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Teprotumumab (TEPEZZA®) for moderate-to-severe thyroid eye disease

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Final Review

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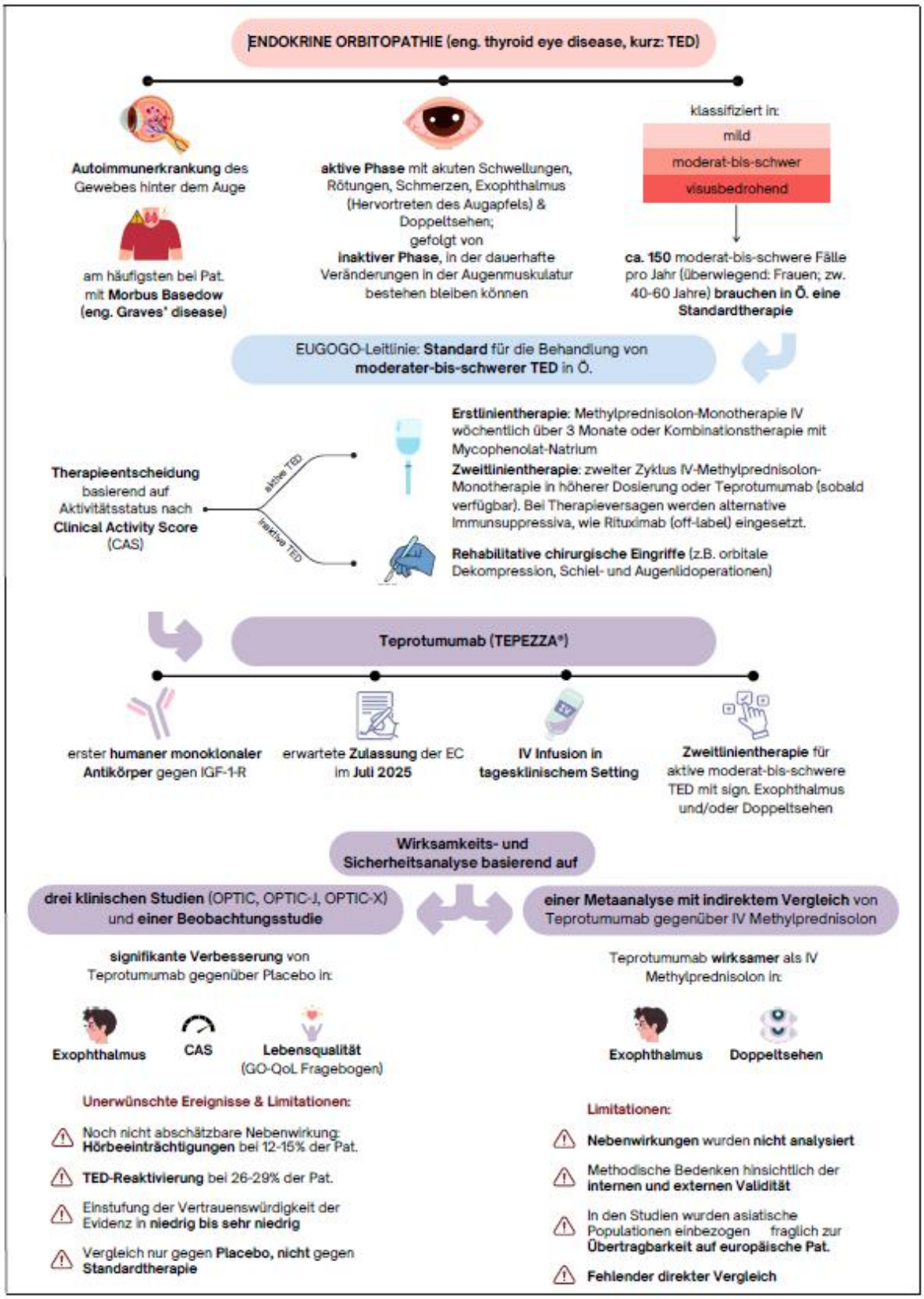
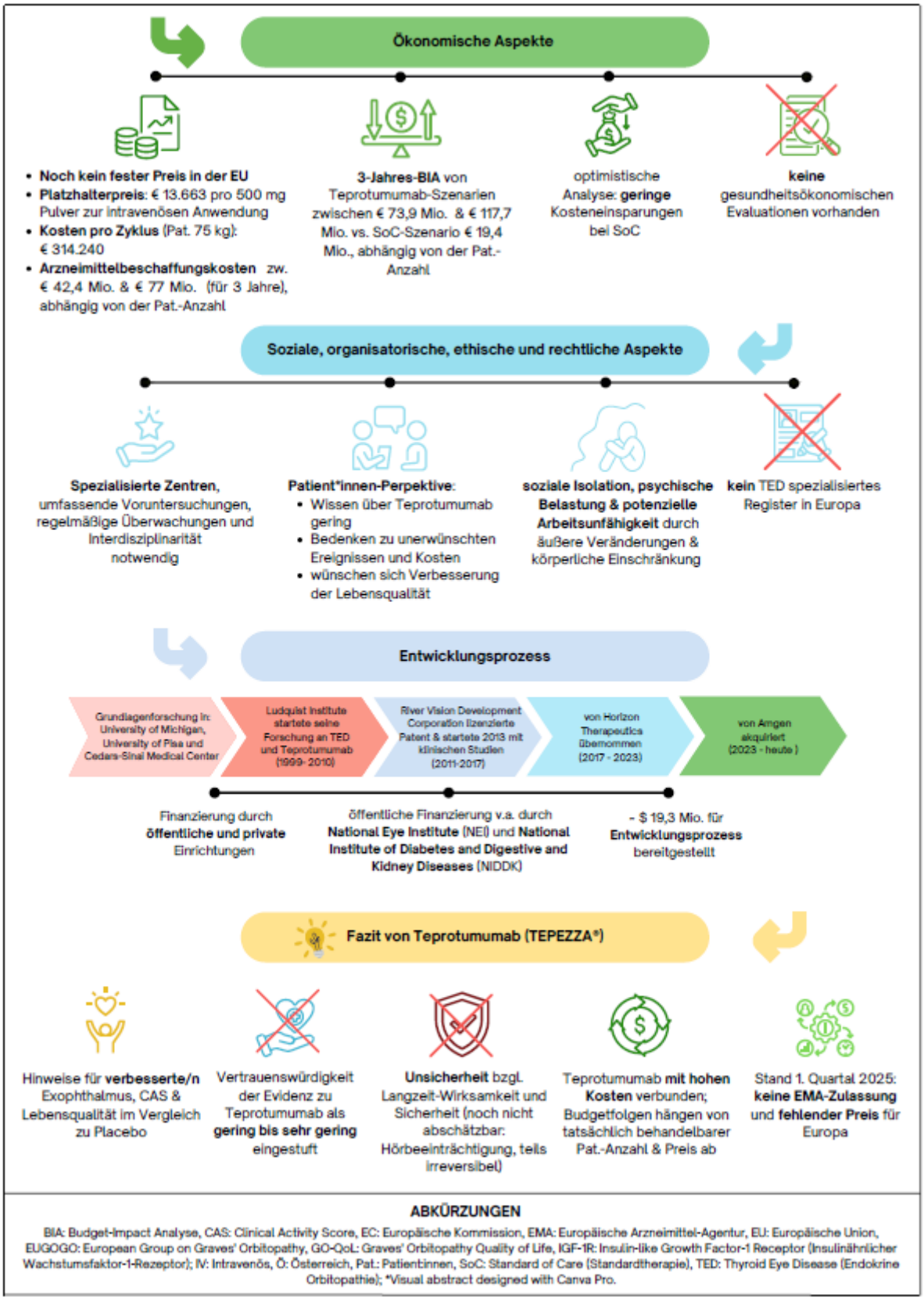




