotumumab versus IVMP + MMF, the included studies were matched on three covariates (smokers, baseline diplopia and baseline proptosis).⁴ Table 3.21 below presents the ESS and means for the covariates.

Table 3.21: Covariates after matching for studies included for the proptosis outcome (teprotumumab versus IVMP + MMF)

Covariate	Teprotumumab baseline characteristics		IVMP + MMF baseline characteristics
	Before MAIC	After MAIC – 3 covariate adjustment	
ESS	n=83	n=30.57	n=76
Smoker (%)	24.10	53.00	53.00
Baseline diplopia (%)	79.52	66.00	66.00
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	21.09 (3.14)	21.09 (3.45)
Based on Table 8 of company clarification response ⁴ ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; MMF = mycophenolate mofetil; mm = millimetres; n = number; RIT = radioiodine therapy; SD = standard deviation			

Table 3.22 below presents the ESS and covariates for teprotumumab before and after matching for the IVMP diplopia response rate outcome.

Table 3.22: Covariates after matching for studies included for the diplopia outcome (teprotumumab versus IVMP)

Covariate	Teprotumumab baseline characteristics		IVMP baseline characteristics
	Before MAIC	After MAIC – 4 covariate adjustment	
ESS	n = 83	n = 49.48	n = 101
Smoker (%)	24.10	23.96	23.96
Baseline diplopia (%)	79.52	71.47	71.47
Baseline proptosis (mm), Mean (SD)	23.01 (3.22)	21.16 (3.01)	21.16 (2.76)
RIT (%)	7.23	17.59	17.59
Based on Table 9 of company clarification response ⁴ ESS = effective sample size; IVMP = intravenous methylprednisolone; MAIC = matching-adjusted indirect comparison; mm = millimetres; n = number; RIT = radioiodine therapy; SD = standard deviation			

3.4.5 Sensitivity analysis

The EAG asked the company to include single-arm studies in the ITCs, given that unanchored MAIC was used to estimate relative efficacy between different treatments. The company performed the MAIC by including single-arm studies as a sensitivity analysis.⁴ Three non-RCT studies were included for the change from baseline proptosis outcome (see Table 3.23 below).

Table 3.23: Non-RCT studies included for the proptosis outcome.

Study	Study design	Treatment arm
Ahn et al., 2020	Retrospective observational study	IVMP
Xu et al., 2023	Prospective study	IVMP
Li et al., 2021	Prospective study	IVMP
Based on Table 10 of company clarification response ⁴ IVMP = intravenous methylprednisolone; RCT = randomised controlled trial		

Sensitivity analysis by including RCT and real-world evidence (RWE) studies showed teprotumumab to be more effective at reducing proptosis compared with IVMP.⁴ The results comparing sensitivity analysis to base-case results are presented in Table 3.24.

Table 3.24: Mean difference in change from baseline proptosis MAIC results (teprotumumab versus IVMP)

	ESS	MD in change from baseline proptosis (mm) (SE)	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	████	████████	████	████
Unadjusted results	N/A	████████	████	████
Scenario 2 (RCTs and RWE)				
Adjusted results	████	████████	████	████
Unadjusted results	N/A	████████	████	████
Based on Table 11 of company clarification response ⁴ CI = confidence interval; ESS = effective sample size; mm = millimeter; N/A = not applicable; RCT = randomised controlled trial; RIT = radioiodine treatment; RWE = real world evidence; SE = standard error				

Three non-RCT studies were included for the diplopia response outcome. Two studies were single-arm studies (see Table 3.25 below).

Table 3.25: Non-RCT studies included for the diplopia outcome

Study	Study design	Study arms
Ahn et al., 2020	Retrospective observational study	IVMP
Yang et al., 2014	Retrospective observational study	IVMP
Beleslin et al., 2020	Retrospective observational study	IVMP
		IVMP + prednisone
Table 12 of company clarification response ⁴ IVMP = intravenous methylprednisolone; RCT = randomised controlled trial		

Scenario analysis by including RCT and RWE studies showed that teprotumumab increased the odds of achieving a diplopia response compared to IVMP. Table 3.26 below presents the diplopia response rate MAIC results (teprotumumab versus IVMP).⁴

Table 3.26: Diplopia response rate MAIC results (teprotumumab vs IVMP)

	ESS	OR	95% Lower CI	95% Upper CI
Base-case (smoking, baseline diplopia, baseline proptosis and RIT)				
Adjusted results	■	■	■	■
Unadjusted results	N/A	■	■	■
Scenario 2 (RCTs and RWE)				
Adjusted results	■	■	■	■
Unadjusted results	N/A	■	■	■
Based on Table 13 of company clarification response ⁴ CI = confidence interval; mm = millimetre; N/A = not applicable; RCT = randomised controlled trial; RIT = radioiodine treatment; RWE = real-world evidence; SE = standard error				

The sensitivity analyses of MAIC by including additional single-arm studies showed that the results from sensitivity analyses were generally consistent with those results of base-case MAIC analyses.

EAG comment:

- The ITC base-case analysis in the company evidence submission was based on a MAIC analysis. The base-case MAIC analysis of CFB proptosis outcome for the comparison of teprotumumab versus IVMP was based on the data from seven IVMP RCT studies and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. These studies were matched on the basis of four covariates: proportion of smokers, baseline diplopia, baseline proptosis, RIT of Grave's disease.
- The base-case analysis of CFB proptosis outcome for the comparison of teprotumumab versus IVMP + MMF was based on the data from one IVMP + MMF RCT study and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. These studies were matched on the basis of three covariates: proportion of smokers, baseline diplopia, and baseline proptosis.
- The EAG asked the company to provide mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm (IVMP; IVMP + MMF) before and after matching where appropriate. The EAG also asked the company to provide the standardised mean difference for the comparison of the intervention arm and the comparator arm after matching where appropriate. The company provided relevant data in responding to the EAG's request.
- By following the assessment of relevant data provided by the company, the EAG considers that the teprotumumab matched cohort were well balanced across all these baseline covariates being adjusted in the MAIC versus the comparator arm (IVMP; IVMP + MMF) after matching.
- However, the EAG considers that there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to limited availability of these variables or lack of overlap of one of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations. It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables. The duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, IVMP and IVMP + MMF

populations Therefore, this limitation may have introduced uncertainties in the results of ITC analysis, which implies a key issue.

- The EAG asked the company to include single-arm studies in the ITCs, given that unanchored MAIC was used to estimate relative efficacy between different treatments. In responding to EAG's request, the company performed the MAIC analysis by including single-arm studies as a sensitivity analysis. The EAG considered that the sensitivity analyses of MAIC by including additional single-arm studies showed that the results from sensitivity analyses were generally consistent with those results of base-case MAIC analyses.
- The EAG asked the company to conduct a simulated treatment comparison (STC) as a sensitivity analysis on the basis that it is listed as a method of population adjustment alongside MAIC in NICE Technical Support Document (TSD) 18. The company stated that due to the timeframe issue, the company was not able to conduct a further STC as a sensitivity analysis during clarification response stage, which implies a key issue.
- The EAG considers that, given that the sensitivity analysis by using alternative adjustment methods such as the STC approach were not conducted for the data of the base-case analyses, it was unclear whether the results of base-case MAIC analyses were robust.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS, Appendices and response to clarification^{1,4,9} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of teprotumumab and other treatments for TED. Searches were conducted in June 2023 and updated in September 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The study selection criteria for participants, interventions, comparators and outcomes in the SLR of clinical effectiveness generally encompassed those specified by the NICE final scope. The data extraction process was satisfactory and in line with recommended good practice in SLRs. The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The number of studies retrieved, screened and included was clear based on the PRISMA flow chart.

Two RCTs were identified as being relevant to the SLR: one RCT (OPTIC; NCT03298867) provided the main source of evidence and another Phase 2 trial (NCT01868997) provided additional data. The OPTIC trial was Phase 3, multicentre, double-blind, randomised, placebo-controlled study that assessed the efficacy and safety of teprotumumab (administered every 3 weeks for 24 weeks) compared with placebo for the treatment of patients with moderate-to-severe active TED.

The findings from the OPTIC trial showed that the teprotumumab group was associated with a higher response rate across all timepoints (week 6, week 12, week 18 and week 24) compared to the placebo group. The findings from this trial also showed that the teprotumumab group was associated with a

significantly greater mean change in proptosis from baseline compared to the placebo group at all time points (week 6, week 12, week 18 and week 24).

In terms of ITC analysis, the base-case analysis in the company evidence submission was based on a MAIC analysis. The base-case MAIC analysis of CFB proptosis outcome for the comparison of teprotumumab versus IVMP was based on the data from seven IVMP RCT studies and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. These studies were matched on the basis of four covariates: proportion of smokers, baseline diplopia, baseline proptosis, RIT of Grave's disease. The base-case analysis of CFB proptosis outcome for the comparison of teprotumumab versus IVMP + MMF was based on the data from one IVMP + MMF RCT study and the pooled IPD from the two teprotumumab trials NCT01868997 and NCT03298867. These studies were matched on the basis of three covariates: proportion of smokers, baseline diplopia, and baseline proptosis.

The EAG asked the company to provide mean and standard deviation of the covariates which were adjusted for in the MAIC analysis for the intervention arm and the comparator arm (IVMP; IVMP + MMF) before and after matching where appropriate. The EAG also asked the company to provide the standardised mean difference for the comparison of the intervention arm and the comparator arm after matching where appropriate. The company provided relevant data in responding to the EAG's request. By following the assessment of relevant data provided by the company, the EAG considers that the teprotumumab matched cohort were well balanced across all these baseline covariates being adjusted in the MAIC analysis versus the comparator arm (IVMP; IVMP + MMF) after matching. However, the EAG considers that there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to limited availability of these variables or lack of overlap of one of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations. It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables. The duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations. Therefore, this limitation may have introduced uncertainties in the results of ITC analysis.

The EAG asked the company to include single-arm studies in the ITC, given that unanchored MAIC was used to estimate relative efficacy between different treatments. In responding to EAG's request, the company performed the MAIC analysis by including single-arm studies as a sensitivity analysis. The sensitivity analyses by including additional single-arm studies showed that the results from sensitivity analyses were generally consistent with those results of base-case MAIC analyses.

The EAG asked the company to conduct a STC as a sensitivity analysis on the basis that it is listed as a method of population adjustment alongside MAIC in NICE TSD 18. The company stated that due to the timeframe issue, the company was not able to conduct a further STC as a sensitivity analysis during clarification response stage. Given that the sensitivity analyses by using alternative adjustment methods such as the STC approach were not conducted for the data of the base-case analyses, it was unclear whether the results of base-case MAIC analyses were robust.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains to the review of cost-effectiveness analysis (CEA) studies. However, Section 4.1.1 also contains summaries and critiques of other searches related to cost effectiveness (CE) presented in the CS. Therefore, the following section includes searches for the CEA review, measurement and evaluation of health effects, and cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to CE, health-related quality of life (HRQoL) and resource use identification presented in the CS.¹ The CADTH evidence-based checklist for the PRESS, was used to inform this critique.¹⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendices G and H of the CS provide details of SLRs conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in moderate-to-severe active TED.⁹ The CE searches were conducted in May 2023 and the HRQoL searches were conducted in June 2023. Both sets of searches were updated in October 2024.

EAG comment:

- A single set of searches was undertaken to identify relevant studies on the economic evidence and health care resource use in moderate-to-severe active TED. An additional set of searches was conducted to identify relevant HRQoL data. The CS, Appendices G and H and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 4, 9}
- The following databases were searched for the economic evidence and healthcare resource use SLR on 22 May 2023: Embase, MEDLINE, the Health Technology Assessment (HTA) database, the NHS Economic Evaluation Database (NHS EED) and EconLit. Update searches were conducted on 3 October 2024.
- The HRQoL SLR searches included the following databases: MEDLINE, Embase, the Database of Abstracts of Reviews of Effects (DARE), CENTRAL, CDSR, the HTA database, NHS EED and EconLit. These were originally searched on 9 June 2023 and updated on 3 October 2024.
- For all CE searches, four key conference proceedings were manually searched for the last four years (where available). Eighteen HTA sources and the Cost-Effectiveness Analysis (CEA) Registry were searched in May 2023 and updated in October 2024. Bibliographies of systematic reviews and meta-analyses and other selected studies were reference checked.
- Searches were limited to economic evidence and healthcare resource use studies published since 2012. No date limit was applied to the HRQoL searches.
- The economic evidence and healthcare resource use searches contained a population facet for TED. This was then combined with a study design filter containing terms for costs and economic evaluations. The HRQoL searches contained the same population facet for TED. This was then combined with a study design filter containing terms for HRQoL.
- All searches were well structured, transparent and reproducible. Full details of the update searches for the HRQoL SLR were not originally included in the CS, but were provided in response to clarification.⁴

- Searches contained a good range of search terms, synonyms and subject headings. None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- Search results were limited to studies published only in English. The EAG was concerned that limiting the MEDLINE, Embase and CENTRAL searches to English language may have introduced potential language bias. Current best practice states that 'To reduce the risk of introducing bias, searches should not be restricted by language'.¹¹

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, utilities and costs and resource use are presented by the company in Appendix G and H of the CS.⁹ The EAG agrees in general that the in- and exclusion criteria are suitable to fulfil the company's objective to identify relevant CE studies. However, the limit on the publication year of 2013 or more recent appears overly restrictive, and it is possible that relevant studies, especially for utilities and resource use, may have been missed.

4.1.3 Findings of the cost-effectiveness review

The PRISMA flow diagrams for the overall economic SLR can be found in Figure 6 of Appendix G of the CS.⁹ In total, thirteen publications (seven retrospective, two RCTs, and four cross-sectional) were included in the economic/healthcare resource utilisation (HCRU) SLR. From these, only one study examined economic evaluation associated with TED treatment. Ten studies reported on the cost and/or HCRU with TED, from which only one reported HCRU data in moderate-severe TED.

In addition, the PRISMA diagram for the overall HRQoL/utilities SLR was shown in Figure 9 of Appendix G of the CS.⁹ In total, 91 publications from 79 original studies were identified, reporting on humanistic burden or utility values, across the HRQoL and clinical SLRs. Twenty-two were retrospective studies, 21 were prospective, 15 each were RCTs or cross-sectional, three were single-arm trials, two were utility mapping/valuation studies, and one was a non-RCT. From these, only one study examined utility values in active moderate-severe TED, and the remaining studies reported humanistic burden associated with TED.

4.1.4 Conclusions of the cost effectiveness review

The CS, Appendices and response to clarification^{1,4,9} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in moderate-to-severe active TED. Searches were conducted May/June 2023 and updated in October 2024. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, conference proceedings and HTA resources were searched. Overall, the EAG has no major concerns about the literature searches conducted.

Since no economic models were identified to address the cost effectiveness of teprotumumab for the treatment of moderate-to-severe active TED, a de novo cost effectiveness model was built by the company, which is discussed in the remainder of this section.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist²³

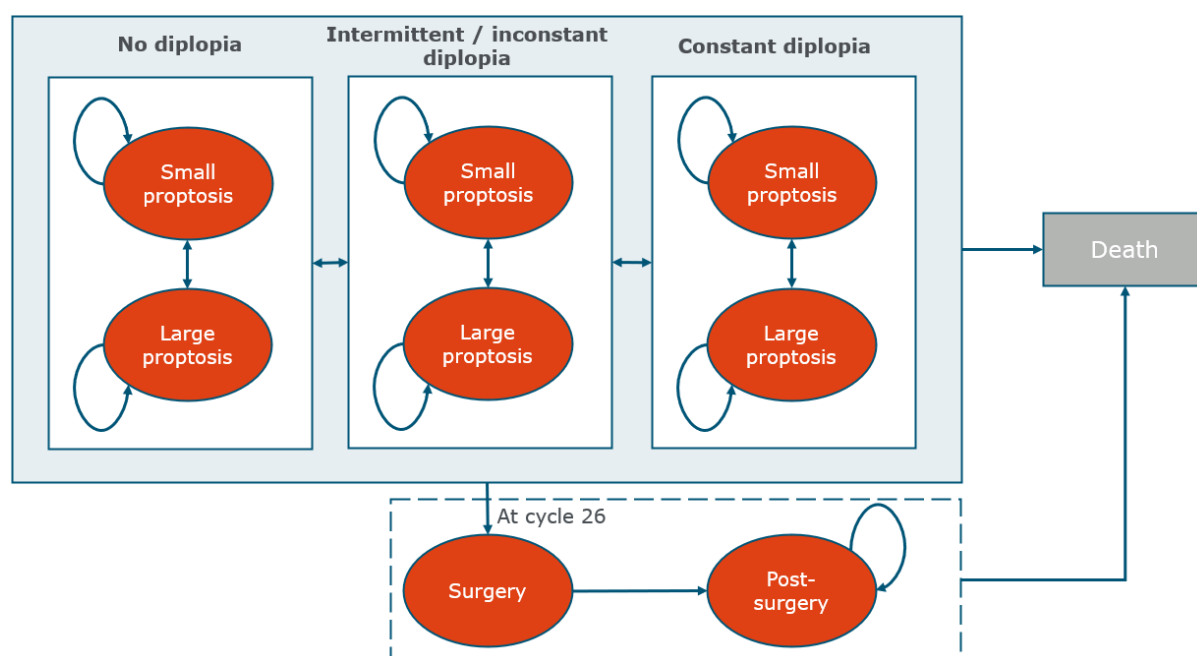
Element of health technology assessment	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to reference case
Perspective on costs	NHS and PSS	According to reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	According to reference case
Synthesis of evidence on health effects	Based on systematic review	According to reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As the EQ-5D is generally considered to be less suitable for eye diseases, a TTO study was done based on vignettes that described the various health states. ¹⁷
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Vignettes describing health states were based on information from the pivotal RCTs and interviews with patients ¹⁷
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	A representative sample of the US population valued the vignettes. According to four UK clinical experts these utility values can be generalised to the UK. ¹⁶
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	According to reference case
CS = company submission; EQ-5D = EuroQoL-5 Dimensions; EAG = External Assessment Group; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; RCT = randomised controlled trial; TTO = time trade off; UK = United Kingdom; US = United States of America		

4.2.2 Model structure

The company developed a de novo CE model in Microsoft Excel® to assess the CE of teprotumumab compared to IVMP and IVMP + MMF as first-line therapy for treating adults with moderate-to-severe active TED.

The model adopts a cohort (Markov) approach consisting of nine mutually exclusive health states. Patients enter the model into one of six active TED health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints. The six states represent combinations of diplopia (no diplopia, intermittent or inconstant diplopia, constant diplopia) and proptosis symptoms (small, large). Additional health states are included to represent surgery, post-surgery and death, which is an absorbing health state. Individuals can occupy one state at a time. The choice and robustness of the health state definitions were validated for their relevance to the clinical management and impact of TED by a selected group of UK clinical experts.¹⁶ Figure 4.1 shows the schematic model structure.

Figure 4.1: Model structure



Based on Figure 33 of the CS.¹

CS = company submission

The company adopt a lifetime horizon modelling patients up to age 100 years. The model cycle length was 6 weeks to align with patient efficacy assessment timepoints in the Phase 2 and Phase 3 OPTIC clinical trials and dosing regimens for teprotumumab and included comparators.^{18, 19}

The definitions used to categorise proptosis are aligned with the American Thyroid Association severity classification.²⁰ Proptosis is described by the change from the upper limit of normal for a non-TED patient of the same race and sex, with the upper limits of normal for proptosis by race and sex are given in Table 4.2. Small proptosis is defined as <3mm above the upper limit for a non-TED patient of the same race and sex. Large proptosis is when it is ≥ 3 mm above the upper limit. Since proptosis is expected to be present for this population the company did not include a 'no proptosis' state.

The definition used to characterise diplopia are aligned with the Clinical Measures of Severity assessment: no diplopia (Clinical Measures of Severity assessment score of 0), intermittent/inconstant diplopia (score of 1 or 2), constant diplopia (score of 3).²¹ The company combined the intermittent and inconstant scores into one diplopia state to reduce the number of distinct health states in the cost effectiveness model and for consistency with the utility data from Smith et al. 2023.¹⁷

Table 4.2: Upper limit of normal proptosis by race and sex

Race	Female (mm)	Male (mm)
African American	23	24
White	19	21
Asian	16	17 (Thai) 18.6 (Chinese)
Based on Table 33 in the CS. ¹ CS = company submission; mm = millimetres		

Patients enter the model in one of the TED clinical states according to the pooled baseline distribution of patients from the Phase 2 and Phase 3 OPTIC trials.^{18, 19} The starting distribution is presented in Table 4.3.

Table 4.3: Distribution of patients by health state at model start

State	Percentage
Small proptosis, no diplopia	████
Large proptosis, no diplopia	████
Small proptosis, intermittent/inconstant diplopia	████
Large proptosis, intermittent/inconstant diplopia	████
Small proptosis, constant diplopia	████
Large proptosis, constant diplopia	████
Based on Table 34 in the CS. ¹ CS = company submission	

Within the first 26 cycles (3 years) patients can move between any of the TED clinical symptom states (or death) in each cycle but not to surgery. Only at cycle 26 (3 years) can patients move to the surgery health state which they then remain in for 30 cycles (3.5 years) after which they move to the post-surgery health state for the remainder of model duration (unless they move to the death state). The proportion of patients transitioning to the surgery state at cycle 26 depends on the TED state. These probabilities were informed by expert opinion (UK clinicians) due to a lack of data in the literature and are presented in Table 4.4.¹⁶ Surgery procedure and complication costs are applied as a one-off cost in the model.

Table 4.4: Percentage of patients transiting to the Surgery health state at cycle 26

Health state	Percentage
Small proptosis, no diplopia	████
Large proptosis, no diplopia	████
Small proptosis, intermittent/inconstant diplopia	████
Large proptosis, intermittent/inconstant diplopia	████
Small proptosis, constant diplopia	████

Health state	Percentage
Large proptosis, constant diplopia	████
Based on Table 35 in the CS. ¹ CS = company submission	

EAG comment: The EAG considers the modelling approach used by the company appropriate for the decision problem. The main issues identified by the EAG are:

- In the company's model, patients are only able to transition to the surgery health state at cycle 26 rather than throughout follow-up time. In response to the EAG clarification question (B1)⁴ the company explain this time point reflects the change in disease course from active to inactive (chronic) TED and patients can only receive surgery in the inactive disease stage. The estimate of time to surgery and surgery duration were informed by UK clinicians.¹⁶ While more complex approaches to modelling time to surgery could have been adopted to be more realistic, the company noted that the cost effectiveness results were largely insensitive to these assumptions.
- The approach to modelling transition probabilities for teprotumumab and its comparators risks overfitting to the Phase 2 and Phase 3 data on teprotumumab and results in high variation in particular transitions and issues due to small or zero patient counts. The company approach and EAG comments are provided in further detail in Section 4.2.6.
- The distribution of patients by TED state was based on that observed from the Phase 2 and Phase 3 OPTIC trials. There is some uncertainty about the extent to which this represents patients in UK clinical practice due to the limited data available. However, as noted in Section 4.2.3, UK clinical experts considered the patient characteristics from the studies similar to patients they see in clinical practice. This may also apply to the distribution of patients across health states.

4.2.3 Population

The population included in the economic analyses reflects the indication under appraisal, i.e., patients in England and Wales with moderate-to-severe active TED. The company expects this population to be very similar to the populations included in both the Phase 2 clinical trial and the Phase 3 OPTIC clinical trial, with the model base-case populated using pooled clinical data to maximise the sample size.^{18, 19} The baseline patient characteristics used in the model are presented in Table 4.5.

Table 4.5: Patient characteristics used in the model

Characteristic	Pooled Phase 2 and Phase 3 OPTIC, ^{18, 19} used in model	Phase 2 UK patients
Number of patients	171	████
Mean age (years), (SD)	51.58 (12.34)	████
Male (%)	27.03	████
Mean weight (kg), (SD)	78.07 (19.08)	77.54 (15.78)
Based on Table 32 CS and response to clarification letter. ^{1, 4} CS = company submission; kg = kilogram; SD = standard deviation; UK =United Kingdom		

In response to clarification question A8, the company provided data on patients from the UK enrolled in the Phase 2 clinical trial; no UK patients were included in the Phase 3 OPTIC study.⁴ The characteristics of these patients are also provided in Table 4.5, and it can be seen that only the average age of patients in the UK subset is slightly different from the whole study population. Also in their response, the company further explained that UK clinicians had advised that “the baseline

characteristics, demographics and previous medical histories of the study subjects are broadly representative of the TED patients they would treat in clinical practice”.

4.2.4 Intervention and comparators

The intervention considered in the CS is teprotumumab, which is administered IV at a dose of 10 mg/kg patient body weight for the first infusion, and 20 mg/kg once every 3 weeks thereafter for an additional seven infusions.¹⁸ The dosage assumed in the model is the same as patients received in the two clinical studies.^{18, 19}

In the CEA, the company assumed that the comparator could be either IVMP, or IVMP combined with MMF. Both these options are used off-label; however, they are consistent with the main 1st line treatment options for moderate-to-severe and active TED as detailed in the EUGOGO 2021 clinical practice guidelines.²² These guidelines are typically adhered to by UK clinicians, given that there are no published UK guidelines for TED.¹⁶ According to the EUGOGO guidelines, the recommended dose is 500 mg weekly for the first 6 weeks, followed by 250 mg weekly for the next 6 weeks. For IVMP + MMF, the dosing regimen of IVMP is the same as IVMP monotherapy, with the addition of a 1,000 mg MMF oral tablet taken daily for 24 weeks.²²

Other treatment options are also possible, such as orbital radiotherapy and various immunosuppressive agents, such as mycophenolate, rituximab, tocilizumab and ciclosporin. However, as discussed in their response to the clarification letter (question A4), these treatments are not really expected to be used in the 1st line treatment, according to UK clinical experts, though some might be used as a 2nd line option after IVMP with or without MMF (see also Section 2.3 of this report). The company provided an exploratory scenario analysis in which teprotumumab is used as 2nd line treatment and where it is compared to IVMP (+ MMF) & radiotherapy, IVMP (+ MMF) & ciclosporin, and IVMP (+ MMF) & azathioprine. All these comparisons yielded incremental cost-effectiveness ratios (ICERs) quite comparable to the base-case ICERs presented by the company.

4.2.5 Perspective, time horizon and discounting

The economic analysis was performed from the NHS and PSS perspective, following the NICE reference case.²³ The model has a lifetime horizon, e.g., up to a patient age of 100 years, again following the NICE reference case. Furthermore, costs and QALYs were discounted at 3.5% as per the NICE reference case.²³

4.2.6 Treatment effectiveness and extrapolation

Teprotumumab treatment affects model outcomes by changing the probability of transitioning between TED clinical states. Transitions to surgery are determined by health state occupancy. The probability of transitioning to surgery or death for patients in a given health state is the same regardless of treatment received. Transition probabilities for teprotumumab are estimated every 6 weeks (cycles) from week 0 to 24 directly from observed transitions in the pooled Phase 2 and Phase 3 OPTIC trials.^{18, 19} These are combined with treatment effect estimates from the indirect treatment comparisons to generate transition probabilities for IVMP and IVMP + MMF. Different approaches are taken for estimating these transition probabilities for IVMP and IVMP + MMF and for proptosis and diplopia outcomes. Each of these components is described in greater detail below.

4.2.6.1 Transition probabilities between TED states for teprotumumab

The company calculated teprotumumab transition probabilities for each 6-week cycle, up to 24 weeks. Patient counts and probabilities of transition were taken directly from observed data in the pooled Phase 2 and Phase 3 OPTIC clinical trials.^{18, 19} Patient counts and transition probabilities are presented in Table 4.6. In the probabilistic sensitivity analysis (PSA), the company uses Dirichlet distributions based on the patient counts to model uncertainty in the transition probabilities. For transitions with 0 (zero) counts no variation occurs in the PSA.

Table 4.6: Transition counts and probabilities over cycles 1-4 for teprotumumab from pooled Phase 2 and Phase 3 OPTIC trials

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Baseline to cycle 1 (week 6)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Cycle 1 to cycle 2 (week 12)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Cycle 2 to cycle 3 (week 18)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Cycle 3 to cycle 4 (week 24)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Based on Table 57 in Appendix J of CS, ⁹ and data in the economic model. ²⁴ Note that rows indicate health state at start of cycle, columns at end of cycle. CD = constant diplopia; CS = company submission; ID = intermittent/inconstant diplopia; LP = large proptosis; ND = no diplopia; SP = small proptosis.						

EAG comment:

- The company modelled transitions between TED states every 6 weeks up to cycle 4 (24 weeks) using actual counts observed in the pooled Phase 2 and Phase 3 OPTIC trials. The available sample size was low resulting in many transitions with zero observations (■ of all possible transitions) and substantial variation in transition probabilities for the same transition across cycles. This approach risks overfitting to the pooled trial data with limited sample size. The EAG raised this issue in the clarification letter (question B6) and asked the company if it had considered alternative

approaches to modelling transition probabilities over time.⁴ The company retained its approach after the clarification letter noting that alternative approaches (e.g., regression modelling) are more complex and require additional assumptions about changes in these outcomes over time. The EAG also notes that while there are limitations to the company's approach, the overall cost effectiveness results are relatively insensitive to how transitions are modelled over the first 24 weeks of the lifetime model. They determine cost effectiveness insofar as they affect the TED state membership at cycle 4 after which patients remain in that state for the remainder of the model.

- The approach to modelling transition probabilities is especially problematic for the PSA. Where zero counts were observed the company assumed zero variation in the PSA simulations (i.e., the count is always zero) which leads to an underestimation of uncertainty in the model outcomes.
- The company used a cycle length of 6 weeks to align with patient efficacy assessment timepoints and dosing schedules for teprotumumab and comparators.^{18, 19} A longer cycle length could have reduced issues due to low patient numbers with limited impact on estimates of cost-effectiveness. Given the limited impact of transitions between health states within the first 4 cycles on the model outcomes, the company could have also directly modelled transitions up to cycle 4 which would have avoided issues of zero counts. While the EAG would prefer to explore this approach in scenario analyses we are not able to undertake this because we do not have access to the individual patient level data on which this modelling depends. This would also have obviated the need for approaches such as regression modelling discussed above.

4.2.6.2 Transition probabilities between TED states for IVMP and IVMP + MMF

The company estimated transition probabilities by combining the data on teprotumumab with treatment effect estimates from the ITC. Transition probabilities are first calculated separately for proptosis (i.e., between small proptosis and large proptosis) and diplopia (i.e., between no diplopia, intermittent/inconstant diplopia and constant diplopia), assuming the outcomes are independent. The methods differ based on the outcome as described below. The company then multiplies transition probabilities for proptosis and diplopia to derive the transition probabilities between TED states.

The ITC reported differences in change in proptosis scores between teprotumumab at 24 weeks and IVMP at 12 weeks (see Table 3.16 and 3.18). In the model, proptosis is modelled dichotomously as small or large proptosis. To estimate transition probabilities for IVMP the company first creates pseudo-IPD data for IVMP. They did this using the following approach:

1. Calculated the change in proptosis scores from baseline to 24 weeks for each patient receiving teprotumumab.
2. Calculated the overall change as a percentage of the MD in change in proptosis scores from the ITC.
3. Calculated the absolute change in proptosis score from baseline to the end of each cycle (6, 12, 18, and 24 weeks).
4. Estimated the predicted change in proptosis score from baseline for each cycle by multiplying the absolute change in scores from #3 by the percentage change from baseline in #2 and subtracting the predicted change from the baseline score.

From this pseudo-IPD for IVMP, the company then classifies patient status at the end of cycle as small or large proptosis based on difference from standards by sex and race (Table 4.2). Since outcomes for IVMP were only measured to 12 weeks versus 24 weeks for teprotumumab, the company assumed the estimated changes in proptosis scores from the pseudo-IPD data from week 0 to 12 would apply to

IVMP cycle 1 (weeks 0 to 6) and from weeks 12 to 24 to IVMP cycle 2 (weeks 6-12). Patients would remain in the same states as at the end of cycle 2 in cycles 3 (12 to 18) and 4 (weeks 18 to 24). To calculate transition probabilities the company created 2:2 tables of transitions from the pseudo-IPD data from which transition probabilities were directly calculated. The company has not provided the IPD data for this calculation and we do not directly observe the estimated transitions for proptosis (only combined proptosis and diplopia TED state transitions).

A different approach was used for diplopia which had three different outcomes in the model (no diplopia [ND], intermittent/inconstant diplopia [ID], constant diplopia [CD]). The treatment effect from the ITC was the OR of an improvement in diplopia score. The company assumed that the OR applied to all improvements whether by one category (ID to ND or CD to ID) or two (CD to ND). The treatment effect was only applied to improvements in diplopia scores and not to deteriorations because there were not reported from the MAIC. The company estimated transition probabilities between diplopia states using the following approach:

1. Created a transition matrix for diplopia outcomes between each cycle for patients receiving teprotumumab based on the observed counts from the pooled Phase 2 and Phase 3 OPTIC trial data
2. Calculated the probability and odds of improving diplopia score from baseline to 24 weeks from the counts in #1
3. Calculated the odds of improving diplopia score for IVMP by multiplying the odds from #2 by the odds ratio from the ITC
4. Calculated the probability of improving diplopia score for IVMP based on the odds estimated in #3
5. Calculated the relative risk of improving the diplopia score for IVMP by dividing the probability of improvement estimated from #4 by the probability estimated in #2
6. For those states that represent improvement in diplopia (i.e., ID to ND, CD to ID, CD to ND) calculated the probability of each transition by multiplying observed transition probabilities from the teprotumumab data by the relative risk calculated in #6
7. Other transition probabilities were calculated as follows
 - ND to ND and ND to ID: same as for teprotumumab
 - ID to ID and ID to CD: 1-calculated probability for transition from ID to ND, with result scaled according to relative proportion transitioning from ND to ID and ID to CD for teprotumumab
 - CD to CD: 1 – calculated probabilities for transitions CD to ND and CD to ID.

As with proptosis outcomes, the company assumed that estimated transitions from weeks 0 to 12 would apply to cycle 1 of IVMP and transitions from week 12 to 24 would apply to cycle 2 of IVMP.

After separately estimating the transitions between proptosis and diplopia states, the company multiplied these together to derive estimated transition probabilities of TED states in the model. The estimated transition probabilities are reported in Table 4.7.

Table 4.7: Estimated transition probabilities over cycles 1-2 for IVMP

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Baseline to cycle 1 (week 6)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Cycle 1 to cycle 2 (week 12)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Based on the company's updated economic model. ²⁵ CD = constant diplopia; ID = intermittent/inconstant diplopia; IVMP = intravenous methylprednisolone; LP = large proptosis; ND = no diplopia; SP = small proptosis						

A similar approach as described above was used to calculate proptosis probabilities for IVMP+MMF. The only difference was that proptosis scores for IVMP + MMF were obtained up to 24 weeks (the same as for teprotumumab) and therefore the company did not make the adjustments to weeks 0 to 12 only as with IVMP. Diplopia outcomes were not recorded for IVMP + MMF. The company assumed the effects would be the same as for IVMP and therefore used the transition probabilities for IVMP. Table 4.8 presents the estimated transition probabilities of IVMP after multiplying the estimated probabilities for the proptosis and diplopia outcomes.

Table 4.8: Estimated transition probabilities over cycles 1-4 for IVMP + MMF

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Baseline to cycle 1 (week 6)						
Small proptosis, no diplopia (SP, ND)	■	■	■	■	■	■
Large proptosis, no diplopia (LP, ND)	■	■	■	■	■	■

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Small proptosis, intermittent/inconstant diplopia (SP, ID)						
Large proptosis, intermittent/inconstant diplopia (LP, ID)						
Small proptosis, constant diplopia (SP, CD)						
Large proptosis, constant diplopia (LP, CD)						
Cycle 1 to cycle 2 (week 12)						
Small proptosis, no diplopia (SP, ND)						
Large proptosis, no diplopia (LP, ND)						
Small proptosis, intermittent/inconstant diplopia (SP, ID)						
Large proptosis, intermittent/inconstant diplopia (LP, ID)						
Small proptosis, constant diplopia (SP, CD)						
Large proptosis, constant diplopia (LP, CD)						
Cycle 2 to cycle 3 (week 18)						
Small proptosis, no diplopia (SP, ND)						
Large proptosis, no diplopia (LP, ND)						
Small proptosis, intermittent/inconstant diplopia (SP, ID)						
Large proptosis, intermittent/inconstant diplopia (LP, ID)						
Small proptosis, constant diplopia (SP, CD)						
Large proptosis, constant diplopia (LP, CD)						
Cycle 3 to cycle 4 (week 24)						
Small proptosis, no diplopia (SP, ND)						
Large proptosis, no diplopia (LP, ND)						

State	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Small proptosis, intermittent/inconstant diplopia (SP, ID)	■	■	■	■	■	■
Large proptosis, intermittent/inconstant diplopia (LP, ID)	■	■	■	■	■	■
Small proptosis, constant diplopia (SP, CD)	■	■	■	■	■	■
Large proptosis, constant diplopia (LP, CD)	■	■	■	■	■	■
Based on the company's updated economic model. ²⁵ CD = constant diplopia; ID = intermittent/inconstant diplopia; IVMP = intravenous methylprednisolone; LP = large proptosis; MMF = mycophenolate mofetil; ND = no diplopia; SP = small proptosis						

In the original submission, the company had not incorporated the uncertainty from the ITCs into the estimated transition probabilities for IVMP or IVMP + MMF. They also had multiplied estimated probabilities by 1,000 and used these derived counts in application of the Dirichlet distributions within the PSA. This led to an underestimation of uncertainty. In response to the clarification letter the company updated the model such that the uncertainty in the treatment effect is incorporated into the transition probabilities by repeating the processes described above for simulated estimates of the treatment effects. This led to a 10% increase in the probabilistic ICER for teprotumumab versus IVMP and a 7% increase for teprotumumab versus IVMP+MMF.

EAG comment:

- The updated approach to PSA better captures the uncertainty in the transition probabilities resulting from statistical uncertainty in the ITC. However, the pseudo-IPD generated for IVMP is not provided by the company who cite confidentiality concerns. This makes it impossible for the EAG to fully validate the PSA results and explore EAG scenario analyses using PSA.
- In order to derive transition probabilities for IVMP and IVMP + MMF, the company made various (simplifying) assumptions. As a result, the uncertainty about the transition probabilities for IVMP and IVMP + MMF goes beyond the uncertainty associated with the ITC used but cannot be quantified. Key assumptions include:
 - The company uses different approaches to model changes in proptosis and diplopia states for IVMP and IVMP + MMF. This was due to the nature of the endpoints, as diplopia is a binary endpoint whereas proptosis is a continuous endpoint. The approach implicitly assumes these outcomes are independent rather than correlated (as for teprotumumab transition probabilities), and it is unclear how this might impact the results.
 - The company only modelled improvements in diplopia scores and not worsening of diplopia since these were not reported in the MAIC. This was because diplopia response (i.e. improvement) was the commonly reported outcome that could be used for comparison whilst no common outcome on deterioration of diplopia was identified. It was assumed that the IVMP probabilities for diplopia worsening or remaining the same were the same as for teprotumumab.
 - The company assumes that the OR for moving to the adjacent diplopia score category (i.e., intermittent to no diplopia or constant to intermittent diplopia) is the same as moving two

categories from constant to no diplopia. This assumption was made because diplopia response was defined as a ≥ 1 Grade reduction.

- Diplopia outcomes were not available for IVMP + MMF as insufficient data were identified in the literature. The company made the assumption that they would be the same for IVMP. The estimated transition probabilities are structurally dependent on the transitions observed among patients receiving teprotumumab. As described in Section 4.2.6.1 the limited sample size given the number of potential transitions between TED states leads to very low and often zero counts for particular transitions. This propagates through to the pseudo-IPD data used to estimate proptosis transition probabilities for IVMP and IVMP + MMF.
- In the company submission they noted that the participants in OPTIC had higher degrees of disease activity at baseline than might be expected in UK clinical practice but stated that the outcomes observed in the pivotal trials will be generalisable to TED patients in the UK. While the comparative treatment effects may indeed be generalisable, the (absolute) transition probabilities for teprotumumab may not be generalisable, and the transition probabilities for IVMP and IVMP + MMF are dependent on both the treatment effects and the transition probabilities observed for teprotumumab. The EAG would have liked to explore the potential impact of lower disease activity on transitions between health states but were limited in the capacity to do so by the absence of the patient-level data underlying the model. However, the impact would operate through state membership from 24 weeks which we explore in a separate scenario analysis related to extrapolation (see Section 4.2.6.3).

4.2.6.3 Extrapolation

The company assumed that everyone stayed in the TED state they occupied at cycle 4 (24 weeks) until the model end unless they transitioned to the surgery or death state. This assumes no further improvements or deterioration in proptosis or diplopia scores after 24 weeks and no increase in, or waning of, the treatment effect.

The company noted in the original submission that follow-up data on efficacy outcomes was collected for patients in the Phase 2 and Phase 3 OPTIC trials but provided little information on the design of these follow-up studies or the results. It reports response rates at 72-weeks for proptosis and diplopia among those treated with teprotumumab as 67% (38/57) and 69% (33/48), respectively, based on pooled outcome data. The company did not incorporate this long-term data into the model transition probabilities arguing that calculating robust long-term transition probabilities from this data would add considerable uncertainty to the model.

In the clarification letter (question B4), the EAG requested more information on the methods and results of the long-term follow-up.⁴ The company provided data separately for the Phase 2 and Phase 3 OPTIC studies. Results from the original company submission and the data provided in the clarification letter are summarised in Table 4.9.

The Phase 2 study collected additional efficacy data at week 72 for all subjects. At 24 weeks, 30/42 (71%) of patients allocated teprotumumab achieved proptosis response. Of these, [REDACTED] had not maintained response at 72 weeks and [REDACTED] did not provide data. Assuming the remaining [REDACTED] maintained the response, this implies a response rate at 72 weeks of [REDACTED]. The company did not provide separate data on diplopia response at 72 weeks from the Phase 2 study although this data appears to have been collected. The submitting company has confirmed that these data were not reported in the main CSR Week 72 addendum and so were omitted in error but can be provided.

Participants in the Phase 3 OPTIC trial who did not respond to treatment were eligible to enrol in the open label OPTIC-X where patients received teprotumumab. Responders or non-responders who chose not to enrol in OPTIC-X entered an additional 48-week follow-up period. Of the 39 subjects in the teprotumumab group who completed week 24 follow-up, 36 continued into the follow-up study, of which 20 completed the follow-up. According to data from Kahaly et al. (2019)²⁶ non-completion of the follow-up study occurred because of non-response (n=5), withdrawal to receive other therapies (n=3), withdrawal due to non-compliance (n=1), and flares (n=9). Of those in the placebo group only 3 entered the follow-up study and completed the 48-week follow-up.

At 24 weeks 34/41 (83%) of patients in the teprotumumab group achieved proptosis response. At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].

At 24 weeks 19/28 (68%) of patients in the teprotumumab group with diplopia at baseline had achieved diplopia response. At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].

The estimates of response rates in the original CS are substantially higher than those estimated from the data provided in the response to the clarification letter. This appears to be related to which patients are included in the denominator based on the Phase 3 OPTIC trial. In the original company submission, they exclude patients who did not complete the 72-week follow-up. In the data presented in the response to the clarification letter, response rates are also estimated including these patients as non-responders at 72 weeks.

Table 4.9: Estimated response rates for proptosis and diplopia at 24 and 72 weeks

Data source and method	Proptosis		Diplopia	
	24 weeks	72 weeks	24 weeks	72 weeks
Phase 2 data only	71% (30/42)	[REDACTED]	68% (26/38)	NR
Phase 3 data ^a	83% (34/41)	[REDACTED]	68% (19/28)	[REDACTED]
Phase 3 data ^b	83% (34/41)	[REDACTED]	68% (19/28)	[REDACTED]
Pooled data ^a	77% (65/84)	[REDACTED]	70% (46/66)	NR
Pooled data ^{b,c}	77% (65/84)	[REDACTED]	70% (46/66)	[REDACTED]
Based on the company submission Section B.2.6 and the response to the EAG clarification letter, Table 16. ^{1, 4}				
^a Assumes non-completion of 72-week follow-up in Phase 3 OPTIC trial indicates non-response				
^b Excludes non-respondents to 72-week follow-up in Phase 3 OPTIC trial				
^c This is data presented in the original company submission. All other numbers are estimated by the EAG based on the data provided by the company.				
EAG = External Assessment Group; NR = not reported				

In the response to the EAG clarification letter (question B9) the company note that they considered alternative extrapolation approaches namely:

- last observation carried forward (LOCF), in which the final transition probabilities from the on-treatment period were extended to the end of the model
- average observation carried forward, in which the average transition probabilities while on treatment were extended to the end of the model.

In response to the clarification letter the company state that they did not consider either of these approaches appropriate because they extrapolate patient transitions while on treatment to the off-

treatment period. The LOCF is included within the company's economic model but not presented in the company's submission.

EAG comment: The EAG considers the approach to extrapolating the transition probabilities beyond 24 weeks a key issue. The cost effectiveness results are highly dependent on the state occupancy at week 24 (cycle 4) after which patients are assumed to remain in that state for the rest of the model (unless they transition to surgery or death). This assumption does not seem entirely consistent with the 72-week follow-up results provided by the company in response to the clarification letter (question B4), which appear to suggest a reduction in the proptosis and diplopia response rates over time for patients treated with teprotumumab. In the company submission, no scenario analyses were implemented that explored treatment effect waning over time. While the company's specific criticisms of the LOCF and average approaches are reasonable, scenario analyses around treatment effect waning are essential to better understand the impact of the company's assumption that patients remain in the 24-week TED state throughout the model on the cost effectiveness results.

It is also important to note that the state occupancy at 24 weeks is based on limited patient numbers with potential overfitting to the observed data from the Phase 2 and Phase 3 OPTIC trials (see EAG comments in Section 4.2.6.1). This reinforces the need to explore different distributions of TED state occupancy after 24 weeks.

Furthermore, the data provided by the company on the long-term follow-up outcomes in response to the clarification letter were not complete. Most importantly, outcomes for diplopia response at 72-weeks were missing for the Phase 2 study. As noted earlier, the company confirmed these data were omitted in error but can be provided.

In addition, the outcomes available at 72-weeks differ from the construction of TED health states and the ITC outcomes. This limits the extent to which they can be directly incorporated into scenarios around long-term cost effectiveness. Despite this limitation, the EAG has made an attempt to explore how treatment waning in the first three years after treatment initiation may impact the cost effectiveness outcomes (see Section 6.1.2).

4.2.6.4 Treatment discontinuation and compliance

4.2.6.4.1 Treatment discontinuation

The company modelled all cause discontinuation values. In the original company submission, it was stated that patients remained in the health state they were in when they discontinued treatment. In response to the EAG clarification question B20 the company clarified that discontinuation does not in fact impact on transition probabilities or treatment effect estimates. This is because the data on transition probabilities and treatment effects is modelled directly from data that includes patients who both did and did not discontinue treatment.

Data on discontinuation for teprotumumab was estimated from the pooled phase 2 and phase 3 OPTIC trials.^{18, 19} For IVMP and IVMP + MMF discontinuation was estimated from an RCT of IVMP versus IVMP + MMF in active, moderate-to-severe Graves' orbitopathy.²⁷ Observed discontinuation rates were converted to probabilities per 6-week cycle assuming constant rate. Estimates are presented in Table 4.10.

Table 4.10: Estimated discontinuation probabilities per 6-week cycle

Treatment	Probability of discontinuation per cycle	Source
Teprotumumab	██████	Pooled Phase 2 and Phase 3 OPTIC trials ^{18, 19}
IVMP	1.34%	Kahaly et al. (2018) ²⁸
IVMP+MMF	1.29%	Kahaly et al. (2018) ²⁸
Based on Table 39 of CS. ¹ CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil		

4.2.6.4.2 Treatment compliance

Using the pooled Phase 2 and Phase 3 OPTIC trial data,^{18, 19} the company calculated compliance for teprotumumab as the total number of doses received by all patients as a percentage of the total number of doses that would have been received under full compliance prior to treatment discontinuation (██████%). Due to a lack of data on compliance for IVMP or IVMP + MMF the company assumed it was the same as for teprotumumab.