ABKÜRZUNGEN

BIA: Budget-Impact Analyse, CAS: Clinical Activity Score, EC: Europäische Kommission, EMA: Europäische Arzneimittel-Agentur, EU: Europäische Union, EUGOGO: European Group on Graves' Orbitopathy, GO-QoL: Graves' Orbitopathy Quality of Life, IGF-1R: Insulin-like Growth Factor-1 Receptor (Insulinähnlicher Wachstumsfaktor-1-Rezeptor); IV: Intravenös, Ö: Österreich, Pat.: Patientinnen, SoC: Standard of Care (Standardtherapie), TED: Thyroid Eye Disease (Endokrine Orbitopathie); *Visual abstract designed with Canva Pro.

Zusammenfassung

Beschreibung der Erkrankung und Behandlungsoptionen

Endokrine Orbitopathie (englisch: thyroid eye disease, TED) ist eine Autoimmunerkrankung des Augengewebes, die hauptsächlich bei Patient:innen mit Morbus Basedow auftritt. Die European Group on Grave's Orbitopathy (EUGOGO) klassifiziert TED in drei Schweregrade: mild, moderat-bis-schwer und visusbedrohend. Zu den wesentlichen Risikofaktoren gehören das biologische Geschlecht (erhöhtes Risiko bei Frauen), genetische Veranlagung, Rauchen und Radiojodtherapie.

TED verläuft in zwei Phasen: einer aktiven Entzündungsphase (mit periorbitaler Schwellung, Rötung, Schmerzen, Exophthalmus, Diplopie) und einer inaktiven Phase, in der dauerhafte Veränderungen bestehen bleiben können. Die Beurteilung der Krankheitsaktivität erfolgt mittels Clinical Activity Score (CAS), wobei eine aktive TED bei ≥3 Punkten vorliegt. Ohne Behandlung dauert der Verlauf typischerweise 18–24 Monate, jedoch können ohne adäquate Therapie bleibende Schäden entstehen.

Mit Inzidenzraten von 0,54–0,9 Fällen pro 100.000 Männern und 2,67–3,3 Fällen pro 100.000 Frauen pro Jahr ist TED eine seltene Erkrankung. In Österreich werden jährlich etwa 148 neue Fälle mit moderater-bis-schwerer TED diagnostiziert.

Für moderate-bis-schwere TED sind laut EUGOGO-Richtlinien Erst- und Zweitlinientherapien verfügbar, die einem schrittweisen Protokoll basierend auf Krankheitsaktivität und Patient:innen-Reaktion folgen. In Österreich besteht die Erstlinienbehandlung bei aktiver TED aus Methylprednisolon-Monotherapie, während EUGOGO eine Kombination mit Mycophenolat oder höhere Methylprednisolon-Dosen empfiehlt. Bei unzureichendem Ansprechen folgen Zweitlinienoptionen: In Österreich höher dosiertes Methylprednisolon, Teprotumumab (falls zukünftig verfügbar) oder Rituximab (off-label) bei Therapieversagen. Nach Übergang in die inaktive Phase wird bei Bedarf eine rehabilitative Operation oder Orbitalbestrahlung empfohlen.

Überblick über das neue Arzneimittel

Teprotumumab (TEPEZZA®) zur Behandlung der moderaten-bis-schweren TED befindet sich derzeit im Zulassungsverfahren bei der Europäischen Arzneimittelagentur (EMA), wobei die Zulassung durch die Europäische Kommission für Juli 2025 erwartet wird[1]. Es handelt sich um den ersten humanen monoklonalen Antikörper gegen den insulin-ähnlichen Wachstumsfaktor (IGF)-1-Rezeptor, der eine wichtige Rolle bei der TED-Entwicklung spielt.

Die Verabreichung erfolgt als intravenöse Infusion mit einer Initialdosis von 10 mg/kg, gefolgt von 20 mg/kg alle drei Wochen für sieben weitere Behandlungen. Die Therapie erfordert Monitoring von Infusionsreaktionen, Blutzuckerwerten, entzündlichen Darmerkrankungen und der Hörfunktion.

Relative klinische Wirksamkeit und Sicherheit

Die Evidenzbasis zu Teprotumumab in der Behandung von Patient*innen mit aktiver, moderater bis schwerer endokriner Orbitopathie (TED) umfasst drei klinische Studien (OPTIC, OPTIC-J, OPTIC-X) und eine Beobachtungsstudie. In den randomisierten kontrollierten Phase-3 Studien OPTIC und OPTIC-J zeigte Teprotumumab signifikant bessere Ergebnisse als Placebo in: Exophthalmus-Ansprechrate (83–89 % vs. 10–11 % bei Placebo), CAS (Clinical Activity Score)-Ansprechen (59 % vs. 21–22 % bei Placebo) und signifikante Verbesserung der Lebensqualität (GO-QoL-Score). Die OPTIC-X-Studie (einarmige Erweiterungsstudie) zeigte eine Exophthalmus-Ansprechrate von 89,2 % bei Erstanwender:innen und 62,5 % bei Patient:innen mit Krankheitsschub. Ein kritisches Ergebnis war die TED-Reaktivierung,

[1] Bei Fertigstellung des Berichtes (16. April 2025) lag noch keine CHMP Empfehlung zur Zulassung bzw. Zulassung durch die Europäische Kommission vor.

die bei 29,4 % der Teprotumumab-Patient:innen in der OPTIC-Studie innerhalb der 72-wöchigen Nachbeobachtung und bei 26 % der Patient:innen in der Beobachtungsstudie auftrat.

Die häufigsten unerwünschten Ereignisse waren Muskelkrämpfe, Haarausfall, Übelkeit und Müdigkeit. In 12-15 % der mit Teprotumumab behandelten Patient:innen kam es zu einer Hörbeeinträchtigung, welche in einigen Fällen langanhaltend bzw. irreversibel war.

Ein indirekter Behandlungsvergleich zeigte, dass Teprotumumab der IV-Methylprednisolon-Monotherapie beim Exophthalmus- und Diplopie-Ansprechen überlegen ist. Allerdings bestehen methodische Bedenken hinsichtlich der internen und externen Validität dieses Vergleichs.

Die Vertrauenswürdigkeit der Evidenz wurde nach GRADE-Methodik als niedrig bis sehr niedrig eingestuft. Bei beiden randomisierten Studien wurden methodische Bedenken identifiziert, darunter unvollständige Baseline-Angaben, unklare Protokolle und potenzielle Entblindung.

Ökonomische Aspekte

Teprotumumab hat in Europa noch keinen festgelegten Preis. Die Budget-Impact-Analyse basiert auf einem Platzhalterpreis von € 13.663 pro 500 mg, wonach sich acht Verabreichungen im Abstand von drei Wochen pro Patient:in (75 kg) auf ca. € 314.240 belaufen würde. Bei 45 Patient:innen jährlich würde die Therapie etwa € 14,1 Millionen (€ 42,4 Millionen über drei Jahre) kosten. In der Szenarioanalyse mit steigender Patient:innen-Anzahl (Jahr 1: 40, Jahr 2: 90, Jahr 3: 115) steigen die Kosten auf € 77 Millionen über drei Jahre. Der Gesamtbudgeteinfluss liegt zwischen € 73,9 und € 117,7 Millionen für drei Jahre, während die Standardbehandlung nur etwa € 19,4 Millionen kosten würde, also nur ein Viertel bis ein Sechstel der Teprotumumab-Kosten. Mögliche Einsparungen durch vermiedene Rituximab-Behandlungen und Operationen betragen lediglich € 22.978. Gesundheitsökonomische Bewertungen fehlen, da der Hersteller kein Modell vorgelegt hat.

Soziale, organisatorische, ethische und rechtliche Aspekte

Die Verabreichung von Teprotumumab erfordert Voruntersuchungen, laufende Überwachungen und spezialisierte Zentren mit geschultem Personal. Vor Beginn der Infusionstherapie ist eine ausführliche Aufklärung notwendig. Klinische Expert:innen betonen die Notwendigkeit einer interdisziplinären Zusammenarbeit verschiedener Fachrichtungen (Ophthalmologie, Endokrinologie, Nuklearmedizin, Chirurgie).

TED verursacht körperliche Symptome (v. a. Augenschmerzen, Sehstörungen) sowie psychischen Stress, der die Lebensqualität erheblich einschränken und bis zu Arbeitsunfähigkeit und sozialer Isolation führen kann. Patient:innen kämpfen oft mit einer verzögerten Diagnose und wünschen sich eine schnellere Linderung mit Teprotumumab, haben aber Bedenken wegen potenziellen Nebenwirkungen und der intravenösen Verabreichung.

Zu den Herausforderungen gehören der Mangel an spezialisierten Behandlungszentren, hohe Behandlungskosten und die Zuweisung von Ressourcen. Aus ethischer Perspektive sind besonders die hohen Therapiekosten, die Kostenverteilung und der gleichberechtigte Versorgungszugang problematisch.

Ein spezifisches Register für TED existiert in Österreich nicht, was die systematische Erfassung von Daten zur vergleichenden Wirksamkeit und zu langfristigen Ergebnissen einschränkt.