4.2.7 Adverse events

In the base-case analysis the company included only adverse events grade ≥ 3 and that occurred in $\geq 5\%$ of patients. The company argue that grade 1 and 2 AEs can be managed by the patient at home and therefore have minimal impact on NHS costs. In scenario analyses all recorded AEs which occurred in $\geq 5\%$ of patients were included. Table 4.11 reports the probabilities of experiencing each AE per cycle for the base-case and sensitivity analyses for teprotumumab and IVMP and IVMP + MMF.

The data for teprotumumab came from the Phase 2 and Phase 3 OPTIC trials. No AEs met both criteria and hence no AEs for teprotumumab were included in the model. Eight adverse events were included for teprotumumab in a scenario analysis.

Data on AEs for IVMP were informed by published literature. Due to a lack of published data for IVMP + MMF, AEs were assumed to be the same as for IVMP. The source of data for the base-case was Salvi et al. 2015 since it was the only study reporting grade ≥ 3 events occurring in $\geq 5\%$ of patients.²⁹ Three AEs which meet these criteria were included in the base-case analysis: hyperglycaemia, 10-fold increase of aminotransferases, and 5-fold increase of gamma-glutamyl transferase. Three other relevant studies were identified which only reported the incidence of AEs but not the grade.³⁰⁻³² The rates reported in these studies are explored in three separate scenario analyses, one for each source of data. Event rates are translated to probabilities per 6-week cycle.

Table 4.11: Adverse event rates per 6-week cycle by treatment and analysis

Adverse event	Teprotumumab ^a		IVMP/IVMP + MMF			
	Base-case ^a	Scenario ^b	Base-case (Salvi et al. 2015) ^a	Scenario 1 (Roy et al. 2015) ^b	Scenario 2 (Marocci et al. 2001) ^b	Scenario 3 (Aktaran et al. 2007) ^b
Muscle spasms	██████	██████	0.00%	0.00%	0.00%	0.00%
Alopecia	██████	██████	0.00%	0.00%	0.00%	0.00%

Adverse event	Teprotumumab ^a		IVMP/IVMP + MMF			
	Base-case ^a	Scenario ^b	Base-case (Salvi et al. 2015) ^a	Scenario 1 (Roy et al. 2015) ^b	Scenario 2 (Marocci et al. 2001) ^b	Scenario 3 (Aktaran et al. 2007) ^b
Nausea	████	████	0.00%	0.00%	0.00%	0.00%
Sleepiness/fatigue	████	████	0.00%	0.00%	0.00%	4.08%
Diarrhoea	████	████	0.00%	0.00%	0.00%	0.00%
Dry skin	████	████	0.00%	0.00%	0.00%	0.00%
Dysgeusia	████	████	0.00%	0.00%	0.00%	0.00%
Headache	████	████	0.00%	0.00%	0.00%	0.00%
Amenorrhoea	████	████	0.00%	0.00%	0.00%	0.00%
Dizziness	████	████	0.00%	0.00%	0.00%	0.00%
Stomatitis	████	████	0.00%	0.00%	0.00%	0.00%
Abdominal pain	████	████	0.00%	0.00%	0.00%	0.00%
Cough	████	████	0.00%	0.00%	0.00%	0.00%
Influenza	████	████	0.00%	0.00%	0.00%	0.00%
Cushingoid habitus	████	████	0.00%	3.74%	5.42%	0.00%
Weight gain	████	████	0.00%	7.75%	0.00%	4.08%
Hypertension	████	████	0.00%	2.47%	0.00%	0.00%
Depression	████	████	0.00%	2.47%	0.00%	0.00%
Myalgias	████	████	0.00%	2.47%	0.00%	0.00%
Glucose intolerance	████	████	0.00%	0.00%	10.08%	0.00%
Gastritis	████	████	0.00%	0.00%	4.30%	4.08%
Urinary tract infection	████	████	0.00%	0.00%	8.88%	0.00%
Palpitation	████	████	0.00%	0.00%	0.00%	6.19%
Hyperglycaemia	████	████	1.60%	0.00%	0.00%	6.19%
10-fold increase of aminotransferases	████	████	1.60%	0.00%	0.00%	0.00%
5-fold increase of gamma-glutamyl transferase	████	████	1.60%	0.00%	0.00%	0.00%

Based on Tables 41 and 42 from CS.¹

Data for teprotumumab was based on phase 2 and phase 3 OPTIC trials

^a Includes only AEs that are grade ≥ 3 and occur in $\geq 5\%$ of patients

^b Includes all AEs that occur in $\geq 5\%$ of patients

AE = adverse event; CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil

EAG comment: The approach to incorporating AEs into the model is largely appropriate. However, the rationale provided by the company for not considering grade 1 and 2 AEs in the base-case is partial, citing limited impact on NHS costs. Some of the events that were excluded do have meaningful, if transient, impact on patient HRQoL.

4.2.8 Health-related quality of life (HRQoL)

4.2.8.1 HRQoL data from clinical trials

In the Phase 3 OPTIC trial, the GO-QOL questionnaire, recommended by the EUGOGO guidelines, was used to assess HRQoL.²² The company did not include the European Quality of Life-5 Dimensions (EQ-5D) questionnaire in the OPTIC trial, in light of the Decision Support Unit (DSU) statement that EQ-5D is probably not appropriate for assessing specific forms of visual impairment,³³ and various studies indicating that the EQ-5D is inferior to disease-specific alternatives in several eye diseases.³⁴⁻³⁶ The company further explained that mapping to EQ-5D would not overcome these limitations, and also that there is no mapping algorithm available from GO-QOL to EQ-5D.²³

EAG comment: The EAG considers the decision not to include the EQ-5D in the clinical studies as a missed opportunity to assess the validity of this instrument in TED. Whilst it is true that the DSU has indicated that for some specific forms of visual impairments the EQ-5D might not be appropriate,³³ this does not necessarily mean that the EQ-5D would not be appropriate for TED. As TED involves more than only problems with eyesight, but also e.g., pain, discomfort, and negative feelings about appearance, the EQ-5D might actually be responsive enough to value the health states defined in the current model.

4.2.8.2 Published HRQoL studies

The company used a targeted literature review to search for publications providing utility values for the model health states. Only one study was found that reported utility values by different grades of diplopia in patients with strabismus, by Beauchamp et al. (2005), but this study did not report whether patients had active TED.³⁷

EAG comment: The EAG concurs that Beauchamp is indeed not useful for the current assessment, not only because it was not clear if part of their population involved patients with active TED, but also because of methodological issues.³⁷ For example, the TTO valuation of health states was done by patients themselves, and rather than using the common time horizon of 10 years in framing the trade-off question, each patient was asked to trade based on their own life expectancy.

The SLR for HRQoL excluded papers before 2013, and it is not clear to the EAG why this year was chosen as a limit.⁹ It is also not clear how the targeted literature review differed from the SLR, but EAG noticed that in the SLR, Choi et al. was excluded based on publication date 2012, whilst it was included in the targeted literature review.³⁸ This raises the question whether other potentially relevant studies from the SLR have been excluded solely because of year.

4.2.8.3 Health state utilities

As no HSUV were found in the literature, the company commissioned a new utility study specific to active moderate-to-severe TED.¹⁷ For each of the six main health states defined in the model (though not for surgery and post-surgery), vignettes were developed based on interviews with six US patients with TED and two placebo-controlled clinical trials.^{13,27, 39} The vignettes were subsequently validated

by three clinicians and three TED patient advocates, and align with the six-health state Markov model in this appraisal.¹⁷

A total of 111 participants, a demographically representative sample of the US general population and without TED, was recruited for a time-trade off (TTO) study in which a trade-off had to be made between 10 years in the health state described by a vignette versus a certain number of years in perfect health followed by death.¹⁷

The utility values thus found were further validated by UK clinicians, who agreed they were reflective of the quality of life seen for moderate-to-severe active TED patients in the UK.¹⁶ The utility values obtained can be found in Table 4.12.

Multiple regression analysis was performed to validate the HSUV derived from the TTO study with GO-QOL scores.⁴⁰ This study showed a linear relationship between score on GO-QOL and the HSUV, with a higher GO-QOL score being associated with a higher utility value.

Utility values associated with the surgery and post-surgery health states are averages of the four lowest utility values and the four highest utility values, respectively.¹⁷ This assumption was made in the absence of published alternatives, given patients post-surgery are likely to have a greater quality of life (QoL) compared with patients currently undergoing surgery.

Table 4.12: Summary of utility values for cost-effectiveness analysis

State	Mean utility value (standard deviation)	95% CI	Justification
Small Proptosis, No Diplopia	0.60 (0.34)	0.54-0.67	Smith <i>et al.</i> , 2023 ¹⁷
Large Proptosis, No Diplopia	0.46 (0.32)	0.40-0.52	
Small Proptosis, Intermittent/Inconstant Diplopia	0.52 (0.33)	0.45-0.58	
Large Proptosis, Intermittent/Inconstant Diplopia	0.43 (0.33)	0.36-0.49	
Small Proptosis, Constant Diplopia	0.34 (0.31)	0.29-0.40	
Large Proptosis, Constant Diplopia	0.30 (0.31)	0.24-0.36	
Surgery	0.38	-	Assumed to be the average of four lowest utility values
Post-surgery	0.50	-	Assumed to be the average of four highest utility values
Source Table 40, CS. ¹ CI = confidence interval; CS = company submission			

EAG comment: At the request of the EAG (question B12 of the clarification letter),⁴ the company tried to validate the utility values obtained through the TTO study.¹⁷ The company did this by selecting NICE submissions for eye-related diseases in which TTO approaches have been used. Four submissions were

identified, two related to age-related macular degeneration, one related to inherited retinal dystrophies and one concerning diabetic macular oedema.^{4, 41-44} In general, these studies showed a range of utilities largely the same as the range of utility values in the current submission, with lowest values quite similar to the utility value of the worst state in this submission, i.e., 0.30 for patients with large proptosis and constant diplopia. In all these submissions, health states were defined based on visual acuity, with the worst health state matching a visual acuity near blindness. The company explained that these studies provide validation of the HSUVs, but that TED has disease features that were not part of the health states in the four NICE submissions, such as pain, eyelid retraction and living with a facial disfigurement, and that thus, the company-initiated study by Smith et al. is the only suitable source for utility values.

The EAG agrees with this assessment but would like to point out that whilst TED has various disease features that are not present in the other eye related diseases, at the same time the level of reduced visual acuity cannot be assumed to be the same as for the other diseases. In that regard it might have been preferable to focus the validation efforts on TTO studies in patients with eye diseases that are also more characterised by pain/discomfort and strabismus. Whilst the EAG did not have time to do a full-scale literature search for such studies, some simple pragmatic searches did not yield any useful studies.

The main reason why the EAG is somewhat hesitant regarding the validity of the relatively low utility values found by Smith et al. is related to the very long descriptions of the health states.¹⁷ The EAG wonders to what extent respondents were able to notice all differences between vignettes and considers that the trade-off task may have been a cognitive challenge for many respondents. However, based on the comparison to other NICE submissions these concerns are somewhat alleviated.

In the CS it was already mentioned that the face validity of the utility values had been confirmed by four UK clinical experts.¹⁶ From the summary of the interviews with these experts it is clear that one expert considered that QoL would be little impacted in the “no diplopia, small proptosis” health state and that thus, this health state should be closer to the population average. In the clarification letter (question B13) the EAG asked the company to comment on this suggestion from the expert. The company explained that even with small proptosis, according to patients and UK clinicians, there might be a significant impact on patients’ perceived appearance, and a patient may experience pain, swelling and redness of the eye. Hence, they consider the utility values reflective of patients with active moderate-to-severe TED.

However, the company explored several scenario analyses to see how adjustments to the utility values might impact the cost effectiveness. In their response to the clarification letter the results of these scenario analyses were presented, showing that none of the scenarios led to ICERs for teprotumumab that were higher than for the base-case. These scenarios will further be discussed in Section 5.2.3

4.2.8.4 Disutility values

4.2.8.4.1 Adverse events

For each of the identified AEs the company identified estimates of disutility from the literature or previous NICE guidance and estimates of duration from literature or expert opinion. This data is presented in Table 4.13. The reported disutility is divided by 365 and then multiplied by the duration to derive the disutility per event. The disutility applies to each cycle while on treatment.

Table 4.13 Adverse event disutilities and durations

Adverse event	Disutility	Average duration (days)	Disutility Source and assumptions	Duration source and assumptions
Muscle spasms	0.035	63	Matza <i>et al.</i> (2019) ⁴⁵	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸
Alopecia	0.040	168	Hall <i>et al.</i> (2019) ⁴⁶	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸ assumed AEs occur over the treatment course
Nausea	0.062	2	Hagiwara <i>et al.</i> (2018) ⁴⁷	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸
Sleepiness/fatigue	0.030	32	Sullivan <i>et al.</i> (2011) ⁴⁸	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸
Diarrhoea	0.047	3		
Dry skin	0.000	75		
Dysgeusia	0.027	23		
Headache	0.027	23		
Amenorrhoea	0.056	168	Disutility for hormone dysfunction assumed same as cushingoid habitus.	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸ assumed AEs occur over the treatment course
Dizziness	0.027	9	Sullivan <i>et al.</i> (2011) ⁴⁸	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸
Stomatitis	0.140	114	Paracha <i>et al.</i> (2018) ⁴⁹	
Abdominal pain	0.051	11	NICE TA804 (2022) ⁵⁰	
Cough	0.014	75	Sullivan <i>et al.</i> (2011) ⁴⁸	
Influenza	0.014	59	Sullivan <i>et al.</i> (2011) ⁴⁸	
Cushingoid habitus	0.056	105	NICE HST14 ⁵¹	Roy <i>et al.</i> (2015), ³² Marcocci <i>et al.</i> (2001), ³¹ assumed AEs occur over the treatment course
Weight gain	0.008	98	Smith-Palmer <i>et al.</i> (2016) ⁵²	Roy <i>et al.</i> (2015) ³² Aktaran <i>et al.</i> (2007) ³⁰ assumed AEs occur over the treatment course
Hypertension	0.046	112	Sullivan <i>et al.</i> (2011) ⁴⁸	Roy <i>et al.</i> (2015) ³² assumed AEs occur over the treatment course

Adverse event	Disutility	Average duration (days)	Disutility Source and assumptions	Duration source and assumptions
Depression	0.080	10	Kolovos <i>et al.</i> (2017) ⁵³	Matza <i>et al.</i> (2015) ⁵⁴
Myalgias	0.090	3	Sullivan <i>et al.</i> (2011) ⁴⁸	Sullivan <i>et al.</i> (2011) ⁴⁸
Glucose intolerance	0.000	98	Assumed to be 0.	Marcocci <i>et al.</i> (2001), ³¹ assumed AEs occur over the treatment course
Gastritis	0.051	3	NICE TA804 (2022) ⁵⁰	Amgen (2017) ¹⁹ Amgen (2020) ¹⁸ assumed equal to diarrhoea
Urinary tract infection	0.100	14	NICE TA127 (2007) ⁵⁵	NICE TA127 (2007) ⁵⁵
Palpitation	0.039	1	Sullivan <i>et al.</i> (2011) ⁴⁸	Aktaran <i>et al.</i> (2007) ³⁰
Hyperglycaemia	0.005	84	Drummond <i>et al.</i> (2018) ⁵⁶	Aktaran <i>et al.</i> (2007) ³⁰ assumed AEs occur over the treatment course
10-fold increase of aminotransferases	0.000	168	Disutility assumed to be 0.	Salvi <i>et al.</i> (2015) ²⁹ assumed AEs occur over the treatment course
5-fold increase of gammaglutamyltransferase	0.000	168	Disutility assumed to be 0.	Salvi <i>et al.</i> (2015) ²⁹ assumed AEs occur over the treatment course
Based on Table 43 from CS ¹ AEs = adverse events; CS = company submission; NICE =National Institute for Health and Care Excellence				

Total disutility by arm depends on which AEs are modelled. In the base-case no AEs were included for teprotumumab because they did not meet the criteria of grade ≥ 3 , occurring in $\geq 5\%$ of patients. For IVMP and IVMP + MMF only the disutility due to hyperglycaemia was included. The other two AEs which meet inclusion criteria were assumed to have zero disutility. Table 4.14 reports the average disutility per cycle, while on treatment, by treatment arm. Various scenario analyses were implemented excluding adverse event disutilities and also including additional disutilities for AEs of any grade occurring in $\geq 5\%$ of patients are included.

Table 4.14: Total AE disutilities by treatment arm

Treatment	Adverse event disutility
Teprotumumab	0.0000000
IVMP	0.0000184
IVMP+MMF	0.0000184
Based on Table 44 from CS. ¹	

AE = adverse event; CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil

4.2.8.4.2 Intravenous administration disutilities

In the base-case the company includes disutilities arising from IV infusions. These are excluded in scenario analyses. Disutilities for IV infusions were sourced from Matza et al. (2013) which reported a monthly disutility for 30 minute and 2-hour infusions as 0.023 and 0.037, respectively.⁵⁷ Teprotumumab involved two 1.5 hours IV administrations in cycle 1 and two 1-hour IV administrations in cycles 2-4. For IVMP and IVMP + MMF, six 1-hour IV administrations per cycle were assumed. The company calculated disutility of a given IV duration by combining the 30-minute infusion disutility with a weighted average of the 3-minute and 2-hour disutilities over the remaining time. These estimated disutilities are divided by the number of days in a month to derive daily disutilities and then multiplied by the number of IV infusions per cycle. Disutilities from IV administration by treatment arm are given in Table 4.15.

Table 4.15: Total IV administration disutilities by treatment and cycle

Treatment	Disutility per cycle	Source and assumptions
Teprotumumab (cycle 1)	0.00213	Two 1.5-hour IV administration ⁵⁷
Teprotumumab (cycle 2 – 4)	0.00182	Two 1-hour IV administration ^{22, 57}
IVMP	0.00546	Six 1-hour IV administration ^{22, 57}
IVMP + MMF	0.00546	Six 1-hour IV administration ^{22, 57}
Based on Table 45 from CS ¹ CS = company submission; IV = intravenous; MP = methylprednisolone; MMF = mycophenolate mofetil		

4.2.9 Resources and costs

The analysis considered healthcare use and costs related to:

- Drug acquisition (for teprotumumab and the comparator drugs)
- Drug administration (for teprotumumab and the comparator drugs)
- Surgery, including surgical complications
- Subsequent treatment
- Routine monitoring and disease management (also referred to as ‘health state unit costs’)
- AEs/adverse reactions associated with teprotumumab and the comparator drugs.

EAG comment: Overall, the approach used to assess resource use and costs seems appropriate. A wide range of costs was included, and cost prices were based on UK sources. Given the perspective of the analysis (i.e., the NHS and PSS perspective), no important cost categories appear to be missing. Nevertheless, several comments can be made. These are detailed in Sections 4.2.9.1 to 4.2.9.6 below, which explain how resource use and unit cost prices were determined for each cost category.

4.2.9.1 Drug acquisition costs

The unit price for teprotumumab was based on the list price, including a Patient Access Scheme (PAS) discount. Costs per administration were calculated according to the dosing regimen based on the Phase 2 and Phase 3 OPTIC clinical trials and the expected UK summary of product characteristics (SmPC). Furthermore, the base-case analysis accounted for vial wastage, which was estimated using the method of moments. Compliance was also considered in the base-case, based on pooled data from the Phase 2

and Phase 3 OPTIC trials. The resulting cost per administration is presented in Table 4.16, with a distinction made between the first and subsequent infusions.

Table 4.16: Teprotumumab acquisition costs (per infusion)

Infusion	Mean weight (kg)	Dose (mg)	Unit size (mg)	Cost per unit (£)	Dose per admin (mg)	Vials per admin	Cost per admin (£)
1	78.07	10.00	500.00	[REDACTED]	780.70	[REDACTED]	[REDACTED]
2 – 8		20.00	500.00		1,561.40	[REDACTED]	[REDACTED]
Based on Table 46 from the CS. ¹ admin = administration; CS = company submission; kg = kilogram; mg = milligram							

To calculate the acquisition costs for the comparators (i.e., IVMP and IVMP + MMF), unit prices were sourced from the British National Formulary (BNF), selecting the least expensive option available.⁶² The dosing regimens for IVMP and for IVMP + MMF were based on EUGOGO clinical practice guidelines.²² Both for IVMP and IVMP + MMF, no wastage was applied, since there were fixed doses for administration that aligned with the available unit sizes. Due to a lack of specific data, the model assumed the same compliance rates for IVMP and IVMP + MMF as for teprotumumab. The resulting per-cycle acquisition costs based on these inputs are shown in Table 4.17.

Table 4.17: Acquisition costs for IVMP and for IVMP + MMF (per cycle)

Infusion	Dose per admin (mg)	Admin per cycle	Dose per cycle (mg)	Unit size (mg)	Units per cycle	Cost per unit	Cost per cycle
IVMP							
IVMP dose 1	500.00	6.00	3,000	500.00	6.00 vials	£9.60	£57.60
IVMP dose 2	250.00		1,500	125.00	12.00 vials	£4.75	£57.00
IVMP + MMF							
IVMP dose 1	500.00	6.00	3,000	500.00	6.00 vials	£9.60	£57.60
IVMP dose 2	250.00		1,500	125.00	12.00 vials	£4.75	£57.00
MMF	1,000	42	42,000	500.00	84 tablets	£0.11	£9.39
Based on Tables 49 and 50 from the CS. ¹ admin = administration; CS = company submission; IVMP = intravenous methylprednisolone; mg = milligram; MMF = mycophenolate mofetil							

4.2.9.2 Drug administration costs

The cost effectiveness model included drug administration costs for teprotumumab and IVMP, as both are administered intravenously. Since MMF is administered orally, no cost for administration were assumed for this drug. Teprotumumab was assumed to be administered over 2 hours for the first two infusions (rounded up) and 1 hour per infusion thereafter, while IVMP was conservatively assumed to be administered over 1 hour. Costs were determined based on 2022-2023 NHS reference costs, using

the chemotherapy code ‘SB12Z’ at a cost of £411.99 for a 1-hour IV administration. Table 4.18 presents the resulting costs.

Table 4.18: Treatment-specific drug administration costs

Treatment		Admin duration	Admin cost	Admin per cycle	Total cost per cycle	Source
Teprotumumab	Infusion 1- 2	2 hours	£823.98	2	£1,647.96	EUGOGO (2021) ²² , NHS reference costs 2022/2023 ⁵⁸ , SmPC
	Infusion 3-8	1 hour	£411.99	2	£823.98	
IVMP		1 hour	£411.99	6	£2,471.94	
IVMP + MMF		1 hour	£411.99	6	£2,471.94	
Based on Table 51 from the CS. ¹ admin = administration; CS = company submission; EUGOGO = European Group on Graves Ophthalmopathy; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; NHS = National Health Service; SmPC = summary of product characteristics						

4.2.9.3 Costs of surgery, including surgical complications

The cost effectiveness model applied surgery procedure and complication costs as a one-off cost for patients who transition to the surgery state at cycle 26. The model considered three types of surgeries: orbital decompression, strabismus surgery, and eyelid surgery (upper and lower blepharoplasty). The average number of surgeries a patient undergoes, determined by health state and treatment arm, was informed by UK clinicians.¹⁶ The unit cost of each surgery was calculated as a weighted average from the relevant 2022-2023 National Schedule of NHS Costs.⁵⁸ The numbers of surgeries and the surgery procedure costs are summarised in Table 4.19. As shown in the table, the calculations resulted in one-off surgery costs of £6,966.43 for teprotumumab and £11,670.76 for both IVMP and IVMP + MMF.

Table 4.19: Numbers of surgeries per health state and treatment arm and total surgery costs per treatment arm

	Average number of surgeries per patient						Unit cost of surgery	Total one-off costs of surgery
	Small Proptosis, No Diplopia	Large Proptosis, No Diplopia	Small Proptosis, Intermittent/ Inconstant Diplopia	Large Proptosis, Intermittent/ Inconstant Diplopia	Small Proptosis, Constant Diplopia	Large Proptosis, Constant Diplopia		
Teprotumumab								
OD	■	■	■	■	■	■	£5,206.79	£6,966.43
Strabismus	■	■	■	■	■	■	£2,605.84	
Eyelid	■	■	■	■	■	■	£1,269.37	
Total	■	■	■	■	■	■		
IVMP								
OD	■	■	■	■	■	■	£5,206.79	£11,670.76
Strabismus	■	■	■	■	■	■	£2,605.84	
Eyelid	■	■	■	■	■	■	£1,269.37	
Total	■	■	■	■	■	■		
IVMP + MMF								
OD	■	■	■	■	■	■	£5,206.79	£11,670.76
Strabismus	■	■	■	■	■	■	£2,605.84	
Eyelid	■	■	■	■	■	■	£1,269.37	
Total	■	■	■	■	■	■		
Based on Tables 52, 53 and 54 from the CS. ¹ CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; OD = orbital decompression.								

The costs of surgical complications were also applied as a one-off cost for patients entering the surgery health state, with the same cost applied regardless of the active disease health state the patients were previously in. The incidence rates of surgical complications of any grade were sourced from the literature,⁵⁹⁻⁶¹ while the surgery complication unit costs were obtained from 2022-2023 NHS reference costs.⁵⁸ Both the incidence rates and the unit costs are provided in Table 4.20.

Table 4.20: Incidence rates and unit costs of surgical complications

Surgical complication	Incidence complication per surgery			Unit cost
	Orbital decompression	Strabismus	Eyelid surgery	
Post-operative numbness	25.00%	0.00%	0.00%	£0.00
New post-operative diplopia	19.00%	0.00%	0.00%	£139.38
Hematoma	0.00%	0.00%	0.50%	£44.65
Chemosis	0.00%	0.00%	6.00%	£124.13
Perioperative stroke	0.00%	0.00%	0.00%	£915.64
Persistent post-operative facial nerve frontal branch palsy	0.00%	0.00%	0.00%	£11,898.18
Scleral perforation	0.00%	0.00%	0.00%	£1,106.42
Lower lid malpositioning	0.00%	0.00%	3.00%	£139.38
Dellen	0.00%	0.00%	0.00%	£148.53
CSR leakage	0.00%	0.00%	0.00%	£466.34
Based on Tables 55 and 56 from the CS. ¹				
CS = company submission; CSR = central serous retinopathy				

By multiplying the probabilities of complication occurrence for each surgery procedure by the unit cost of surgical complications and the number of surgeries per health state per treatment, the total one-off costs of surgical complications per treatment were calculated as £29.23 for teprotumumab and £45.92 for both IVMP and IVMP + MMF.

EAG comment: The costs of surgery and surgical complications were applied as a one-time cost for patients who transition to the surgery state at cycle 26. As the company clarified in the response to the clarification letter, the costs beyond cycle 30 were not discounted to calculate present value costs at cycle 26. The company acknowledges that this may have led to a slight overestimation of costs. The EAG considers that the impact on the ICER is likely to be modest, as also shown by the discounting scenarios described in the company's response to the clarification letter.

In Section B.3.5.1.3 of the CS,¹ the company explained that the average number of surgeries a patient receives was determined based on health state and treatment arm, and that these numbers were informed by UK clinicians. From Table 53 of the CS (see also Table 4.19 above), it appeared that in the base-case analysis, the numbers of surgeries depended on the treatment arm—with more surgeries required for people receiving IVMP or IVMP + MMF than for those receiving teprotumumab—but not on the health state.

In the response to the clarification letter, the company explained that clinicians confirmed that the number of surgeries received by patients would vary by treatment arm, while there seemed to be less consensus among clinicians regarding surgery rates by health state. To the EAG it seems most plausible

that the number of surgeries vary by treatment because treatment with teprotumumab keeps patients in less severe health states where fewer surgeries are required.

The company presented an additional scenario in which the average number of surgeries was dependent on health state, rather than treatment arm. This scenario generated an ICER of [REDACTED] per QALY for IVMP, reflecting an increase of 1.4% from base-case, and [REDACTED] for IVMP + MMF, a 1.6% decrease from base-case.

4.2.9.4 Costs of subsequent treatment

The model included the costs of a course of subsequent treatments for all patients in the four most severe health states (i.e., large proptosis, no diplopia; large proptosis, intermittent/inconstant diplopia; small proptosis, constant diplopia; large proptosis, constant diplopia). These costs were applied as a one-off cost in the cycle following the completion of the patient's primary treatment (i.e., cycle 5 for teprotumumab and IVMP + MMF, and cycle 3 for IVMP) and were applied to all patients. Calculations were based on unit prices obtained from the BNF,⁶²⁻⁶⁴ and from 2022-2023 NHS reference costs.⁵⁸ Subsequent treatment costs were also applied to any patients who discontinue their primary treatment. The subsequent treatments considered in the model's base-case were informed by clinical expert opinion given a lack of available market share data. Table 4.21 provides an overview of the subsequent treatments received by patients in the three treatment arms and the total costs of these treatments.

Table 4.21: Costs, incidence rates, and total costs of subsequent treatments

Subsequent treatment	Total one-off cost	Proportion of patients receiving the treatment		
		Following teprotumumab	Following IVMP	Following IVMP + MMF
IVMP	£5,058.48	[REDACTED]	[REDACTED]	[REDACTED]
MMF	£37.56	[REDACTED]	[REDACTED]	[REDACTED]
Radiotherapy	£287.48	[REDACTED]	[REDACTED]	[REDACTED]
Ciclosporin	£1,119.43	[REDACTED]	[REDACTED]	[REDACTED]
Azathioprine	£36.48	[REDACTED]	[REDACTED]	[REDACTED]
Total cost		£4,910.94	£4,650.50	£4,650.50
Based on Table 59 from the CS. ¹ CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil.				

4.2.9.5 Costs of routine monitoring and disease management ('health state unit costs')

This cost category was included in the model to capture the costs associated with routine monitoring and disease management for moderate-to-severe active TED. Resource use was identified through UK clinical interviews, as no relevant UK data were identified in the available literature.¹⁶ Given inconsistencies across these interviews, the model assumed the same resource use for all treatments, only varied by health state and time: more frequent resource use was included for the more severe health states, and separate frequencies were applied for cycle 1, cycle 2-35, and cycle 36 onwards, where relevant. Hearing appointments were included for teprotumumab only, [REDACTED]. The calculation of these costs was based on the unit cost prices provided in Table 4.22, which were derived from the BNF,^{65, 66} 2022-2023 NHS reference costs,⁵⁸ and Personal Social Services Research Unit (PSSRU) unit costs.⁶⁷

Table 4.22: Unit prices of resources used for routine monitoring and disease management

Healthcare resource	Unit cost
Artificial tears	£0.20
Ophthalmic gels/ointments	£2.05
CT scans	£158.20
MRI	£219.87
Ophthalmologist visit	£139.38
Orthoptics visit	£139.38
Hormone test	£1.61
Endocrinologist visit	£199.84
Primary care visit	£49.00
Hearing appointment	£113.67
Based on Table 60 from the CS. ¹	
CS = company submission; CT = computed tomography; MRI = magnetic resonance imaging.	

The frequencies of resource use are provided in Table 4.23. By multiplying these frequencies with the unit prices, cost per resource per cycle and total costs per cycle were calculated, with a distinction according to health state.

Table 4.23: Resource use and costs of routine monitoring and disease management

		Health state											
		Small proptosis, no diplopia		Large proptosis, no diplopia		Small proptosis, ID		Large proptosis, ID		Small proptosis, constant diplopia		Large proptosis, constant diplopia	
		Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle
Artificial tears		■	£1.77	■	£4.71	■	£4.71	■	£5.89	■	£5.89	■	£8.25
Ophthalmic gels/ointments		■	£0.00	■	£18.45	■	£18.45	■	£43.05	■	£43.05	■	£86.10
CT scans	Cycle 1	■	£55.76	■	£187.60	■	£187.60	■	£240.33	■	£240.33	■	£240.33
	Cycles 2+	■	£9.10	■	£9.10	■	£9.10	■	£9.10	■	£9.10	■	£9.10
MRI	Cycle 1	■	£126.43	■	£236.36	■	£236.36	■	£318.82	■	£318.82	■	£327.61
	Cycles 2+	■	£65.96	■	£65.96	■	£65.96	■	£65.96	■	£65.96	■	£65.96
Ophthalmologist visit		■	£27.86	■	£54.31	■	£54.31	■	£56.99	■	£66.78	■	£66.85
Orthoptics visit	Cycle 1	■	£40.88	■	£64.11	■	£64.11	■	£64.11	■	£74.13	■	£74.13
	Cycles 2+	■	£0.00	■	£64.11	■	£64.11	■	£64.11	■	£74.79	■	£74.79
Hormone test	Up to cycle 35	■	£0.56	■	£0.72	■	£0.72	■	£0.72	■	£0.72	■	£0.72
	Cycle 36+	■	£0.49	■	£0.71	■	£0.71	■	£0.71	■	£0.71	■	£0.71
Endocrinologist visit	Up to cycle 35	■	£57.45	■	£68.94	■	£68.94	■	£68.94	■	£77.56	■	£77.56
	Cycle 36+	■	£45.96	■	£61.28	■	£61.28	■	£61.28	■	£73.02	■	£73.02
Primary care visit		■	£8.45	■	£22.54	■	£22.54	■	£22.54	■	£22.54	■	£22.54
Hearing appointment ^a	Cycle 1	■	£113.67	■	£113.67	■	£113.67	■	£113.67	■	£113.67	■	£113.67
	Cycles 2-35	■	£6.69	■	£6.69	■	£6.69	■	£6.69	■	£6.69	■	£6.69
Total cycle 1^b			£319.15		£657.74		£657.74		£821.37		£849.80		£904.08
Total cycle 2 to 35^b			£171.14		£308.84		£308.84		£337.29		£366.38		£411.86
Total cycle 36+^b			£93.62		£235.21		£235.21		£263.66		£295.88		£341.36

	Health state											
	Small proptosis, no diplopia		Large proptosis, no diplopia		Small proptosis, ID		Large proptosis, ID		Small proptosis, constant diplopia		Large proptosis, constant diplopia	
	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle	Resource use	Costs per cycle
Based on Table 61 from the CS and Table 56 from Appendix I to the CS. ^{1, 9}												
^a Hearing appointments were included for teprotumumab only.												
^b Excluding the costs of hearing appointments.												
* For these values the EAG noticed a discrepancy between the value reported in Appendix I and the electronic model, the values here reported are those used in the electronic model.												
CS = company submission; CT = computed tomography; ID = intermittent/inconstant diplopia; MRI = magnetic resonance imaging												

Furthermore, costs of routine monitoring and disease management were calculated for the two surgery health states (i.e., ‘surgery’ and ‘post-surgery’), independent of the treatment regimen. Resource use was again informed by UK clinicians. The calculations used the same unit prices as those used for the active disease health states (Table 4.22). For the surgery health state, all resource use was considered for the entire duration of this health state. For the post-surgery health state, where patients remain for the remainder of the modelled lifetime, resource use was applied for 26 cycles, except for the use of artificial tears and ophthalmic gels/ointments, which were applied indefinitely. The resulting costs per cycle are shown in Table 4.24.

Table 4.24: Resource use and costs of routine monitoring and disease management in the surgery and the post-surgery health state

		Resource use	Costs per cycle
Artificial tears	Cycles 0-26	■	£8.25
	Cycles 26+	■	£1.18
Ophthalmic gels/ointments	Cycles 0-26	■	£86.10
	Cycles 26+	■	£12.30
CT scans	Cycles 0-26	■	£36.51
	Cycles 26+	■	£0.00
MRI	Cycles 0-26	■	£38.06
	Cycles 26+	■	£0.00
Ophthalmologist visit	Cycles 0-26	■	£208.40
	Cycles 26+	■	£29.15
Orthoptics visit	Cycles 0-26	■	£127.77
	Cycles 26+	■	£8.04
Hormone test	Cycles 0-26	■	£0.91
	Cycles 26+	■	£0.43
Endocrinologist visit	Cycles 0-26	■	£92.23
	Cycles 26+	■	£46.12
Primary care visit	Cycles 0-26	■	£40.99
	Cycles 26+	■	£25.50
Total costs per cycle in the surgery health state, cycle 0-26			£639.21
Total costs per cycle in the post-surgery health state, cycle 1-26			£122.72
Total costs per cycle in the post-surgery health state, cycle 26+^a			£13.48
Based on Tables 62 and 63 from the CS. ¹			
^a These costs only include the costs of artificial tears and ophthalmic gels/ointments.			
CS = company submission; CT = computed tomography; MRI = magnetic resonance imaging			

4.2.9.6 Costs of adverse events/adverse reactions

The cost effectiveness model assumed that grade 1 and 2 AEs can be managed by the patient at home and, therefore, had minimal cost implications for the NHS. Consequently, the base-case analysis included only the costs of $\geq$ grade 3 adverse events occurring in $\geq 5\%$ of patients. Since no adverse events met this criterion for teprotumumab, the adverse event cost per cycle for teprotumumab treatments was zero.

For IVMP and for IVMP + MMF, the adverse event costs were assumed to be equal. For these treatment arms, the incidence rates of adverse events were informed by the literature.²⁹ In total, only three adverse events (i.e., hyperglycaemia, 10-fold increase of aminotransferases, and 5-fold increase of gamma-glutamyl transferase) were included in the analysis, as they met the criterion of being $\geq$ grade 3 adverse events occurring in $\geq 5\%$ of patients. The costs per cycle of the adverse events were based on published literature and unit prices sourced from 2022-2023 NHS reference costs.⁵⁸ The adverse event costs per cycle were calculated by multiplying the unit costs by the incidence rate, as detailed in Table 4.25.

Table 4.25: Adverse event costs per cycle for IVMP and for IVMP + MMF

Adverse event	Cost of the adverse event per cycle	Probability per cycle	Cost per cycle
Muscle spasms	£315.00	████	████
Alopecia	£91.26	████	████
Nausea	£128.83	████	████
Sleepiness/fatigue	£0.00	████	████
Diarrhoea	£421.23	████	████
Dry skin	£517.65	████	████
Dysgeusia	£0.00	████	████
Headache	£408.22	████	████
Amenorrhoea	£75.47	████	████
Dizziness	£408.22	████	████
Stomatitis	£514.11	████	████
Abdominal pain	£412.62	████	████
Cough	£116.35	████	████
Influenza	£419.69	████	████
Cushingoid habitus	£55.00	████	████
Weight gain	£249.00	████	████
Hypertension	£358.47	████	████
Depression	£378.00	████	████
Myalgias	£213.00	████	████
Glucose intolerance	£55.00	████	████
Gastritis	£421.23	████	████
Urinary tract infection	£353.63	████	████
Palpitation	£55.00	████	████

Adverse event	Cost of the adverse event per cycle	Probability per cycle	Cost per cycle
Hyperglycaemia	£55.00	■	■
10-fold increase of aminotransferases	£870.15	■	■
5-fold increase of gamma-glutamyl transferase	£870.15	■	■
Total costs			£28.73
Based on Tables 42, 64 and 65 from the CS. ¹			
CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil.			

4.2.10 Disease severity

The NICE reference case stipulates that the committee will regard all QALYs as being of equal weight. However, the committee may consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Severity can be then taken into account quantitatively in the cost effectiveness analyses through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.26. Whichever implies the greater severity level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.²³

Table 4.26: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
Based on NICE health technology evaluations: the manual, 2023. ²³		
QALY = quality adjusted life year		

The company did not present any QALY shortfall analysis results, but indicated that the impact of TED on patients' lives is severe given the low utility scores in this population, and the suicide ideation present in this patient group.^{68, 69} The company further indicated that evidence to support a case for the severity modifier is limited, *“in part due because the severity modifier calculations are reliant on utilities and there are inherent challenges of deriving utility values, especially EQ-5D, for conditions in eyes”*.¹ However, the EAG is unclear what the company meant with this statement. The company concluded that they believe that *“the sentiment of the severity modifiers does apply to TED; in that its purpose is to identify conditions that have such severity additional value should be applied”*.¹

EAG comment: It is not clear to the EAG why the company did not present an estimation of the QALY weight, given that they estimated utilities for all health states and report the model outcomes as QALYs. Therefore, the EAG conducted the QALY shortfall analysis where the total lifetime QALYs associated with IVMP alone or with MMF were obtained from the model results of the base-case analysis, and the estimated total QALYs for the general population reflected the baseline characteristics of the pooled Phase 2 clinical trial and the Phase 3 OPTIC clinical trial (27.03% male and 51.58 years). Using the Schneider et al. calculator, we found an absolute shortfall of 5.87 and a proportional shortfall of 38.4%.⁷⁰ These results suggest that a QALY weight of 1.0 can be applied to this population.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

Table 5.1 shows the company's base-case deterministic CE results for teprotumumab compared to IVMP and IVMP + MMF. All results are discounted and assuming a PAS price for teprotumumab. Teprotumumab was more costly but also more effective than both IVMP and IVMP + MMF, resulting in 0.82 and 0.83 incremental QALYs and [REDACTED] and [REDACTED] incremental costs, with ICERs of [REDACTED] and [REDACTED] per QALY gained. Disaggregated discounted QALYs for teprotumumab compared to IVMP + MMF are shown in Table 5.2. Disaggregated discounted costs by health state and by resource use category for teprotumumab compared to IVMP + MMF are shown in Table 5.3 and Table 5.4, respectively.

Table 5.1: Company base-case deterministic CE results (teprotumumab PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
IVMP + MMF	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	0.83	[REDACTED]
IVMP	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	0.82	[REDACTED]
Teprotumumab	[REDACTED]	[REDACTED]	[REDACTED]				

Based on Table 68 in the CS and economic model.¹

CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; IVMP = intravenous methylprednisolone; LYG = life years gained; MMF = mycophenolate mofetil; PAS = patient access scheme; QALY = quality-adjusted life year

Table 5.2: Disaggregated QALY results (teprotumumab versus IVMP + MMF, discounted)

Health state	QALY teprotumumab	QALY IVMP + MMF	Increment	Absolute increment	(%) Absolute increment
Small Proptosis, No Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Large Proptosis, No Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Small Proptosis, Intermittent/Inconstant Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Large Proptosis, Intermittent/Inconstant Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Small Proptosis, Constant Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Large Proptosis, Constant Diplopia	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Surgery	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Post-surgery	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Based on Table 60 in Appendix J of the CS.⁹

Health state	QALY teprotumumab	QALY IVMP + MMF	Increment	Absolute increment	(%) Absolute increment
CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; QALY = quality-adjusted life year					

Table 5.3: Disaggregated health state cost results (teprotumumab – PAS price – versus IVMP + MMF, discounted)

Health state	Teprotumumab (£)	IVMP + MMF (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Small Proptosis, No Diplopia	████	████	████	████	████
Large Proptosis, No Diplopia	████	████	████	████	████
Small Proptosis, Intermittent/Inconstant Diplopia	████	████	████	████	████
Large Proptosis, Intermittent/Inconstant Diplopia	████	████	████	████	████
Small Proptosis, Constant Diplopia	████	████	████	████	████
Large Proptosis, Constant Diplopia	████	████	████	████	████
Surgery	████	████	████	████	████
Post-surgery	████	████	████	████	████
Total	████	████	████	████	████
Based on Table 61 in Appendix J of the CS. ⁹ CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; PAS = Patient Access Scheme					

Table 5.4: Disaggregated cost results by category (teprotumumab – PAS price – versus IVMP + MMF, discounted)

Cost item	Teprotumumab (£)	IVMP + MMF (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Treatment	████	████	████	████	████
Health state	████	████	████	████	████
Adverse event	████	████	████	████	████
Societal	████	████	████	████	████
Subsequent	████	████	████	████	████
Total	████	████	████	████	████
Based on Table 62 in Appendix J of the CS. ⁹ CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; PAS = Patient Access Scheme					

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by increasing the number of patients in the “no diplopia, small proptosis” health state, which is associated with a better quality of life

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Increasing costs due to treatment acquisition
- Reducing costs due to surgery
- Reducing the costs related to routine monitoring and disease management, due to more patients being in a better health state.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a PSA where all relevant parameters were sampled simultaneously from their corresponding probability distributions over 10,000 iterations. The company assumed a standard error of 20% around the mean value when uncertainty (e.g., standard errors, confidence intervals (CI)) was not reported. The input parameters and the probability distributions used in the PSA can be found in Table 66 of the CS. The average PSA results are summarised in Table 5.5. Although the costs and QALYs per treatment are very close to the deterministic estimates, the ICERs are somewhat higher than in the deterministic analysis, which is likely related to some skewness in the distributions defined.

Table 5.5: Company base-case probabilistic CE results (teprotumumab PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
IVMP + MMF	■	NR	■	■		0.77	■
IVMP	■	NR	■	■		0.75	■
Teprotumumab	■	NR	■				

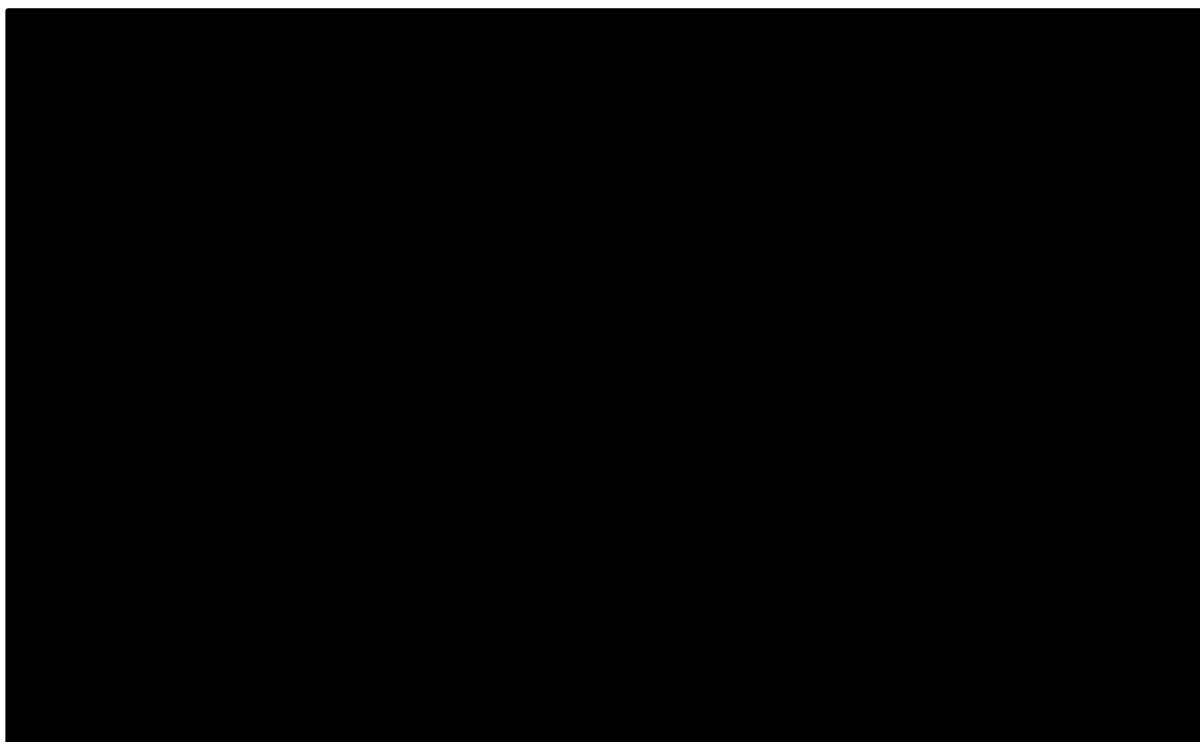
Based on the economic model after clarification.²⁴

CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; IVMP = intravenous methylprednisolone; LYG = life years gained; MMF = mycophenolate mofetil; NR = not reported; PAS = Patient Access Scheme; QALY = quality-adjusted life year

The company also plotted the PSA outcomes on a CE-plane. These are shown in Figure 5.1, as pairwise comparisons between teprotumumab versus IVMP + MMF, and teprotumumab versus IVMP alone. ■

■. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and shown in Figure 5.2. The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that teprotumumab is cost effective was approximately ■ and ■, respectively.