Öffentliche Investition

Die Entwicklung von Teprotumumab begann als Krebstherapie und wurde später auf TED umgelenkt. Das Ludquist Institute forschte von 1999 bis 2010, bevor das Patent an River Vision Development Corporation lizenziert wurde. Diese wurde 2011 gegründet, 2017 von Horizon Therapeutics übernommen und 2023 von Amgen akquiriert.

Die Grundlagenforschung erfolgte hauptsächlich an der University of Michigan, University of Pisa und dem Cedars-Sinai Medical Center. Insgesamt flossen etwa 19,3 Millionen Dollar öffentliche Mittel in die Entwicklung.

Schlussfolgerung

Teprotumumab zeigt eine signifikante Wirksamkeit bei aktiver, moderater-bis-schwerer TED mit deutlicher Verbesserung bei Exophthalmus, CAS und Lebensqualität im Vergleich zu Placebo. Allerdings bestehen Bedenken hinsichtlich der Dauer der Wirkung, da Reaktivierungsraten zwischen 26–29 % in den Anfangsstudien und sogar höheren Raten in weiteren Analysen gezeigt wurden. Eine weitere Einschränkung betrifft die Sicherheit, insbesondere durch das Auftreten von Hörschäden in 12–15 %, die in manchen Fällen irreversibel sein können. Neue Studiendaten könnten möglicherweise zu einer validen Einschätzung der Reaktivierungsraten als auch des Nebenwirkungsprofil beitragen.

Die Evidenzbasis zeigt methodische Limitationen und wird mit niedriger bis sehr niedriger Vertrauenswürdigkeit bewertet. Es liegt kein direkter Vergleich von Teprotumumab gegenüber der derzeitigen Standardbehandlung vor. Neben relevanten wirtschaftlichen Aspekten müssen auch Herausforderungen bei der Umsetzung berücksichtigt werden, darunter der Bedarf an spezialisierten Zentren, umfassender Überwachung und potenziellen Versorgungsschwierigkeiten.

Eine laufende Phase-3b/4-Post-Marketing-Studie untersucht die Sicherheit und Verträglichkeit verschiedener Dosierungsregime von Teprotumumab. Es liegen derzeit keine abgeschlossenen Health Technology Assessment-Berichte für Teprotumumab bei TED vor, es sind derzeit aber Bewertungen sowohl durch NICE als auch durch NIHR in Bearbeitung. Dennoch fehlen nach wie vor direkte Vergleichsstudien mit Standardtherapien. Aufgrund der genannten Limitationen ist eine valide Beurteilung des Stellenwerts von Teprotumumab in der Behandlung der aktiven, moderaten-bis-schweren TED nicht abschließend möglich, die Anwendung sollte unter definierten Kriterien und strukturierter Dokumentation erfolgen.

Executive summary

Disease description and standard of care

Thyroid eye disease (TED) is an autoimmune condition affecting tissues behind the eyes, which primarily occurs in patients with Graves' disease. The European Group on Grave's Orbitopathy (EUGOGO) classifies TED into mild, moderate-to-severe, and sight-threatening. Risk factors include female sex, genetic predisposition, smoking, and radioiodine therapy.

TED progresses through an active inflammatory phase (with periorbital swelling, redness, pain, proptosis, diplopia) and an inactive chronic phase where permanent changes may persist. Without treatment, the process typically lasts 18–24 months, potentially leaving permanent damage that may require surgical correction. Approximately 0.161 per 10,000 persons (148 cases annually in Austria) are newly diagnosed with moderate-to-severe TED requiring treatment.

The treatment of moderate-to-severe TED in Austria primarily refers to the EUGOGO Guideline 2021, which recommends first- and second-line therapies that follow a stepwise protocol based on disease activity and patient response. In Austria, first-line treatment for active TED consists of methylprednisolone monotherapy, while EUGOGO recommends a combination with mycophenolate or higher methylprednisolone doses. In case of inadequate response, second-line options follow: In Austria, higher-dosed methylprednisolone, teprotumumab (if available in the future), or rituximab (off-label) in case of treatment failure. After the transition to inactive status, rehabilitative surgery or orbital radiation is recommended if needed.

Overview of the new medicinal product

Teprotumumab is currently under EMA evaluation, with EC approval expected in July 2025 for moderate-to-severe TED indication[2]. It is the first human monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R), which plays an important role in TED development. Teprotumumab is administered intravenously (IV) with an initial dose of 10mg/kg, followed by 20mg/kg every three weeks for seven further treatments. The therapy requires monitoring of infusion reactions, blood glucose levels, inflammatory bowel disease and hearing function.