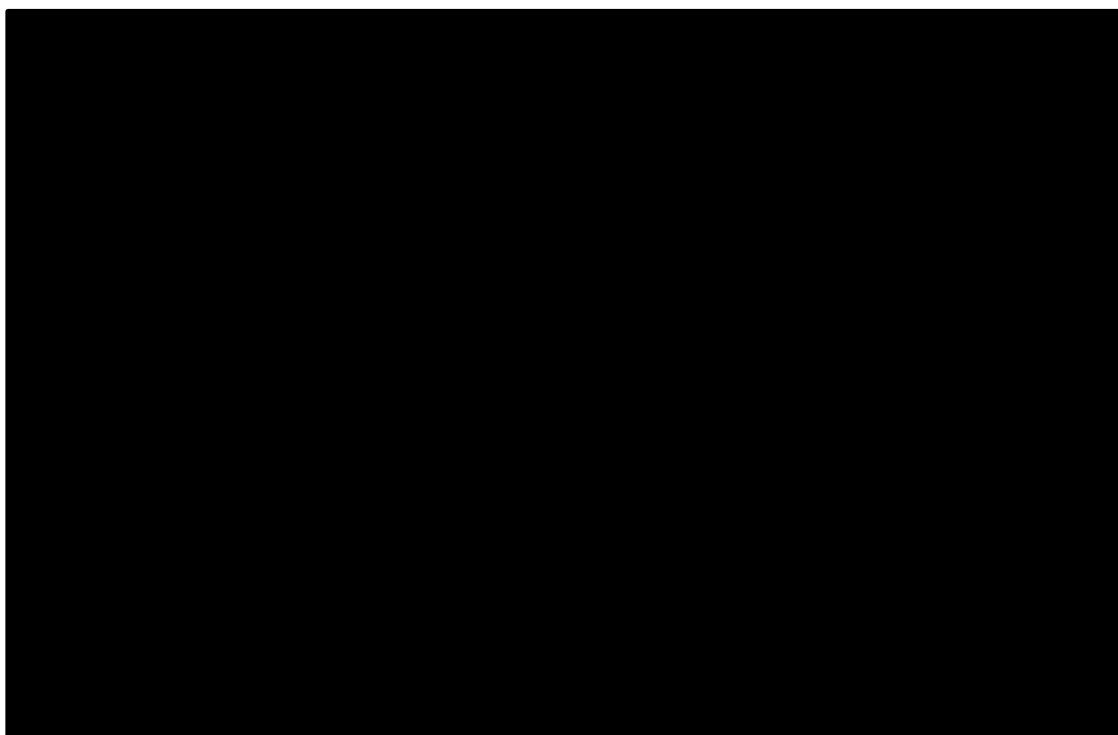
Figure 5.1: PSA CE-plane (teprotumumab PAS price, discounted)



Based on Figure in electronic model after clarification.²⁵

CE = cost effectiveness; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (teprotumumab PAS price, discounted)



Based on Figure in electronic model after clarification.²⁵

CEAC = cost effectiveness acceptability curve; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; PAS = patient access scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

EAG comment: There are two major issues related to the PSA. The first relates to the fact that the model provided after clarification is not able to run a meaningful PSA. This is the result of the fact that in order to incorporate the uncertainty around the ITC estimates, it is, according to the company, necessary to incorporate patient level data from the patients treated with teprotumumab in the RCTs. However, the company was not willing to share that data with the EAG citing confidentiality reasons. As an alternative, suggested by the EAG, the company provided synthetic data with the same mean values and the same variance-covariance structure between all variables. However, this data set was not provided in a format consistent with the calculation of transition probabilities from the pseudo-IPD in the submitted model. Also, the EAG received the synthetic data set too late for any analyses.

As a result of this, the EAG was not able to address the second issue, that of implicitly assuming all zero probabilities in the various transition matrices are fixed. In the clarification letter (question B17) the EAG had asked the company to explore approaches to fully represent uncertainty in cell count of zero. The company declined to address this issue by applying a prior distribution to the transition matrix, indicating that a formal expert elicitation to inform such prior distribution was not possible in the time available and that a noninformative prior would not be appropriate as any adjustment would have a disproportionately large impact on the transition probabilities, thus creating bias. They furthermore cited from the NICE manual that for rare diseases "committee may be able to make recommendations accepting a higher degree of uncertainty."

Regarding the latter statement, the EAG considers it preferable to quantify all those uncertainties that can be quantified, so that committee may make a more informed decision about how much uncertainty they are accepting. Furthermore, it is true that using a noninformative prior may distort the outcomes, but it is possible to select a noninformative prior such that this impact is kept modest.

For the current model, the EAG looked at the impact of adding 1, 0.5 or 0.1 patient to each cell in the transition matrix, and indeed adding 1 patient per cell would lead to a large distortion. However, adding just 0.1 patient to each cell has only a small impact on the point estimates, but provides a range for the transition probability of approximately 0-5% for those probabilities for which the cell count was 0.

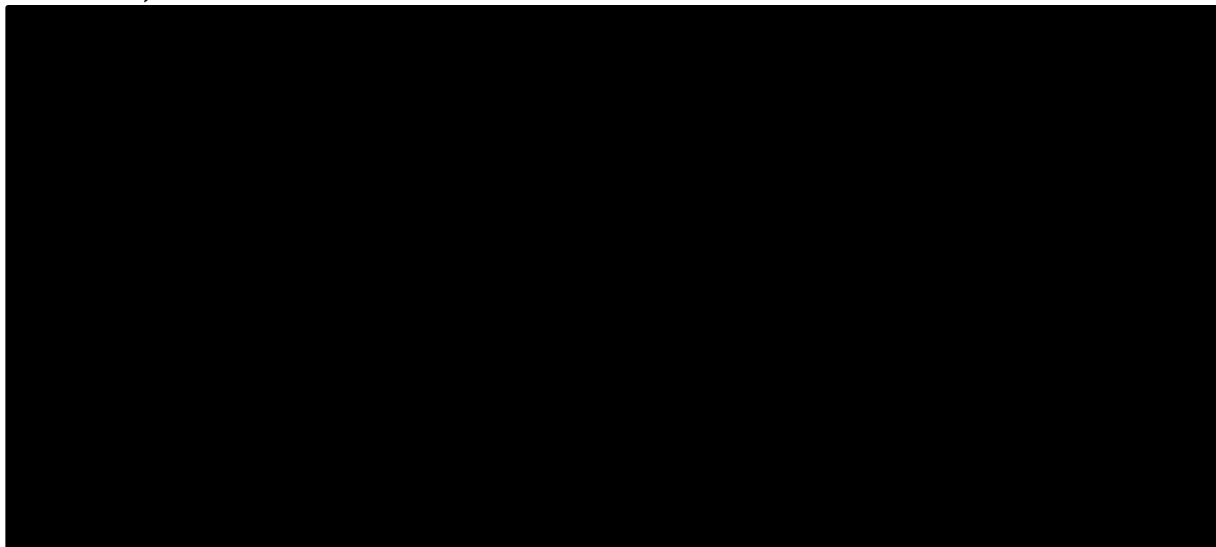
The EAG had intended to explore how this noninformative prior might influence the incremental costs and QALYs, this was not possible due to the lack of IPD for patients treated with teprotumumab to facilitate the PSA.

5.2.2 *Deterministic sensitivity analysis*

The company also conducted a deterministic one-way sensitivity analysis (DSA) where input parameters were varied using the lower and upper bound values of their 95% confidence intervals, if available. Otherwise, parameters were varied by $\pm 20\%$ of their mean value. Tornado diagrams for the top 10 most influential parameters on the ICER are presented in Figure 5.3 and Figure 5.4 for the comparisons versus IVMP alone and IVMP + MMF, respectively.

The ICER was most sensitive to [REDACTED]. In interpreting this results it should be kept in mind that the transition matrices were not part of the DSA, as there is not one meaningful way to vary transition probabilities in a univariate sensitivity analysis.

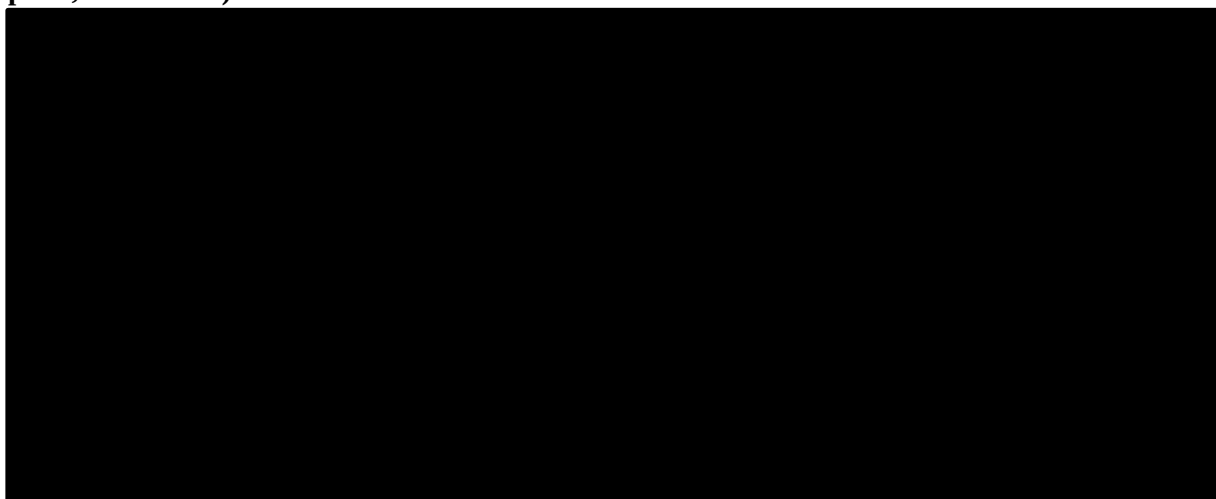
Figure 5.3: Tornado diagram for teprotumumab versus IVMP (teprotumumab PAS price, discounted)



Based on Figure 36 in CS.¹

ICER = incremental cost-effectiveness ratio; IVMP = intravenous methylprednisolone; PAS = Patient Access Scheme

Figure 5.4: Tornado diagram for teprotumumab versus IVMP + MMF (teprotumumab PAS price, discounted)



discount rates, and assuming different values for the cycles where surgery occurs and surgery recovery time. Across all scenarios presented by the company, ICER estimates ranged between [REDACTED] (1.5% discount rate for costs and outcomes) to [REDACTED] (Douglas et al. (2022)¹⁵ as data source for the IVMP active population) for teprotumumab versus IVMP, and [REDACTED] (1.5% discount rate for costs and outcomes) to [REDACTED] (costs of subsequent treatments included) versus IVMP + MMF.

EAG comment: In their response to the clarification letter, the company provided a few additional scenario analyses.

The first relates to a simplified estimation of the cost effectiveness of teprotumumab at 2nd line for radiotherapy, ciclosporin, and azathioprine (all in addition to IVMP and IVMP + MMF). In essence, in each of these scenarios only the treatment and administration costs were adjusted. Furthermore, it was

assumed that all other input would remain the same as IVMP and IVMP + MMF. As a result, the ICERs for these scenarios are near identical to those for 1st line treatment.

The second set of scenario analysis was done to explore the impact of a higher utility value for the best health state in the model, i.e. no diplopia and small proptosis. The following three variations were defined:

1. Align the HSUV of “small proptosis, no diplopia” to general population norms, while keeping the HSUVs for other health states the same
2. Anchor “small proptosis, no diplopia” to general population norms and apply absolute decrements across the remaining health states
3. Apply a proportionate increase (44%) to all health states such that “small proptosis, no diplopia” is aligned more closely to general population norms.

The company reported for the first scenario a decrease in the ICER from [REDACTED] to [REDACTED] for the comparison against IVMP, and [REDACTED] to Dominated for the comparison against IVMP + MMF. Some exploration of this somewhat extreme impact for the comparison against IVMP + MMF showed an error in the Excel calculations for this scenario, and in fact this ICER should again be close to that of teprotumumab versus IVMP. The decrease in the ICER is explained by the much higher utility for the best health state and the fact that patients receiving teprotumumab spent more time in this health state.

The second scenario leads to identical ICERs as the utility distance between the health states remains the same.

Finally, the third scenario of the second set shows a decrease in the ICER from [REDACTED] to [REDACTED] for the comparison against IVMP, and [REDACTED] to [REDACTED] for the comparison against IVMP + MMF.

The last set of scenario analyses done by the company in their response to the clarification letter relates to the inclusion of the number of surgeries per patient.

In the first scenario of this set, the company explored the impact of discounting the one-off cost applied upon entry to the surgery state at different times. Discounting surgery cost to its present value halfway through the surgery follow-up period, cycle 41, or to the end of the surgery follow-up period, cycle 56, has a negligible impact on the ICERs.

In the second scenario of the set, the estimated number of surgeries per patients was varied, as these were defined based on treatment received by the patient but not varied between health states. At the request of the EAG the company ran a scenario in which surgery numbers depended on health state but not on treatment. This scenario generated an ICER per QALY of [REDACTED] for IVMP, an increase of 1.4% from base-case, and [REDACTED] for IVMP + MMF, a 1.6% decrease from base-case.

Additionally, a scenario was explored where the average number of surgeries was dependent only on the surgery type. The scenario used the average number of surgeries for the middle two health states, 1.06 for orbital decompression, 1.63 for strabismus and 1.50 for eyelid surgery. This scenario generated an ICER of [REDACTED] for IVMP, an increase on 1.7% from base-case, and [REDACTED] for IVMP + MMF, a 1.3% decrease from base-case. These scenarios showed the limited sensitivity to variations in the number of surgeries per patient within the model.

Table 5.6: Company scenario analysis results (teprotumumab PAS price, discounted)

Scenario number	Scenario and cross reference	Scenario detail	Brief rationale	ICER teprotumumab versus IVMP (£)	ICER teprotumumab versus IVMP + MMF (£)
0	Base-case	N/A	N/A	████	████
1	Sourcing data from IVMP de-novo ITC with different covariates	Covariates: Smoking, baseline diplopia	To assess the impact of applying different covariates from those used in the base-case (smoking, baseline diplopia, baseline proptosis).	████	████
2		Covariates: Smoking, baseline diplopia, baseline proptosis		████	████
3	Data source for the IVMP active population	Douglas et al. (2022) ¹⁵	To assess the impact of varying the efficacy for teprotumumab; the MAIC comparison in Douglas et al. 2022 included non-RCT studies, so the de-novo MAIC was preferred for the base-case.	████	████
4	Include costs of subsequent treatments	No	To assess the impact of removing subsequent treatment cost. Subsequent treatments are recommended in the ETA guidelines and included in the base-case.	████	████
5	Include AEs	No	To assess the impact of removing AE costs and disutility.	████	████
6		Yes (All Grade AEs)	To assess the impact of including AEs for teprotumumab since Phase 2 and OPTIC trials did not report any severe Grade ≥3 AEs occurring in ≥5% of patients in the study population.	████	████
7	Model wastage	No wastage	To establish the impact of vial sharing if used in clinical practice. As TED is a disease with a	████	████

Scenario number	Scenario and cross reference	Scenario detail	Brief rationale	ICER teprotumumab versus IVMP (£)	ICER teprotumumab versus IVMP + MMF (£)
			relatively low prevalence worldwide, the base-case considered wastage.		
8	Include surgery complication costs	No	To assess the impact of removing costs for surgery complications.	████	████
9	Include IV disutility	No	To assess the impact of removing disutility for IV infusions.	████	████
10	Discount rate	1.5% for costs and outcomes	To assess the impact of alternative discount rates.	████	████
11		1.5% for costs only		████	████
12		1.5% for outcomes only		████	████
13	Cycle surgery occurs at	20	To assess the impact of varying the cycle at which surgery occurs.	████	████
14		30		████	████
15	Surgery recovery time (cycles)	21	To assess the impact of varying the surgery recovery time.	████	████
16		39		████	████
Based on Table 73 in CS. ¹					
AE = adverse events; ETA = European Thyroid Association; ICER = incremental cost-effectiveness ratio; IV = intravenous; IVMP = intravenous methylprednisolone; MAIC = match-adjusted indirect comparison; MMF = mycophenolate mofetil; N/A = not applicable; PAS = Patient Access Scheme; RCT = randomised controlled trial; TED = thyroid eye disease					

5.3 Model validation and face validity check

An overview of the validation efforts conducted on the economic model was discussed in the validation Section of the CS (B.3.14).¹ Other validation aspects, such as the validation of some input parameters are scattered over Document B of the CS.¹ In the remainder of this section, the validation efforts performed on the model, as presented by the company, are categorised according to the four main types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.⁷¹

5.3.1 Validation of the conceptual model

The company indicated that the choice and robustness of health state definitions were validated by a selected group of four UK clinical experts for their relevance to the clinical management and impact of TED.¹⁶ The choice of comparators in 1st line and 2nd line was also evaluated by the clinical experts. However, while the conceptual model was presented to the clinical experts there is no record of discussion about the model structure including TED states within the Physician interview summary report.¹⁶

The company noted that this is the first economic model evaluating treatments in TED, which explains why no cross-validation of the conceptual model was reported.

5.3.2 Input data validation

Several input parameters were also reviewed by the UK expert clinicians.¹⁶ Interviews covered: dosing schedules for teprotumumab, IVMP, and IVMP+MMF; rate of 2nd line treatment and distribution by type; quality of life, resource use by TED state; surgery rates, counts (by type), and complications.

5.3.3 Validation of the computerised model (technical verification)

The company indicated that the cost effectiveness model underwent quality control checks from an expert not involved in the development of the model and that transition probability calculations for IVMP and IVMP+MMF were developed in collaboration with an external health economic modelling expert. Quality control checks for the model included systematic examination of calculations, model inputs, Visual Basic for Applications coding accuracy and extreme value testing. The external quality check also included extreme value testing.

5.3.4 Operational validation (validation of model outcomes)

The company used data directly from the Phase 2 and Phase 3 OPTIC trials to model transition probabilities for teprotumumab and patient baseline characteristics including baseline TED state membership. Within the on-treatment period (up to 24 weeks), the state membership reflects patient outcomes within the trials. In response to a clarification question the company provided additional data on proptosis and diplopia outcomes for patients receiving teprotumumab at 72 weeks. This data was not used to validate the economic model which assumed patients remained in TED state they occupied at cycle 4 for the remainder of the model.

6. External Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:⁷²

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

A key assumption in the company's model relates to long-term state membership probabilities. In the company base-case it is assumed that patients remain in the same TED state from 24 weeks (cycle 4) to the end of the model. The 72-week follow-up data provided by the company in response to the clarification letter suggests that the rate of proptosis and diplopia response does reduce between 24 and 72 weeks for people receiving teprotumumab. We cannot directly use these estimates due to conformity issues, i.e. the outcomes from long-term follow-up do not map directly to TED health states or the ITC outcomes. In addition, modelling scenarios is complex due to the dependency of the model on IPD data from the Phase 2 and Phase 3 OPTIC trials which is not available to the EAG. It is therefore challenging to define an alternative base-case but it is essential that the impact of waning treatment effects for proptosis and diplopia on the cost- effectiveness is explored. We have implemented a pragmatic approach to exploring this uncertainty. Note that we can only perform these scenario analyses for the deterministic results because the company has not provided access to the individual patient level data on which the PSA depends.

The EAG scenario analysis works as follows:

1. For teprotumumab identify TED state membership at 3 years (cycle 26) and calculate probabilities of proptosis state (SP, LP) and diplopia (ND, ID, CD) assuming outcomes are independent
2. Implement percentage changes from 5% to 30% (in 5% intervals) in proptosis and diplopia health states, in particular:
 - Proptosis: reduction in SP state membership with patients moving to LP
 - Diplopia: reduction in ND and ID state membership with patients moving to next worse state (ND to ID or ID to CD)
3. Multiply together these adjusted probabilities for each outcome and combine with total number of patients in TED states to calculate adjusted state memberships for teprotumumab at 3 years.

This approach makes several assumptions:

- As with the company base-case we do assume that after a certain time, here 3 years, patients remain in the same TED state to the end of the model.
- We chose to implement the fixed state membership from 3 years rather than 72 weeks (the time of extended follow-up) as 3 years is the upper bound of the time from which symptoms stabilise. Using 3 years rather than 72 weeks is more favourable for teprotumumab since patients maintain the full benefits observed at 24 weeks for longer.
- We modelled an immediate change in state membership at 3 years rather than a gradual change between 24 weeks and 3 years. Modelling a gradual change would have been much more complex, supported by limited data, and would have negligible impact on the outcomes, which are driven by state membership over the long-term (in this case, after 3 years). In addition, the approach taken is more favourable to teprotumumab because the full benefits observed at week 24 continue to apply fully up to 3 years.
- We model only deterministic outcomes because the teprotumumab IPD data required for the PSA is not available to the EAG.
- We only apply these adjustments to the teprotumumab arm since we are interested in the difference with IVMP and IVMP + MMF. It is of course clinically plausible that a worsening of symptoms is experienced among those receiving IVMP or IVMP+MMF
- We selected 30% change in risks as the maximum as this gave comparable state membership probabilities to IVMP and IVMP + MMF at that stage. We do not consider this to be realistic in the sense that some additional benefit is highly likely to be maintained but it provides an upper bound cost-effectiveness estimate assuming no difference in long-term outcomes (after 3 years) between treatment arms.

Table 6.2 shows the results of this scenario analysis. It is clear that the ICERs are highly sensitive to the assumed level of treatment waning over 3 years. If a small risk shift of 5% is applied the ICERs increase by approximately 14%, and for a shift of 10% the increase in the ICER is 38%. For the worst-case scenario where treatment effect wanes to the level of IVMP (+/- MMF) after 3 years, the ICERs are approximately [REDACTED] per QALY gained.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG scenario ^b	Required additional evidence or analyses
The EAG disagrees with the company's assumption that patients remain in the same TED state from cycle 4 (24 weeks) to the end of the model.	4.2.6	Bias	Assuming some reduction in proptosis and diplopia outcomes after 24 weeks.	+	Partly	Implement some reduction in proptosis and diplopia response rates after 24 weeks based on/consistent with the long-term follow-up data.
The EAG is concerned with the company's approach taken to teprotumumab transition probabilities and state membership over time using observed transitions within the Phase 2 and Phase 3 OPTIC trials, and the resulting large number of zero counts in transition probabilities between TED states and the fact that the PSA does not capture uncertainty in these counts.	4.2.6 5.2.1	Methods Imprecision	Model the changes in proptosis and diplopia scores/states parametrically Use noninformative priors so that zero counts for a transition are not considered certain	+/-	No	Consider alternative approaches to modelling TED state occupancy within the treatment period. Run deterministic and probabilistic analyses using a noninformative prior for cell counts in transition matrices.
The model provided after clarification is not able to run a meaningful PSA	5.2.1	Methods	Provide the IPD required to run an PSA that includes all parametric uncertainties	None, only on estimated uncertainty around ICER	No	A model with IPD teprotumumab or appropriate alternative
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator ^b Explored EAG = Evidence Assessment Group; ICER = incremental cost effectiveness ratio; IPD = individual patient data; PAS = Patient Access Scheme; TED = thyroid eye disease						

Table 6.2 Modelling reductions in proptosis and diplopia response rates at 3 years

Scenario	Costs (£)			QALYs			Incr. costs (£)		Incr. QALYs		ICER (£)	
	Tepro	IVMP	IVMP + MMF	Tepro	IVMP	IVMP + MMF	Tepro versus IVMP	Tepro versus IVMP + MMF	Tepro versus IVMP	Tepro vs IVMP + MMF	Tepro vs IVMP	Tepro vs IVMP + MMF
Company base-case	■	■	■	■	■	■	■	■	0.82	0.83	■	■
5% risk shift	■	■	■	■	■	■	■	■	0.73	0.73	■	■
10% risk shift	■	■	■	■	■	■	■	■	0.62	0.62	■	■
15% risk shift	■	■	■	■	■	■	■	■	0.51	0.51	■	■
20% risk shift	■	■	■	■	■	■	■	■	0.40	0.41	■	■
25% risk shift	■	■	■	■	■	■	■	■	0.30	0.31	■	■
30% risk shift	■	■	■	■	■	■	■	■	0.20	0.21	■	■
ICER = incremental cost-effectiveness ratio; Incr = incremental; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; QALY = quality-adjusted life year; Tepro = teprotumumab												

6.2 Conclusions of the cost effectiveness section

The company provided a novel model to describing moderate-to-severe active TED. It consists of six active TED health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints. These six states represent combinations of diplopia (no diplopia, intermittent or inconstant diplopia, constant diplopia) and proptosis symptoms (small proptosis, large proptosis). Additional health states are included to represent surgery, post-surgery and death, which is an absorbing health state.

The CE key issues highlighted throughout this report (and summarised in **Error! Reference source not found.**) were the following:

- 1) The EAG disagrees with the company's assumption that patients remain in the same TED health state from week 24 to the end of the model
- 2) The EAG is concerned with the company's approach taken to teprotumumab transition probabilities and state membership over time using observed transitions within the phase 2 and phase 3 OPTIC trials leading to high variation in transition probabilities and many cells with low or zero counts.

The primary concern was the assumption that patients remain in the same TED health state from week 24 through to the end of the model. The large differences in state membership between treatment arms at this point, which lead to improved quality of life and reduced healthcare costs, is a major driver of CE. While it is likely that teprotumumab maintains benefit compared IVMP and IVMP + MMF over time, the data from the 72-week follow-up for patients who received teprotumumab suggests there is some worsening of proptosis and diplopia outcomes between 24 and 72 weeks. No scenario analyses around treatment waning were explored by the company.

The company estimated that transition probabilities between TED states for each cycle up to cycle 4 using observed transitions from the pooled Phase 2 and Phase 3 OPTIC trials. The relatively low patient numbers in relation to the number of modelled transitions leads to substantial variation in the probabilities of given transitions across cycles and to zero values for many. Furthermore, the company does not model uncertainty in transitions with zero counts, leading to an underestimation of uncertainty. The estimates of transition probabilities for IVMP and IVMP + MMF are based simulating effects from the ITC to the patient-level data from teprotumumab, making these transition probabilities similarly dependent on this limited data.

The company base-case PSA results are reliant on individual patient level data for teprotumumab which is not available to the EAG. This limits the ability of the EAG to validate the company's PSA results or perform alternative base-case or scenario analyses using PSA.

The EAG considers the decision not to include the EQ-5D in the clinical studies as a missed opportunity to assess the validity of this instrument in TED. Whilst it is true that the DSU has indicated that for some specific forms of visual impairments the EQ-5D might not be appropriate,³³ this does not necessarily mean that the EQ-5D would not be appropriate for TED. As TED involves more than only problems with eyesight, but also e.g. pain, discomfort, and negative feelings about appearance, the EQ-5D might actually be responsive enough to value the health states defined in the current model.

The company commissioned a new utility study specific to active moderate-to-severe TED.¹⁷ For each of the six main health states defined in the model (though not for surgery and post-surgery), vignettes

were developed and validated. A sample of the US general population without TED, participated in a TTO study to value the six health states. The utilities found had face validity, according to UK clinical experts,¹⁶ and the company found the utilities broadly comparable to those TTO utilities found for various other eye diseases in NICE technology assessments.⁴¹⁻⁴⁴

The EAG agrees with this assessment but notices that for all of these eye diseases the health states were only characterised by (reduced) visual acuity whilst TED is mostly characterised by issues different from visual acuity. Thus, it might have been preferable to focus the validation efforts on TTO studies in patients with eye diseases that are also more characterised by pain/discomfort and strabismus. However, whilst the EAG did not have time to do a full-scale literature search for such studies, some simple pragmatic searches did not yield any useful studies.

The EAG is somewhat concerned regarding the very long descriptions of the health states used for the vignettes in the TTO. The EAG wonders to what extent respondents were able to notice all differences between vignettes and considers that the trade-off task may have been a cognitive challenge for many respondents. However, based on the comparison to other NICE submissions these concerns are somewhat alleviated, and in general the TTO study was done according to best practice, thus providing the best possible estimates of utility values at this moment.

Overall, the approach used to assess resource use and costs seems appropriate. The EAG had one concern related to resource use. In the model, the numbers of surgeries depended on the treatment arm—with more surgeries required for people receiving IVMP or IVMP + MMF than for those receiving teprotumumab—but not on the health state, which was confirmed as valid by the clinicians in the expert panel. To the EAG it seems most plausible that the number of surgeries vary by treatment because treatment with teprotumumab keeps patients in less severe health states where fewer surgeries are required, and that in fact, the number of surgeries should have been modelled as health state dependent rather than treatment dependent. The company presented an additional scenario in which the average number of surgeries was dependent on health state, rather than treatment arm, and this showed only a very minimal impact on the ICERs.

While the EAG contend that a more accurate representation of the cost-effectiveness of teprotumumab would take into account some worsening of proptosis and diplopia symptoms after 24 weeks based on the results of the long-term follow-up data, the EAG has chosen to explore this issue in scenario analysis rather than specify an alternative base-case. This is due to the difficulties in using the 72 week results directly which are not directly compatible with how the outcomes are included in the model or the ITC. Instead, we present a range of scenario analyses ranging from a small (5%) shift in risk from small to large proptosis and to more severe stages of diplopia to 30%, which is approximately the point at which outcomes are the same for teprotumumab as IVMP or IVMP + MMF. Note the EAG does not argue that this is a reasonable assumption, but it is presented as a worst-case scenario. The EAG scenario analyses illustrates that the results are quite sensitive to relatively small changes in risk. Using a 10% risk shift, for example, increases the deterministic ICER by around 38% from approximately [REDACTED] per QALY for both teprotumumab versus IVMP and teprotumumab versus IVMP + MMF. Thus, the EAG considers it important that some reduction in proptosis and diplopia response rates after 24 weeks is implemented based on or consistent with the long-term follow-up data.

Other scenarios explored by the company, either in the main submission or in response to clarification questions by the EAG led to ICERs quite close to the company base-case or slightly more favourable.

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Single Technology Appraisal

Teprotumumab for treating thyroid eye disease [ID6432]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 1 April 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **'confidential'** should be highlighted in turquoise and all information submitted as **'depersonalised data'** in pink.

Issue 1 Lack of evidence presented for all comparators in scope at second line (EAG key issue 1)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 11, Table 1.2 Key issue 1: Lack of evidence for some comparators at 2nd line: Page 15, Table 2.1: “Also, there is a lack of evidence presented for those comparators other than methylprednisolone at 2nd line i.e., azathioprine, ciclosporin and orbital radiotherapy, although it does appear that the company SLR was robust enough to demonstrate that it is unlikely that there is evidence that would permit an ITC.” This statement is incorrect.	The company proposes the wording on page 11 and page 15 is updated to: “Also, as identified by the SLR conducted by the company, there is a lack of available evidence for those comparators other than methylprednisolone at 2nd line i.e., azathioprine, ciclosporin and orbital radiotherapy. It does appear that the company SLR was robust enough to demonstrate that it is unlikely that there is evidence that would permit an ITC.”	This statement is incorrect because it implies that the company has failed to submit available evidence for those comparators at 2nd line. In fact, the company has presented all of the evidence identified in the clinical SLR, which the EAG has concluded was robust. To clarify that the Company presented all available evidence for all comparators. As noted in Section 2.3 of the EAG report, the EAG concluded that no studies were reported to have been excluded that could have provided data for an ITC.	Not a factual inaccuracy. The EAG did not state that the evidence was robust, but that: “...it does appear that the company SLR was robust enough to demonstrate that it is unlikely that there is evidence that would permit an ITC.”

Page 20-21: “They then provide an informal summary of some studies for these comparators, rather than the full systematic literature review (SLR) requested by the EAG, although they state that the studies were included in the SLR from the company submission (CS).” This statement is highly misleading.	The company proposes the wording on pages 20-21 is updated to: “They then provide an informal summary of some studies for these comparators, rather than the full systematic literature review (SLR) requested by the EAG, as they confirmed that the requested studies were already included in the SLR from the company submission (CS).”	To clarify that the Company has provided a full systematic review of all clinical effectiveness evidence for all interventions of interest in its original submission (B.2.1; Appendix D). In the clarification call on 10 February 2025, the EAG confirmed that in the response to clarification question A4, they were not asking the Company to revisit the existing systematic literature review. The EAG requested further detail on the evidence for comparators which was provided during the clarification response stage.	Not a factual inaccuracy.
Page 21: “Wu et al. (2015) – double-blind, self-controlled study in a single hospital outpatient ophthalmology clinic in China (population description and sample size not reported).” This statement is incorrect.	The company proposes the wording on page 21 is updated to: “Wu et al. (2015) – double-blind, self-controlled study of 51 moderate-to-severe TED patients in a single hospital outpatient ophthalmology clinic in China”	The population description and sample size were previously reported by the company on pages 20 and 23 of the Company’s response to the EAG clarification questions, respectively, and thus should be included in the statement.	Corrected.

Page 21: “Stoyanova et al. (2023) – single-arm, 26 patients (population description and location not reported).” This statement is incorrect.	The company proposes the wording on page 21 is updated to: “Stoyanova et al. (2023) – single-arm, 26 moderate-to-severe TED patients in Bulgaria.”	The population description and location were previously reported by the company on page 23 of the Company’s response to the EAG clarification questions.	
Page 21 and reference list: The EAG report contains referencing errors	The company proposes the following reference is added to the reference list: Rajendram R, Taylor PN, Wilson VJ, Harris N, Morris OC, Tomlinson M, Yarrow S, Garrott H, Herbert HM, Dick AD, Cook A, Gattamaneni R, Jain R, Olver J, Hurel SJ, Bremner F, Drummond SR, Kemp E, Ritchie DM, Rumsey N, Morris D, Lane C, Palaniappan N, Li C, Pell J, Hills R, Ezra DG, Potts MJ, Jackson S, Rose GE, Plowman N, Bunce C, Uddin JM, Lee RWJ, Dayan CM. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2 × 2 factorial, double-blind, randomised	The reference for the CIRTED study (Rajendram et al. 2018) is missing from the reference list. In text references are missing where CIRTED is mentioned on page 21.	Reference added.

	controlled trial. Lancet Diabetes Endocrinol. 2018 Apr;6(4):299-309. doi: 10.1016/S2213-8587(18)30021-4. Epub 2018 Jan 31. PMID: 29396245.		
Page 21 and reference list: The EAG report contains referencing errors	The company proposes the following reference is added to the reference list: Nicosia L, Reverberi C, Agolli L, Marinelli L, De Sanctis V, Minniti G, Valeriani M, Osti MF. Orbital Radiotherapy Plus Concomitant Steroids in Moderate-to-Severe Graves' Ophthalmopathy: Good Results After Long-Term Follow-Up. Int J Endocrinol Metab. 2019 Jan 27;17(1):e84427. doi: 10.5812/ijem.84427. PMID: 30881470; PMCID: PMC6408739.	The reference for Nicosia et al. 2019 is missing from the reference list. In text references are missing where Nicosia et al. 2019 is mentioned on page 21.	Reference added.

Page 21 and reference list: The EAG report contains referencing errors	The company proposes the following reference is added to the reference list: Wu Y, Tong B, Luo Y, Xie G, Xiong W. Effect of radiotherapy on moderate and severe thyroid associated ophthalmopathy: a double blind and self-controlled study. Int J Clin Exp Med. 2015 Feb 15;8(2):2086-96. PMID: 25932139; PMCID: PMC4402786.	The reference for Wu et al. 2015 is missing from the reference list. In text references are missing where Wu et al. 2015 is mentioned on page 21.	Reference added.
Page 21 and reference list: The EAG report contains referencing errors	The company propose the following reference is added to the reference list: Stoynova MA, Shinkov AD, Novoselski MT, Petrova VV, Dimitrova ID, Yankova IA, Kovatcheva RD. Changes in therapeutic response, ocular manifestations of Graves' orbitopathy and quality of life during the first year after orbital radiotherapy. Int Ophthalmol. 2023 Nov;43(11):4305-4314. doi: 10.1007/s10792-023-02842-8. Epub 2023 Aug 10. PMID: 37561249.	The reference for Stoynova et al. 2023 is missing from the reference list. In text references are missing where Stoynova et al. 2023 is mentioned on page 21.	Reference added.

Issue 2 Lack of adjustment for some important prognostic variables in the MAIC analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 11, Table 1.3, Key issue 2: Lack of adjustment for some important prognostic variables in the MAIC analysis: “It should be noted that the prognostic variables of diabetes, thyroid function, and duration of TED symptoms were not adjusted for in the MAIC analysis due to the limited availability of these variables.” This statement is highly misleading.	The company proposes the wording on page 11 is updated to read: “It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables. The duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations.”	To provide further clarification on the rationale why some covariates identified by clinicians were not adjusted for in the MAIC conducted by the company.	Amended.

Page 70: “It should be noted that the prognostic variables of diabetes, thyroid function, and duration of TED symptoms were not adjusted for in the MAIC analysis due to the limited availability of these variables.” This statement is highly misleading.	The company proposes the wording on page 70 is updated to read: “It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables. The company adjusted for as many covariates as possible where data were available until the ESS was considered unreasonably small. The duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations. Diabetes was not reported in seven IVMP studies and the IVMP + MMF study, and thyroid function was not reported in four IVMP studies and the IVMP + MMF study”	To clarify that the company attempted to adjust for all important prognostic variables, however, due to paucity of data and lack of overlap this was not feasible without compromising the validity of the results.	Amended

Page 72: “However, the EAG considers that there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to limited availability of these variables.”	The company proposes the wording on page 72 is updated to read: “However, the EAG considers that there was a lack of adjustment for some important prognostic variables in the MAIC analysis due to limited availability of these variables and lack of overlap of one of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations.”	To provide further clarification on the rationale why some covariates identified by clinicians were not adjusted for in the MAIC conducted by the company.	Amended
On page 72: “It should be noted that the prognostic variables of diabetes, thyroid function, and duration of TED symptoms were not adjusted for in the MAIC analysis due to the limited availability of these variables.”	The company propose the wording on page 72 is updated to read: “It should be noted that the prognostic variables of diabetes and thyroid function were not adjusted for in the MAIC analysis due to the limited availability of these variables, whereas the duration of TED symptoms was not adjusted for due to lack of overlap in the distribution of these characteristics between the teprotumumab, IVMP and IVMP + MMF populations.”	To clarify that the company attempted to adjust for all important prognostic variables, however due to paucity of data and lack of overlap this was not feasible without compromising the validity of the results.	Amended

Issue 3 Reduction in response between Week 24 (cycle 4) and Week 72) (EAG key issue 4)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 12-13, Table 1.5: “The 72-week follow-up data provided by the company in response to the clarification letter suggests that the rate of proptosis and diplopia response <u>does reduce between 24 and 72 weeks for people receiving teprotumumab.</u>” This statement is not correct.	The company proposes the wording on pages 12-13 is updated to read: “The 72-week follow-up data provided by the company in response to the clarification letter suggests that the rate of proptosis and diplopia response [REDACTED] [REDACTED] receiving teprotumumab. In the Phase 2 trial, the majority ([REDACTED]) of subjects from the teprotumumab group who met proptosis response criteria at Week 24 did maintain improvement relative to baseline ([REDACTED]) and this was sustained to Week 72 (Amgen [Data on File] Phase 2 CSR NCT01868997. 2018). In the Phase 3 OPTIC trial (48 weeks off-treatment follow-up), [REDACTED] ([REDACTED]) of teprotumumab-	There was [REDACTED] at Week 28, 30 days following the Week 24 double-blind treatment phase, for subjects receiving teprotumumab. The Week 24 primary endpoint, the proportion of proptosis responders, remained statistically significantly higher for teprotumumab ([REDACTED]) compared to placebo ([REDACTED]) at Week 28, with the difference in the proportion of responders in favour of teprotumumab of [REDACTED]. This was a greater response difference than was observed seen at Week 24. The majority ([REDACTED]) of subjects from the teprotumumab group who met proptosis response criteria at Week 24 maintained improvement relative to baseline ([REDACTED]) and did not require additional TED treatment or surgical intervention up to 48	Not a factual inaccuracy. The EAG statement that the “rate of response reduced” is more accurate than the company alternative that the “rate of response reduced for a minority of people”. The “rate” refers to a population and not individuals. In addition, the EAG did not make any statement about acute rebound.

	treated proptosis had a sustained response at Week 72. Fifteen of the 34 had a non-sustained response, 2 were non-responders at Week 72 and 9 were non-responders before Week 72. The remaining 4/34 patients are assumed to have not had a sustained response but follow-up data is lacking for those subjects.”	weeks off treatment. Only [REDACTED] of subjects from the teprotumumab group who met proptosis response criteria at Week 24 did not maintain improvement relative to baseline ([REDACTED]) during the 48-week off-treatment Follow-up Period. In the Phase 3 OPTIC trial (48 weeks off-treatment follow-up), [REDACTED] ([REDACTED]) of teprotumumab-treated proptosis responders maintained response at Week 72. Kahaly G et al Long-Term Efficacy of Teprotumumab in Thyroid Eye Disease: Follow-Up Outcomes in Three Clinical Trials. Thyroid. 2024 Jul;34(7):880-889. a also supports the claim for improved long term proptosis outcomes. This is important to correct because differences in health state membership at week 24 between treatment arms is a key	

		driver of model outcomes and cost-effectiveness.	

Issue 4 Long-term extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 13, Table 1.5, Key issue 4: The EAG disagrees with the company's assumption that patients remain in the same TED state from cycle 4 (24 weeks) to the end of the model "Any modelling of worsening in proptosis and/or diplopia response will increase the ICER since patients derive fewer benefits in QoL from better proptosis and diplopia outcomes and incur higher healthcare costs." This statement is not completely accurate.	The company proposes the wording on page 13 be updated to: "Any modelling of worsening in proptosis and/or diplopia response in the teprotumumab arm will increase the ICER (where no worsening for comparators has been modelled) since patients derive fewer benefits in QoL from better proptosis and diplopia outcomes and incur higher healthcare costs."	It is clinically plausible for patients on IVMP and IVMP + MMF to also experience a worsening of symptoms. No scenario testing has been conducted where the intervention and all the comparators model this worsening. As such, the company have tested a scenario where worsening in proptosis and diplopia was implemented for IVMP using the same methodology as used by the EAG in their scenario analysis, detailed in Section 6 of the EAG report. When using a risk of 5% for both teprotumumab and IVMP, the ICER decreased by 0.09% from the base case ICER. Therefore, this statement is only true in the situation where no worsening is assumed for comparators, so this should be specified for clarity.	Changed text to align with proposed amendment

Page 119: “This data was not used to validate the economic model which assumed patients remained in TED state they occupied at cycle 4 for the remainder of the model.”	The company proposes the wording on page 119 be updated to: “These data were not used to validate the economic model because it was assumed patients remained in the TED state they occupied at cycle 4 for the remainder of the model, due to the sample size in the OPTIC follow-up period being too small to generate robust transition probabilities. Additionally, no longer term comparative data were identified to facilitate a comparison beyond week 24.”	The company note that it is not clear from the sentence that the reason these data were not used for validation by the company was due to the remain in state assumption being made in the absence of suitable long-term data to enable a comparison beyond 24 weeks.	The statement by the EAG is factually correct. The argument by the company that “the sample size in the OPTIC follow-up period being too small to generate robust transition probabilities” is not relevant since the EAG is pointing out that the data was not used for validation, which does not require estimation of transition probabilities. Instead, the long-term data allows for an assessment of the face validity of the company’s assumptions about long-term TED state membership.

Issue 5 Incorrect or misleading descriptions of clinical trial details

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 26-27, Section 3.2.2.1: “Key inclusion criteria included ages from 18 to 75 years, diagnosis of ophthalmopathy within 9	The company proposes the wording on pages 26-27 be updated to: “Key inclusion criteria included ages from 18 to 75 years, diagnosis of ophthalmopathy within	It is important that all details of the clinical trials are accurately described. Study participants were excluded from the Phase 2 trial only if they had previously received surgical or medical	Amended.

months from the onset of symptoms, had a clinical activity score (CAS) of four or more on a seven-point scale (with a score of ≥ 3 indicating acute thyroid-associated ophthalmopathy) in the more severely affected (study) eye, had not previously received surgical or medical treatment.” This final statement is incorrect.	nine months from the onset of symptoms, had a CAS of four or more on a seven-point scale (with a score of ≥ 3 indicating acute thyroid-associated ophthalmopathy) in the more severely affected (study) eye, had not previously received surgical or medical treatment for TED (with the exception of local supportive measures and oral steroids if the cumulative dose was <1000 mg methylprednisolone or equivalent) and did not require immediate surgical ophthalmological intervention.”	treatment for TED, as explained in CS, B.2.3.1.	

Page 38, Table 3.4: “Table 3.4 below summarises the characteristics of patients at baseline. Table 3.4: Baseline characteristics” This is misleading.	The company proposes the wording on page 38 be updated to: “Table 3.4 below summarises the characteristics of patients at baseline <u>(safety population) in the Phase 2 trial.</u> Table 3.4: Baseline characteristics <u>(Safety Population) - Phase 2</u>”	To eliminate any confusion over which trial population is being referred to.	Amended.
Page 44, Section 3.2.6.1.2 Secondary efficacy outcomes: “As the company stated, a summary of <u>the primary and secondary efficacy outcomes from OPTIC</u> was presented in Table 3.8.” This statement is incorrect.	The company proposes the wording on page 44 be updated to: “As the company stated, a summary of <u>the secondary efficacy outcomes from the Phase 2 trial</u> is presented in Table 3.8.”	To eliminate any confusion over which trial outcomes are being referred to.	Amended.

Issue 6 Discordant reporting of baseline data for patients in the Phase 3 OPTIC trial

Description of problem	Description of proposed amendment	Justification for amendment	
Page 38, Section 3.2.4: “It is apparent that Table 12 in the CS which presents the baseline data does not contain all the data to which the company refer. There are no data included on geographical distribution, or for prior use of sulphur-containing imidazole derivatives, or thyroid hormones for treatment of hypothyroidism for instance. Yet these are described in the text. Additionally, some of the data described in the text does not fully align with what are presented in the table.” The EAG’s statement is only partially correct.	The company proposes the wording on page 38 by updated to: “It is apparent that Table 12 in the CS which presents the baseline data does not contain all the data to which the company refer. There are no data included on geographical distribution, or for prior use of sulphur-containing imidazole derivatives, or thyroid hormones for treatment of hypothyroidism for instance. Yet these are described in the text. The baseline data reported in Table 12 of the CS and the accompanying text were derived from the primary publication (Douglas, 2020) and the Phase 3 CSR. The primary publication reports only a sub-set of patient characteristics at baseline, whereas the additional in-text information can be found in the CSR, which the submitting company has provided”.	To provide clarity on the totality of the data provided by the submitting company.	Not a factual inaccuracy.

Issue 7 Transition probabilities and state membership over time

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 79: “Teprotumumab treatment affects model outcomes by changing the probability of transitioning between TED clinical states. It has no direct impact on the probability of surgery or death.”	The company proposes the wording on page 79 be updated to: “Teprotumumab treatment affects model outcomes by changing the probability of transitioning between TED clinical states. Transitions to surgery are determined by health state occupancy. The probability of transitioning to surgery or death for patients in a given health state is the same regardless of treatment received.”	To provide sufficient clarity on the approach used to transition patients to the surgery health state.	Changed text to align with company amendment.

Page 82: “Transition probabilities are first calculated separately for proptosis (i.e., between small proptosis and large proptosis) and diplopia (i.e., between no diplopia, intermittent/inconstant diplopia and constant diplopia), assuming the outcomes are independent.”	The company proposes the wording on page 82 is updated to read: “Transition probabilities are first calculated separately for proptosis (i.e., between small proptosis and large proptosis) and diplopia (i.e., between no diplopia, intermittent/inconstant diplopia and constant diplopia), assuming the outcomes are independent. The company validated the modelling approach with respect to the two outcomes with three TED clinical experts.¹² The experts recognised the limited correlation between diplopia and proptosis and endorsed the approach to model the two endpoints independently, such that a patient’s diplopia severity can be assumed to not impact their proptosis severity, and vice versa.”	To provide sufficient clarity on the approach and justification behind the assumption of independence between proptosis and diplopia.	Not a factual inaccuracy. The sentence is left unchanged.

Page 86: “The company uses different approaches to model changes in proptosis and diplopia states for IVMP and IVMP + MFF. This implicitly assumes these outcomes are independent rather than correlated (as for teprotumumab transition probabilities), and it is unclear how this might impact the results.”	The company proposes the wording on page 86 is updated to: “The company uses different approaches to model changes in proptosis and diplopia states for IVMP and IVMP + MMF. This was due to the nature of the endpoints, as diplopia is a binary endpoint whereas proptosis is a continuous endpoint. The company validated the assumption of independence between proptosis and diplopia with clinicians. This is discussed in section 4.2.6.2.¹² This implicitly assumes these outcomes are independent rather than correlated (as for teprotumumab transition probabilities), and it is unclear how this might impact the results.”	Additional context should be provided to clarify why different approaches were used for proptosis and diplopia, as this is unclear from the text.	Added text to indicate that the different approaches reflect the different outcomes.

Issue 8 The model is not able to run a meaningful probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
On page 86: “The company only modelled	The company proposes the text on page 86 is updated to:	Additional text explaining that this is a conservative assumption should be added to support	Not a factual inaccuracy. But the EAG has amended the text to

improvements in diplopia scores and not worsening of diplopia since these were not reported in the MAIC. As a result, some transition probabilities are fixed at the same value as observed for teprotumumab.” This statement is misleading.	“The company only modelled improvements in diplopia scores and not worsening of diplopia since these were not reported in the MAIC. The ITC only reports the odds of improving diplopia grade, and not of worsening or remaining the same, since the only commonly reported outcome across the IVMP studies was the proportion of patients who had a diplopia response. Therefore, it was assumed that the IVMP probabilities for diplopia worsening or remaining the same were the same as for teprotumumab. This is a conservative assumption in the absence of data. As a result, some transition probabilities are fixed at the same value as observed for teprotumumab.”	assessment of the impact of the uncertainty due to a lack of data reported in the literature.	further explain why the company adopted this approach.

Page 86: “The company assumes that the OR for moving to the adjacent diplopia score category (i.e., intermittent to no diplopia or constant to intermittent diplopia) is the same as moving two categories from constant to no diplopia.” This statement is misleading.	The company proposes the text on page 86 is updated to: “The company assumes that the OR for moving to the adjacent diplopia score category (i.e., intermittent to no diplopia or constant to intermittent diplopia) is the same as moving two categories from constant to no diplopia. This was necessary due to diplopia response being defined as ≥ 1 Grade reduction.”	Additional context should be provided to clarify why this assumption was made, as this is unclear from the text.	Not a factual inaccuracy. However, we have added an additional sentence to explain why this assumption was made
Page 86: “Diplopia outcomes were not available for IVMP + MFF and the company made the assumption that they would be the same for IVMP.” This statement is misleading.	The company proposes the text on page 86 is updated to: “Diplopia outcomes were not available for IVMP + MMF as insufficient data were identified in the literature, therefore, the company made the assumption that they would be the same for IVMP.”	Additional context should be provided to clarify that the outcomes were not available due to insufficient data reported in the literature.	Additional context added

Page 114: “However, the company was not willing to share that data with the EAG.” This statement is incorrect.	The company proposes that the text on page 114 is updated to: “However, due to confidentiality reasons the company was unable to share that data with the EAG.”	Additional context should be provided to clarify why it was not possible to share the IPD.	Not a factual inaccuracy. Added a statement that the data was not shared by the company, citing confidentiality reasons.
Page 114: “As an alternative, suggested by the EAG, the company provided synthetic data with the same mean values and the same variance-covariance structure between all variables. However, this data set only included observation at 12 and 24 weeks, which means that it cannot be used for the comparison to IVMP + MMF.” This statement is misleading.	The company proposes the wording on page 114 is updated to read: “As an alternative, suggested by the EAG, the company provided synthetic data with the same mean values and the same variance-covariance structure between all variables. This was based on observation at 12 and 24 weeks, the only data available.”	The comparison to IVMP + MMF was conducted using 24 week data, which was the only data available, therefore, the pseudo IPD can be used for comparison between teprotumumab and IVMP + MMF populations.	The EAG has amended the comment to read: “The data was not provided in a format consistent with the calculation of transition probabilities from the pseudo-IPD in the submitted model.” However, it is not clear to the EAG why having only data on teprotumumab at 12 and 24 weeks would be sufficient if the model uses separate transition matrices for week1-6, week 6-12, week 12-18 and week 18-24 both for teprotumumab and for IVMP + MMF.

Issue 9 Week 72 diplopia response

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Pages 87 & 89, Section 4.2.6.3, extrapolation The EAG report states that “The company did not provide separate data on diplopia response at 72 weeks from the phase 2 study, although this data appears to have been collected” and “Most importantly, outcomes for diplopia response at 72 weeks were missing for the phase 2 study.”	The company proposes adding the following statement on pages 87 and 89: “The submitting company has confirmed that these data were not reported in the main CSR Week 72 addendum and so were omitted in error but can be provided.”	The EAG statements are correct, and the company apologises for the omission. The company has identified the data concerned and is able to provide it to the EAG, if NICE agrees. This is important because extrapolation of data has been identified as a key issue by the EAG.	We are happy to hear that the data can be made available

Issue 10 Missing rows in adverse events Table 4.11

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment																									
Page 91, section 5.2.7, Table 4.11	The company proposes Table 4.11 is updated to include three missing rows (hyperglycaemia, 10-fold increase of aminotransferases, and 5-fold increase of gamma-glutamyl transferase) and the accompanying adverse event probabilities, as per Table 41 and Table 42 of Document B of the Company’s submission. The additional rows to be included are: <table><tr><th></th><th colspan="2">Teprotumumab^a</th><th colspan="2">IVMP/IVM</th></tr><tr><th>Adverse event</th><th>Base-case^a</th><th>Scenario^b</th><th>Base-case (Silva et al. 2015)^a</th><th>Scenario 1 (Roy et al. 2015)^b</th></tr><tr><td>Hyperglycaemia</td><td>■</td><td>■</td><td>1.60%</td><td>0.00%</td></tr><tr><td>10-fold increase of aminotransferases</td><td>■</td><td>■</td><td>1.60%</td><td>0.00%</td></tr><tr><td>5-fold increase of gamma-glutamyl transferase</td><td>■</td><td>■</td><td>1.60%</td><td>0.00%</td></tr></table>		Teprotumumab ^a		IVMP/IVM		Adverse event	Base-case ^a	Scenario ^b	Base-case (Silva et al. 2015) ^a	Scenario 1 (Roy et al. 2015) ^b	Hyperglycaemia	■	■	1.60%	0.00%	10-fold increase of aminotransferases	■	■	1.60%	0.00%	5-fold increase of gamma-glutamyl transferase	■	■	1.60%	0.00%	It is important that all adverse events are reported, and aligned with the full tables provided in Document B of the Company’s submission.	Added to Table 4.11.
	Teprotumumab ^a		IVMP/IVM																									
Adverse event	Base-case ^a	Scenario ^b	Base-case (Silva et al. 2015) ^a	Scenario 1 (Roy et al. 2015) ^b																								
Hyperglycaemia	■	■	1.60%	0.00%																								
10-fold increase of aminotransferases	■	■	1.60%	0.00%																								
5-fold increase of gamma-glutamyl transferase	■	■	1.60%	0.00%																								

Issue 11 EAG additional analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 121:	The company proposes the wording on page 121 is updated to:	It is clinically plausible for patients on IVMP and IVMP +	Text added to note that it is clinically plausible that a

“We only apply these adjustments to the teprotumumab arm since we are interested in the difference with IVMP+MFF”	“We only apply these adjustments to the teprotumumab arm since we are interested in the difference with IVMP + MMF. The full treatment benefits observed at week 24 for IVMP and IVMP + MMF are maintained, with no changes to health state membership. This is an unfavourable assumption for teprotumumab and does not reflect that it is clinically plausible for patients in the comparator arms to also experience a worsening of symptoms.”	MMF to also experience a worsening of symptoms. The current text requires additional details to be provided about the assumptions made around treatment benefits for IVMP and IVMP+MMF for clarity. In other bullet points on this page, it is explained where assumptions are favourable to teprotumumab or expected to have negligible impact. Therefore, assumptions that are unfavourable for teprotumumab should also be explained for completeness. The company has tested a scenario where worsening in proptosis and diplopia was implemented for IVMP using the same methodology as used by the EAG in their scenario analysis, detailed in Section 6 of the EAG report. When using a risk of 5% for both teprotumumab and IVMP, the ICER decreased by 0.09% from the base case ICER.	worsening of symptoms is experienced among those receiving IVMP or IVMP+MMF. Note that the scenario is focused on assessing the impact of a convergence towards similar long-term outcomes for teprotumumab vs IVMP or IVMP+MMF.

Page 121: "If a small risk shift of 5% is applies the ICERs increase by approximately [REDACTED], and for a shift of 10% the increase in the ICER is [REDACTED]."	The company proposes the wording on page 121 is corrected to: "If a small risk shift of 5% is applied the ICERs increase by approximately 14%, and for a shift of 10% the increase in the ICER is approximately 38%."	Factual inaccuracy (incorrect percentages). Typographical error (spelling error). Incorrect confidential marking (percentage change in ICERs should not be marked as confidential).	Amended
Page 123: In Table 6.2, values reported in the 'Company base-case' row are incorrect.	The company proposes the following corrections to Table 6.2: Total costs for teprotumumab be updated from "[REDACTED]" to "[REDACTED]" Incremental costs for teprotumumab versus IVMP be updated from "[REDACTED]" to "[REDACTED]" Incremental costs for teprotumumab versus IVMP+MMF be updated from "[REDACTED]" to "[REDACTED]" The incremental QALYs for teprotumumab versus IVMP be updated from "0.83" to "0.82" The ICER for teprotumumab versus IVMP be updated from "[REDACTED]" to "[REDACTED]" The ICER for teprotumumab versus IVMP+MMF be updated from "[REDACTED]" to "[REDACTED]"	Factual inaccuracy (incorrect values)	Amended

Page 126: “Using a 10% risk shift, for example, increases the deterministic ICER by around [REDACTED] from approximately [REDACTED] per QALY for both teprotumumab versus IVMP and teprotumumab versus IVMP + MFF.”	The company proposes the wording on page 126 be updated to: “Using a 10% risk shift, for example, increases the deterministic ICER by around 38% from approximately [REDACTED] per QALY for both teprotumumab versus IVMP and teprotumumab versus IVMP + MMF.”	Factual inaccuracy (incorrect percentage). Typographical error (spelling error). Incorrect confidential marking (percentage change in ICERs should not be marked as confidential).	Amended

Typographical errors, formatting errors and minor text alterations

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 13: Table 1.5: Key issue 4: The EAG disagrees with the company’s assumption that patients remain in the same TED state from cycle 4 (24 weeks) to the end of the model. “The scenarios represent different levels of shift from small to large proptosis, no diplopia to intermittent or constant diplopia, and	The company proposes the wording on page 13 is updated to: “The scenarios represent different levels of shift from small to large proptosis, no diplopia to intermittent/inconstant or constant diplopia, and intermittent/inconstant to constant diplopia.”	Typographical error (spelling), “intermittent/inconstant” not “intercurrent”	Amended

intercurrent to constant diplopia.”			
Page 14: “The company’s base-case deterministic ICERs for teprotumumab compared to intravenous methylprednisolone (IVMP) and IVMP + mycophenolate mofetil (MMF) amounted to [REDACTED] and [REDACTED] per QALY gained, respectively.”	The company proposes the wording on page 14 is updated to: “The company’s base-case deterministic ICERs for teprotumumab compared to intravenous methylprednisolone (IVMP) and IVMP + mycophenolate mofetil (MMF) amounted to [REDACTED] and [REDACTED] per QALY gained, respectively.”	Factual inaccuracy (incorrect ICER reported for IVMP)	Amended
Page 14: “If a small risk shift of 5% is applied the ICERs increase by approximately [REDACTED], and for a shift of 10% the increase in the ICER is [REDACTED].”	The company proposes the wording on page 14 is updated to: “If a small risk shift of 5% is applied the ICERs increase by approximately 14%, and for a shift of 10% the increase in the ICER is 38%.”	Factual inaccuracy (incorrect values reported). Confidential marking on percentage increases can be removed.	Amended
Page 21: “Stoyonova et al. (2023)”	The company proposes the spelling of Stoynova on page 21 is corrected.	Incorrect spelling of “Stoynova”.	Amended.
Page 53, Section 3.2.8, Adverse events: “The rate of <u>AEs</u> in the teprotumumab group <u>across these studies</u> ranged from 74% to 85%, compared to 69% to 80% in the placebo group.”	The company proposes the wording on page 53 is updated to: “The rate of <u>TEAEs</u> in the teprotumumab group across these studies ranged from 74% to 85%, compared to 69% to 80% in the placebo group <u>across the Phase 2, OPTIC and Phase 4 (chronic TED only) studies</u> .”	Factual inaccuracy. It is important that AEs are accurately described.	Amended.

Page 64: “The results showed that teprotumumab was associated with a statistically significantly greater mean difference (MD) change from baseline in proptosis compared with IVMP (MD in CFB: [REDACTED] mm [95% CI: [REDACTED]]) (see Table 3.17)”	The company proposes the wording on page 64 is updated to read: “The results showed that teprotumumab was associated with a statistically significantly greater mean difference (MD) change from baseline in proptosis compared with IVMP (MD in CFB: [REDACTED] mm [95% CI: [REDACTED]]) (see Table 3.17).¹” In line with the EAG reference: [1] Amgen. Teprotumumab for treating thyroid eye disease [ID6432]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission: Amgen, 2025. 194p.	The reference for Company Submission is missing.	Amended.
Page 73: “Searches were limited to economic evidence and healthcare resource use studies published since 2012. No date limit was applied to the HRQoL searches.”	The company proposes the wording on page 73 is updated to read: “Searches were limited to economic evidence, healthcare resource use and HRQoL studies published since and including 2013 until present.”	The HRQoL SLR included a date restriction of 2013 to present, detailed in Appendix H of the CS, as did the economic and health care resource use SLRs, detailed in Table 7 of the CS.	The comments on page 73 refer to the search strategy. In the search strategy the date limit was 2012+ for the HCRU studies, and no date limit was applied to the HRQoL searches. This sentence has therefore not been amended.
Page 74:	The company proposes the wording on page 74 is updated to read:	Typographical error, the limit on the	This has been corrected in line

“However, the limit on the publication year of 2012 or more recent”	“However, the limit on the publication year of 2013 or more recent”	publication year was 2013, not 2012, as detailed in Table 7 of the CS and noted in Appendix H and G.	with the inclusion criteria (Table 7), rather than the date in the search strategies
Page 75, Table Error! No text of specified style in document..1: NICE reference case checklist is missing referencing to the NICE	The following reference should be added to “Table 4.1 ¹⁹ :” [19] National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2023 Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 .	The NICE reference case is missing from this table.	Reference added.
Page 75, Table 4.1: “As the EQ-5D is generally considered to be less suitable for eye diseases, a TTO study was done based on vignettes that described the various health states.”	The company proposes that reference to Smith <i>et al.</i> 2023 should be added: “As the EQ-5D is generally considered to be less suitable for eye diseases, a TTO study was done based on vignettes that described the various health states. ¹⁷ ” In line the EAG reference: [17] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility assessment of moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141(2):159-66.	The reference for Smith <i>et al.</i> 2023 is missing from this statement.	Reference added.
Page 75, Table 4.1: Vignettes describing health states were based on information from the pivotal RCTs and interviews with patients”	The company proposes that reference to Smith <i>et al.</i> 2023 should be added: “Vignettes describing health states were based on information from the pivotal RCTs and interviews with patients. ¹⁷ ” In line the EAG reference: [17] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility assessment of	The reference for Smith <i>et al.</i> 2023 is missing from this statement.	Reference added.

	moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141(2):159-66.		
Page 75: “A representative sample of the US population valued the vignettes. According to four UK clinical experts these utility values can be generalized to the UK.”	The company proposes that reference to Clinical validation should be added: “A representative sample of the US population valued the vignettes. According to four UK clinical experts these utility values can be generalised to the UK. ¹² ” In line the EAG reference: [12] Amgen. Data on file: Clinical expert opinion, 2024.	The reference for UK clinical expert opinion is missing from this statement. Spelling error, US rather than UK spelling used.	Reference added and spelling corrected.
Page 76: “Patients enter the model into one of six health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints.”	The company proposes the wording on page 76 is updated to read: “Patients enter the model into one of six active TED health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints.”	The Company believe that the current text is unclear that this refers only to the six active TED health states.	Suggested text added
Page 76, 79, 82, 84, 86, 87, 89, 90, 91, 96, 116, 119, 121, 123, 124 and 125: “IVMP + MFF”	The company propose the wordings on pages 76, 79, 82, 84, 86, 87, 89, 90, 91, 96, 116, 119, 121, 123, 124 and 125 are updated to read: “IVMP + MMF”	Typographical error.	Corrected throughout report
Page 78 in table 4.4: “Based on Table 34 in the CS”	The company proposes the wording on page 78 is updated to read: “Based on Table 35 in the CS”	Typographical error.	Amended
Page 82: “The company used a cycle length of 6 weeks to align with patient efficacy assessment timepoints and dosing schedules for teprotumumab and comparators.”	The company proposes that reference to Phase 2 and Phase 3 OPTIC trials should be added: “The company used a cycle length of 6 weeks to align with patient efficacy assessment timepoints and dosing schedules for teprotumumab and comparators. ^{13,14} ”	The references for Phase 2 and Phase 3 OPTIC trials are missing from this statement.	References added

	In line the EAG references: [13] Amgen. Data on file: CSR for Phase 3 OPTIC study HZNP-TEP-301 (NCT 03298867), 2020, [14] Amgen. Data on file: CSR for Phase 2 Study TED01RV (NCT 01868997), 2017.		
Page 86: “This led to an 8% increase in the ICERs for teprotumumab versus IVMP and a 10% increase for teprotumumab versus IVMP+MFF.”	The company proposes the wording on page 86 is updated to read: “This led to a 10.3% increase in the probabilistic ICERs compared to the base case ICER for teprotumumab versus IVMP and a 7.6% increase for teprotumumab versus IVMP+MMF.”	To provide clarity that the percentage changes cited in the text is for probabilistic ICER and not the base case deterministic results. Furthermore, there is an error in the results reported for the comparators when re-run using the EAG version of the CEM shared with the company at the time of this factual accuracy check.	Text has been added to clarify that the statement relates to the probabilistic ICERs. The percentages have been changed to 10% and 7%, based on the company provided PSA results after clarification, since the EAG cannot perform a correct PSA due to dependency on IPD
Page 88, Table 4.9: Proptosis, Phase 3 data, 72 weeks: “90% (19/21)” Footnote: “Based on the company submission and the response to the EAG clarification letter. ^{1, 4} ”	The company proposes the wording in Table 4.9 is updated to read: Proptosis, Phase 3 data, 72 weeks: “91% (19/21)” Footnote: “Based on the company submission Section B.2.6 and the response to the EAG clarification letter, Table 16. ^{1,4} ”	Rounding error in the reported data. Further clarification added to show where in the CS and EAG clarification letter the data was originally reported.	Text in footnote amended. The reported 90% was not changed, since $19/21 = 0.90476$, which is 90%, not 91%

Page 90, Table 4.11: 'Adverse event rates per 6-week cycle by treatment and analysis' "Silva et al. 2015" "Marocci et al. 2007" "Aktaran et al. 2019"	The company proposes the wording in Table 4.11 is updated to read: "Salvi et al. 2015" "Marocci et al. 2001" "Aktaran et al. 2007"	Spelling and typographical error.	Amended
Page 91: "However, the rationale provided by the company for not considered grade 1 and 2 AEs in the base-case"	The company proposes the wording on page 91 is updated to read: "However, the rationale provided by the company for not considering grade 1 and 2 AEs in the base-case"	Typographical error.	Amended
Page 92: "but EAG noticed that in the SLR, Choi et al. was excluded based on publication date 2012, whilst it was included in the targeted literature review."	The company proposes that reference to Choi et al. 2012 should be added: "but EAG noticed that in the SLR, Choi et al. ³⁴ was excluded based on publication date 2012, whilst it was included in the targeted literature review." In line with EAG reference: [34] Choi YJ, Lim HT, Lee SJ, Lee SY, Yoon JS. Assessing Graves' ophthalmopathy-specific quality of life in Korean patients. <i>Eye</i> 2012; 26(4):544-51.	The reference for Choi et al. 2012 is missing from this statement.	Reference added
Page 92: "The vignettes were subsequently validated by three clinicians and three TED patient advocates, and align with the six-health state Markov model in this appraisal."	The company proposes that reference to Smith <i>et al.</i> 2023 should be added: "The vignettes were subsequently validated by three clinicians and three TED patient advocates, and align with the six-health state Markov model in this appraisal. ¹⁷ " In line the EAG reference: [17] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility assessment of	The reference for Smith <i>et al.</i> 2023 is missing from this statement.	Reference added

	moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141(2):159-66.		
Page 92: “A total of 111 participants, a demographically representative sample of the US general population and without TED, was recruited for a time-trade off (TTO) study in which a trade-off had to be made between 10 years in the health state described by a vignette versus a certain number of years in perfect health followed by death.”	The company proposes that reference to Smith <i>et al.</i> 2023 should be added: “A total of 111 participants, a demographically representative sample of the US general population and without TED, was recruited for a time-trade off (TTO) study in which a trade-off had to be made between 10 years in the health state described by a vignette versus a certain number of years in perfect health followed by death. ¹⁷ ” In line the EAG reference: [17] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility assessment of moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141(2):159-66.	The reference for Smith <i>et al.</i> 2023 is missing from this statement.	Reference added
Page 93: “The main reason why the EAG is somewhat hesitant regarding the validity of the relatively low utility values found by Smith et al. is related to the very long descriptions of the health states.”	The company proposes that reference to Smith <i>et al.</i> 2023 should be added: “The main reason why the EAG is somewhat hesitant regarding the validity of the relatively low utility values found by Smith et al. is related to the very long descriptions of the health states. ¹⁷ ” In line the EAG reference: [17] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, et al. Utility assessment of moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141(2):159-66.	The reference for Smith <i>et al.</i> 2023 is missing from this statement.	Reference added
Page 94: “In the CS it was already mentioned that the face validity	The company propose that reference to Clinical validation should be added:	The reference for UK clinical expert opinion	Reference added

of the utility values had been confirmed by four UK clinical experts.”	“In the CS it was already mentioned that the face validity of the utility values had been confirmed by four UK clinical experts. ¹² ” In line the EAG reference: [12] Amgen. Data on file: Clinical expert opinion, 2024.	is missing from this statement.	
Page 97: “To calculate the acquisition costs for the comparators (i.e., IVMP and IVMP + MMF), unit prices were sourced from the British National Formulary (BNF),”	The company proposes that reference to the BNF should be added: “To calculate the acquisition costs for the comparators (i.e., IVMP and IVMP + MMF), unit prices were sourced from the British National Formulary (BNF), ⁵⁸ ” In line the EAG reference: [58] British National Formulary. BNF (methylprednisolone) [Internet] London: BNF, 2024. Available from: https://bnf.nice.org.uk/drugs/methylprednisolone/medicinal-forms/	The reference for the BNF is missing from this statement.	Reference added
Page 97: “The dosing regimens for IVMP and for IVMP + MMF were based on EUGOGO clinical practice guidelines.”	The company proposes that reference to the EUGOGO clinical practice guidelines should be added: “The dosing regimens for IVMP and for IVMP + MMF were based on EUGOGO clinical practice guidelines. ¹⁸ ” In line the EAG reference: [18] Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185(4):G43-g67.	The reference for the EUGOGO clinical practice guidelines is missing from this statement.	Reference added
Page 99: “The average number of surgeries a patient undergoes,	The company proposes that reference to clinical expert opinion should be added:	The reference for UK clinical expert opinion	Reference added

determined by health state and treatment arm, was informed by UK clinicians.”	“The average number of surgeries a patient undergoes, determined by health state and treatment arm, was informed by UK clinicians.¹²” In line the EAG reference: [12] Amgen. Data on file: Clinical expert opinion, 2024.	is missing from this statement.	
Page 102: “Resource use was identified through UK clinical interviews, as no relevant UK data were identified in the available literature.”	The company proposes that reference to clinical expert opinion should be added: “Resource use was identified through UK clinical interviews, as no relevant UK data were identified in the available literature.¹²” In line the EAG reference: [12] Amgen. Data on file: Clinical expert opinion, 2024.	The reference for UK clinical expert opinion is missing from this statement.	Reference added
Page 104, Table 4.23: Resource use and costs of routine monitoring and disease management, resource use for ‘Small proptosis, no diplopia’ “0.00*”	The company proposes that the asterisk should be removed: “0.00”	Typographical error. The electronic model and Appendix I both report the same value of 0.00 for resource use per cycle for ‘Orthoptics at cycle 2+’.	Amended
Page 110: “Teprotumumab was more costly but also more effective than both IVMP and IVMP + MMF, resulting in 0.82 and 0.83 incremental QALYs and [REDACTED] and [REDACTED] incremental costs, with ICERs of [REDACTED] and [REDACTED] per QALY gained.” and	The ICER for IVMP has been reported incorrectly in the text and table. The company proposes the wording on page 110 should be updated to read: “Teprotumumab was more costly but also more effective than both IVMP and IVMP + MMF, resulting in 0.82 and 0.83 incremental QALYs and [REDACTED] and [REDACTED] incremental costs, with ICERs of [REDACTED] and [REDACTED] per QALY gained.”	Factual inaccuracy (incorrect values)	Amended

Table 5.1 Company base-case deterministic CE results (teprotumumab PAS price, discounted), “IVMP” row, “ICER (£/QALY)” column	and the same ICER reported in Table 5.1 should be corrected from “██████” to “██████”		
Page 112: In Table 5.5, Company base-case probabilistic CE results (teprotumumab PAS price, discounted), the “Inc. costs”, “Inc. QALYs”, and ICER results are the wrong way round for IVMP and IVMP+MMF	The company proposes the reported results for IVMP and IVMP + MMF are substituted for incremental costs, incremental QALYs and ICERs.	Factual inaccuracy (incorrect values)	Amended
Page 112: “The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that teprotumumab is cost effective was █████ and █████, respectively.”	The company proposes the wording on page 112 is updated to: “The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that teprotumumab is cost effective was approximately █████ and █████, respectively.”	These are not exact values so the word approximately should be added.	Amended
Page 113: Caption of Figure 5.1: PSA CE-plane: “Based on Figure in electronic model.”	The company proposes the wording on page 113 is updated to read: “Based on Figure in electronic model after clarification.”	In the caption of Figure 5.2 it specifies the model version after clarification. Therefore, for consistency this should be specified	Amended

		under Figure 5.1 as well.	
Page 116: “ICER estimates ranged between [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (Douglas et al. (2022)¹¹ as data source for the IVMP active population) for teprotumumab versus IVMP, and [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (costs of subsequent treatments included) versus IVMP + MMF.”	The company proposes the wording on page 116 is updated to read: “ICER estimates ranged between [REDACTED] (1.5% discount rate for costs and outcomes) to [REDACTED] (Douglas et al. (2022)¹¹ as data source for the IVMP active population) for teprotumumab versus IVMP, and [REDACTED] (1.5% discount rate for costs and outcomes) to [REDACTED] (costs of subsequent treatments included) versus IVMP + MMF.”	To clarify the scenario analysis relates to a 1.5% discount rate for both costs and outcomes. The ICERs should also be marked as confidential.	Amended
Page 116: “The last scenario analysis done by the company in their response to the clarification letter relates to the number of surgeries per patient.”	The company proposes that an additional paragraph is added to page 116 above this text: “The third type of scenario analysis done by the company explored the impact of discounting the one-off cost applied upon entry to the surgery state at different times. Discounting surgery cost to its present value halfway through the surgery follow-up period, cycle 41, led to an ICER per QALY for IVMP of [REDACTED], a 0.8% increase from base case, and for IVMP+MMF per QALY of [REDACTED], an 0.3% increase from base case. Discounting to the end of the surgery follow-up period, cycle 56, led to an ICER for IVMP of [REDACTED], a 1.0%	The text implies that all scenarios from the clarification document are described in this section, however, the surgery discounting scenario from the clarification document is not described here.	The EAG has added text about the scenario regarding the discounting of surgery costs

	increase from base case, and for IVMP+MMF of [REDACTED], an increase of 0.4% from base case.”		
Page 125: “It consists of six health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints. The six states represent combinations of diplopia (no diplopia, intermittent or inconstant diplopia, constant diplopia) and proptosis symptoms (small, large).”	The company proposes the wording on page 123 is updated to read: “The model consists of six active TED health states that represent the range of clinical presentations of TED and are consistent with clinical trial endpoints. The six active TED states represent combinations of diplopia (no diplopia, intermittent or inconstant diplopia, constant diplopia) and proptosis symptoms (small proptosis or large proptosis).”	The company believe that the current text is unclear that this refers only to the six active TED health states, there are further surgery states and an absorbing health state for death.	Amended
Page 126: “The utilities found had face validity, according to UK clinical experts, and the company found the utilities broadly comparable to those TTO utilities found for various other eye diseases in NICE technology assessments.”	The company proposes that reference to UK Clinical expert opinion, Brown et al. 2003, Rentz et al. 2014, Czoski-Murray 2009 and NICE 2020 should be added: “The utilities found had face validity, according to UK clinical experts,¹² and the company found the utilities broadly comparable to those TTO utilities found for various other eye diseases in NICE technology assessments.³⁷⁻⁴⁰” In line the EAG references: [12] Amgen. Data on file: Clinical expert opinion, 2024. [37] Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss: a time tradeoff utility analysis comparison with	The references for UK Clinical expert opinion, Brown et al. 2003, Rentz et al. 2014, Czoski-Murray 2009 and NICE 2020 are missing from this statement.	Amended

	medical health states. Ophthalmology 2003; 110(6):1076-81. [38] Rentz AM, Kowalski JW, Walt JG, Hays RD, Brazier JE, Yu R, et al. Development of a preference-based index from the National Eye Institute visual function questionnaire-25. JAMA Ophthalmol 2014; 132(3):310-8. [39] Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Health 2009; 12(5):793-9. [40] National Institute for Health and Care Excellence. CHTE methods review. Health-related quality of life. Task and finish group report [Internet]: NICE, 2020. 115p. Available from: https://rees-france.com/wp-content/uploads/2020/12/2020-CHTE-2020-Health-related-quality-of-life-.pdf.		

Incorrect confidentiality marking

To note, the company identified a significant number of errors in confidentiality marking. In part, it appears that the EAG based its marking on v1.0 of Document B and economic model (submitted 14 January 2025) and v1.0 of the company's response to clarification questions (submitted 20 February 2025). In fact, the company updated the confidentiality checklist on 26 February 2025 and provided revised versions (v2.0) of Document B, the model, and responses to clarification questions.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment

Page 20, Table 2.2:	The percentage use of each of the interventions used to treat active moderate-to-severe TED at 1L and 2L should be marked confidential, as per the company's response to clarification questions (version 2.0, submitted 26 February 2025).	Intervention	Percentage use 1L	Percentage use 2L	Company comment	Amended.
		IVMP	■	■	IVMP with or without MMF is mainstay treatment for active moderate-to-severe TED. It is used in almost all patients at 1 st line, and in a large proportion of patients who require a 2 nd line treatment.	
		IVMP with MMF	■	■		
		Orbital radiotherapy (with oral or IV steroids)	■	■	Usually restricted to 2 nd line use after IVMP with or without MMF.	
		Ciclosporin (with oral or IV steroids)	■	■	Usually restricted to 2 nd line use after IVMP with or without MMF.	
		Azathioprine (with oral or IV steroids)	■	■	Usually restricted to 2 nd line use after IVMP with or without MMF.	
		Oral steroids alone	■	■	Usually only used if people are unable to have IV steroids.	
		Rituximab	■	■	Not available nationally (only via individual funding request) and rarely used. As such we have not proposed rituximab or tocilizumab as comparators for this appraisal.	
		Tocilizumab	■	■		
		Triamcinolone	■	■	Not routinely used in UK clinical practice. As such, we have not proposed triamcinolone as a comparator for this appraisal.	
		Based on clarification letter response. ⁴ 1L = 1 st line; 2L = 2 nd line; IV = intravenous; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil; TED = thyroid eye disease; UK = United Kingdom				

Page 40, first paragraph: “The company provided details of the ■ patients in the Phase 2 ITT population¹¹ and these limited data can be found in Table 3.5 below.”	The number of UK patients should be marked confidential, as per the company’s response to clarification questions (version 2.0, submitted 26 February 2025).	“The company provided details of the ■ patients in the Phase 2 ITT population¹¹ and these limited data can be found in Table 3.5 below.”	Amended.

Page 40, Table 3.5:	All the demographic and baseline characteristics of the UK-based patients included in Table 3.5 should be marked confidential, as per the company's response to clarification questions (version 2.0, submitted 26 February 2025).	<table><tr><th colspan="3">Table 3.5: Phase 2 UK based ITT population</th></tr><tr><th>Characteristics</th><th>Placebo UK based (■)</th><th>Teprotumumab (■)</th></tr><tr><td>Age (years) – means (SD)</td><td>■</td><td>■</td></tr><tr><td>Female gender – no. of patients (%)</td><td>■</td><td>■</td></tr><tr><td>Time since initiation of treatment for thyroid disease (months) – median (range)^a</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td>Duration of eye symptoms or signs (months) – means (SD)</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td>Duration of Graves' disease (months) – median (range)</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td colspan="3">Race – no. of patients (%)</td></tr><tr><td>White</td><td>■</td><td>■</td></tr><tr><td>Asian</td><td>■</td><td>■</td></tr><tr><td>Black</td><td>■</td><td>■</td></tr><tr><td colspan="3">Current treatment for thyroid disease – no. of patients (%)</td></tr><tr><td>Antithyroid drug^b</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td>Levothyroxine</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td>Thyroid extract</td><td>Not provided by company</td><td>Not provided by company</td></tr><tr><td colspan="3">Adjustment of medication at trial entry – no. of patients (%)</td></tr></table>	Table 3.5: Phase 2 UK based ITT population			Characteristics	Placebo UK based (■)	Teprotumumab (■)	Age (years) – means (SD)	■	■	Female gender – no. of patients (%)	■	■	Time since initiation of treatment for thyroid disease (months) – median (range) ^a	Not provided by company	Not provided by company	Duration of eye symptoms or signs (months) – means (SD)	Not provided by company	Not provided by company	Duration of Graves' disease (months) – median (range)	Not provided by company	Not provided by company	Race – no. of patients (%)			White	■	■	Asian	■	■	Black	■	■	Current treatment for thyroid disease – no. of patients (%)			Antithyroid drug ^b	Not provided by company	Not provided by company	Levothyroxine	Not provided by company	Not provided by company	Thyroid extract	Not provided by company	Not provided by company	Adjustment of medication at trial entry – no. of patients (%)			Amended.
Table 3.5: Phase 2 UK based ITT population																																																			
Characteristics	Placebo UK based (■)	Teprotumumab (■)																																																	
Age (years) – means (SD)	■	■																																																	
Female gender – no. of patients (%)	■	■																																																	
Time since initiation of treatment for thyroid disease (months) – median (range) ^a	Not provided by company	Not provided by company																																																	
Duration of eye symptoms or signs (months) – means (SD)	Not provided by company	Not provided by company																																																	
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Race – no. of patients (%)																																																			
White	■	■																																																	
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Current treatment for thyroid disease – no. of patients (%)																																																			
Antithyroid drug ^b	Not provided by company	Not provided by company																																																	
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Thyroid extract	Not provided by company	Not provided by company																																																	
Adjustment of medication at trial entry – no. of patients (%)																																																			

		Levothyroxine	Not provided by company	Not provided by company		
		Antithyroid drug	Not provided by company	Not provided by company		
		Smoking status – no. of patients (%)^c				
		Non-smoker	████	████		
		Smoker	████	████		
		Biochemical status				
		TBII (% level of inhibition) – means (SD)	Not provided by company	Not provided by company		
		TSI (% level of stimulation) – means (SD)	Not provided by company	Not provided by company		
		Mean thyroid hormone levels (pmol/L) – means (SD)^d				
		Free triiodothyronine	████	████		
		Free thyroxine	████	████		
		Levels of free triiodothyronine and free thyroxine – no. of patients (%)				
		Euthyroid at baseline and through intervention phase	Not provided by company	Not provided by company		
		Values occasionally outside normal range during intervention phase	Not provided by company	Not provided by company		
		Sustained out-of-range values during intervention phase	Not provided by company	Not provided by company		
		Based on data provided in response to clarification ⁴				

		ITT = intention-to-treat; ng/dL = nanograms per decilitre; pg/mL = picograms per millilitre; pmol/L = picomoles per litre; SD = standard deviation; TBII = thyrotropin-binding inhibitory immunoglobulins; TSI = thyroid-stimulating immunoglobulins	
Page 48, Section 3.2.6.1.2.4: Change in GO-QOL	The number of point changes in the GO-QOL visual functioning score for teprotumumab patients should be marked confidential, as per the CS, Document B.	The company reported that “The phase 2 trial demonstrated that for acute, moderate-to-severe TED, teprotumumab resulted in a significant increase in the GO-QOL visual-functioning score across all time points, ranging from [REDACTED] to [REDACTED] points higher than the placebo group.”	Amended.
Page 78, Table 4.5: ‘Patient characteristics used in the model’: Mean weight (kg), (SD) [REDACTED] and [REDACTED]	Patient weight “78.07 (19.08)” and “77.54 (15.78)” is marked as confidential. However, in v2.0 of the company’s clarification responses dated 26 February, this	Mean weight (kg) “78.07 (19.08)” and “77.54 (15.78)”	Amended.

	is no longer confidential and should be unmarked.		
Page 81: “(████ of all possible transitions)”	It is possible for the reader to ascertain information on transition probabilities based on the text presented. Transition probabilities are not publicly available, and therefore confidential.	“(████ of all possible transitions)”	Amended.
Page 87: “Of these, █████ had not maintained response at 72 weeks and █████ did not provide data. Assuming the	It is possible for the reader to ascertain information on the follow-up period of Phase 2 OPTIC trial based on the text	“Of these, █████ had not maintained response at 72 weeks and █████ did not provide data. Assuming the remaining █████ maintained the response, this implies a response rate at 72 weeks of █████.”	Amended.

remaining [REDACTED] maintained the response, this implies a response rate at 72 weeks of [REDACTED].”	presented. Week 72 individual patient level data from the Phase 2 trial is not publicly available, and therefore confidential.		
Page 88: “At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].”	It is possible for the reader to ascertain information on the follow-up period of Phase 3 OPTIC trial based on the text presented. Week 72 individual patient level data from the Phase 2 trial is not publicly available, and therefore confidential.	“At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].”	Amended.

Page 88: “At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].”	It is possible for the reader to ascertain information on the follow-up period of Phase 3 OPTIC trial based on the text presented. Week 72 individual patient level data from the Phase 2 trial is not publicly available, and therefore confidential.	“At 72 weeks they report that [REDACTED] of 24-week responders still met the response criteria at 72 weeks. This corresponds to a response rate at 72 weeks of [REDACTED].”	Amended.
Pages 90-91, Table 4.11: Adverse event rates per 6-week cycle by treatment and analysis: Teprotumumab, Base-case and Scenario	Adverse event rates from the Phase 2 and Phase 3 OPTIC trials should be marked as confidential.	All results in the table columns listed below should be marked as confidential: Teprotumumab, Base-case^a Teprotumumab, Scenario^b	Amended.

Page 97, Table 4.16: 'Teprotumumab acquisition costs (per infusion)': Mean weight (kg) "[REDACTED]"	Patient weight is marked as confidential, however, this is no longer confidential and should be unmarked.	Mean weight (kg) "78.07"	Amended.
Page 97, Table 4.16: 'Teprotumumab acquisition costs (per infusion)': Dose per admin (mg) "[REDACTED]", "[REDACTED]"	Dose per admin is marked as confidential, however, this is no longer confidential and should be unmarked.	Dose per admin (mg) "780.70", "1,561.40"	Amended.
Page 102, Table 4.21: 'Cost, incidence rates, and total costs of subsequent treatments': Proportion of patients	The proportion of patients receiving each subsequent treatment was collected via clinician interviews which is not publicly	Proportion of patients receiving the treatment: Following teprotumumab: [REDACTED] Following IVMP: [REDACTED] Following IVMP+MMF: [REDACTED]	Amended.

receiving the treatment	available and is therefore confidential.								
Page 102: “ ”	The SmPC is not publicly available and therefore details should be marked confidential, in line with the CS.	“ ”						Amended.	
Page 103, Section 5.2.7, Table 4.11:	Teprotumumab adverse events, both in the base-case and scenario, should be marked confidential, as per the CS, Document B.		Teprotumumab ^a		IVMP/IVMP + MMF				Amended.
		Adverse event	Base-case ^a	Scenario ^b	Base-case (Silva et al. 2015) ^a	Scenario 1 (Roy et al. 2015) ^b	Scenario 2 (Marocci et al. 2007) ^b	Scenario 3 (Aktaran et al. 2019) ^b	
		Muscle spasms			0.00%	0.00%	0.00%	0.00%	
		Alopecia			0.00%	0.00%	0.00%	0.00%	
		Nausea			0.00%	0.00%	0.00%	0.00%	
		Sleepiness/fatigue			0.00%	0.00%	0.00%	4.08%	
		Diarrhoea			0.00%	0.00%	0.00%	0.00%	
		Dry skin			0.00%	0.00%	0.00%	0.00%	
		Dysgeusia			0.00%	0.00%	0.00%	0.00%	
		Headache			0.00%	0.00%	0.00%	0.00%	
		Amenorrhoea			0.00%	0.00%	0.00%	0.00%	
		Dizziness			0.00%	0.00%	0.00%	0.00%	
		Stomatitis			0.00%	0.00%	0.00%	0.00%	
		Abdominal pain			0.00%	0.00%	0.00%	0.00%	

		<table><tr><td>Cough</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>0.00%</td><td>0.00%</td></tr><tr><td>Influenza</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>0.00%</td><td>0.00%</td></tr><tr><td>Cushingoid habitus</td><td></td><td></td><td>0.00%</td><td>3.74%</td><td>5.42%</td><td>0.00%</td></tr><tr><td>Weight gain</td><td></td><td></td><td>0.00%</td><td>7.75%</td><td>0.00%</td><td>4.08%</td></tr><tr><td>Hypertension</td><td></td><td></td><td>0.00%</td><td>2.47%</td><td>0.00%</td><td>0.00%</td></tr><tr><td>Depression</td><td></td><td></td><td>0.00%</td><td>2.47%</td><td>0.00%</td><td>0.00%</td></tr><tr><td>Myalgias</td><td></td><td></td><td>0.00%</td><td>2.47%</td><td>0.00%</td><td>0.00%</td></tr><tr><td>Glucose intolerance</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>10.08%</td><td>0.00%</td></tr><tr><td>Gastritis</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>4.30%</td><td>4.08%</td></tr><tr><td>Urinary tract infection</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>8.88%</td><td>0.00%</td></tr><tr><td>Palpitation</td><td></td><td></td><td>0.00%</td><td>0.00%</td><td>0.00%</td><td>6.19%</td></tr><tr><td colspan="7">Based on Tables 41 and 42 from CS.¹ Data for teprotumumab was based on phase 2 and phase 3 OPTIC trials ^a Includes only AEs that are grade ≥3 and occur in ≥5% of patients ^b Includes all AEs that occur in ≥5% of patients AE = adverse event; CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil</td></tr></table>	Cough			0.00%	0.00%	0.00%	0.00%	Influenza			0.00%	0.00%	0.00%	0.00%	Cushingoid habitus			0.00%	3.74%	5.42%	0.00%	Weight gain			0.00%	7.75%	0.00%	4.08%	Hypertension			0.00%	2.47%	0.00%	0.00%	Depression			0.00%	2.47%	0.00%	0.00%	Myalgias			0.00%	2.47%	0.00%	0.00%	Glucose intolerance			0.00%	0.00%	10.08%	0.00%	Gastritis			0.00%	0.00%	4.30%	4.08%	Urinary tract infection			0.00%	0.00%	8.88%	0.00%	Palpitation			0.00%	0.00%	0.00%	6.19%	Based on Tables 41 and 42 from CS. ¹ Data for teprotumumab was based on phase 2 and phase 3 OPTIC trials ^a Includes only AEs that are grade ≥3 and occur in ≥5% of patients ^b Includes all AEs that occur in ≥5% of patients AE = adverse event; CS = company submission; IVMP = intravenous methylprednisolone; MMF = mycophenolate mofetil							
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Page 105 Table 4.23: ‘Resource use and costs of routine monitoring and disease management’ Resource use for each health state	Resource use by health state was collected via clinician interviews which are not publicly available and is therefore confidential.	Health state resource use: Small proptosis, no diplopia: [REDACTED] [REDACTED] Large proptosis, no diplopia: [REDACTED] [REDACTED] Small proptosis, ID: [REDACTED] [REDACTED] Large proptosis, ID: [REDACTED] [REDACTED]	Amended.																																																																																				

		Small proptosis, constant diplopia: [REDACTED] Large proptosis, constant diplopia: [REDACTED]	
Page 112 Table 5.5: 'Company base-case probabilistic CE results (teprotumumab PAS price, discounted): Inc. QALYs: [REDACTED], [REDACTED]	Incremental QALYs are marked as confidential, however, they are no longer confidential and should be unmarked.	0.75, 0.77	Amended.
Page 116: "ICER estimates ranged between [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (Douglas et al. (2022)¹¹ as data source for the IVMP active population) for	ICERs should be marked as confidential, to avoid estimate of the treatment effect.	"ICER estimates ranged between [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (Douglas et al. (2022)¹¹ as data source for the IVMP active population) for teprotumumab versus IVMP, and [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (costs of subsequent treatments included) versus IVMP + MMF."	Amended.

teprotumumab versus IVMP, and [REDACTED] (1.5% for costs and outcomes) to [REDACTED] (costs of subsequent treatments included) versus IVMP + MMF.”			
On page 116: “Finally, the third scenario shows a [REDACTED] in the ICER from”	Direction of ICER change is marked as confidential, however, it should be unmarked.	“Finally, the third scenario shows a decrease in the ICER from”	Amended.
Page 117 Table 5.6: ‘Company scenario analysis results (teprotumumab PAS price, discounted): ICER tteprotumumab versus IVMP (£) and ICER	ICERs should be marked as confidential, to avoid estimation of the treatment effect.	ICER tteprotumumab versus IVMP (£): [REDACTED] [REDACTED] ICER tteprotumumab versus IVMP + MMF (£): [REDACTED] [REDACTED]	Amended.

teprotumumab versus IVMP + MMF (£)			
Page 121: “If a small risk shift of 5% is applies the ICERs increase by approximately [REDACTED], and for a shift of [REDACTED] the increase in the ICER is 40%.”	Percentage change in ICERs is marked as confidential, however it should be unmarked.	“If a small risk shift of 5% is applies the ICERs increase by approximately 16%, and for a shift of 10% the increase in the ICER is 40%.”	Amended.
Page 123, Table 6.2: ‘Modelling reductions in proptosis and diplopia response rates at 3 years’: ‘Costs (£) Tepro’, ‘Costs (£) IVMP’, ‘Costs (£) IVMP+MMF’	Total costs, QALYs, incremental costs and ICERs should be marked as confidential, to avoid estimation of the treatment effect.	All results in the table columns listed below should be marked as confidential: ‘Costs (£) Tepro’, ‘Costs (£) IVMP’, ‘Costs (£) IVMP+MMF’ ‘QALYs Tepro’, ‘QALYs IVMP’, ‘QALYs IVMP + MMF’ ‘Incr. costs (£) Tepro versus IVMP’, ‘Incr. costs (£) Tepro versus IVMP+MMF’ ‘ICER Tepro versus IVMP’, ‘ICER Tepro versus IVMP+MMF’	Amended.

'QALYs Tepro', 'QALYs IVMP', 'QALYs IVMP + MMF' 'Incr. costs (£) Tepro versus IVMP', 'Incr. costs (£) Tepro versus IVMP+MFF' 'ICER Tepro versus IVMP', 'ICER Tepro versus IVMP+MFF'			
Page 126: "Using a 10% risk shift, for example, increases the deterministic ICER by around [REDACTED]"	The company propose the wording on page 126 be updated to: "Using a 10% risk shift, for example, increases the deterministic ICER by around 38%"	Typographical error and spelling. The percentage increase in the ICER can be unredacted.	Amended.