Clinical effectiveness and safety

Three clinical studies (OPTIC, OPTIC-J, OPTIC-X) and one observational study evaluated teprotumumab for active moderate-to-severe TED.

In the two randomised controlled phase 3 trials (RCT), OPTIC and OPTIC-J, teprotumumab significantly outperformed the placebo for proptosis response (83% vs 10% in OPTIC; 89% vs 11% in OPTIC-J) with similar clinical activity score (CAS) improvements in both studies (59% vs 21–22% for placebo). Also, Graves' ophthalmopathy-specific quality-of-life scores (GO-QoL) significantly improved with teprotumumab in both studies. OPTIC-X, a single-arm, open-label extension study enrolling patients from the OPTIC trial, demonstrated 89.2% proptosis response in first-time users and 62.5% response in patients with disease flare. CAS responses were achieved in 65.6% of first-time teprotumumab users and 57.1% of patients with disease flare, while GO-QoL scores showed moderate to substantial improvements. TED reactivation occurred in 26–29% of teprotumumab patients.

The adverse events were similar in all three clinical studies, the most frequent ones being muscle spasms, alopecia, nausea and fatigue. Hearing impairment occurred in 12–15% of teprotumumab patients, with some unresolved cases.

[2] At the time of completion of the report (April 16th 2025), there was no CHMP recommendation for approval or marketing authorization by the European Commission available.

The certainty of the evidence was assessed as low to very low. Both RCTs had methodological concerns, including incomplete baseline reporting, unclear protocols, potential unmasking, and inter-observer variability issues. OPTIC-X's limitations included the open-label design, varying entry points, diverse disease stages, inadequate statistical planning, and unclear follow-up, resulting in a moderate risk of bias (RoB). The RoB for the observational study was moderate due to its retrospective, unblinded design.

The meta-analysis indirectly compared teprotumumab to methylprednisolone and found that teprotumumab is superior for treating proptosis and diplopia. However, the study had validity issues and a questionable patient population despite ethnic differences in proptosis presentation.

Economic aspects

Teprotumumab does not yet have a set price in Europe. The budget impact analysis is based on a placeholder price of €13,663 per 500mg (cost per cycle of eight infusions per patient (75kg) €314,240), which would cost approximately €14.1 million per year (€42.3 million over three years) for 45 patients. In the scenario analysis with an increasing number of patients (year 1: 40, year 2: 90, year 3: 115), the costs rise to €77 million over three years. The total budget impact is between €73.9 and €117.7 million over three years, while the standard treatment would only cost around €19.4 million – only a quarter to a sixth of the cost of teprotumumab. Potential savings from avoided rituximab treatments and surgeries amount to only €22,978. Health economic evaluations are completely missing as the manufacturer has not provided a model.

Social, organisational, ethical and legal aspects

Teprotumumab requires preliminary examinations and specialised centres with trained staff. In Austria, it is intended as a second-line treatment after methylprednisolone (SoC). However, challenges include a lack of specialised treatment centres, high treatment costs, and resource allocation.

TED causes physical symptoms (eye pain, vision problems) as well as psychological stress, which significantly limits patients' quality of life. In addition, patients struggle with delayed diagnoses and wish for faster relief with teprotumumab. Furthermore, patient education and autonomy are central to treatment decisions and should be considered during medication.

No European registries are specific to thyroid eye disease or Graves' orbitopathy.

Public investment aspect

The development of teprotumumab began as a cancer therapy and was later redirected to TED. The Ludquist Institute conducted research from 1999 to 2010 before their patent was licensed to River Vision Development Corporation, which was founded in 2011, taken over by Horizon Therapeutics in 2017 and acquired by Amgen in 2023.

The basic research was mainly carried out at the University of Michigan, the University of Pisa and the Cedars-Sinai Medical Centre. A total of around 19.3 million dollars in public funding was channelled into development.

Conclusion

Teprotumumab demonstrates significant efficacy in active moderate-to-severe TED, showing marked improvements in proptosis, CAS and quality of life compared to placebo. However, concerns persist regarding the durability of its effects, with reactivation rates between 26–29% in initial studies and even higher rates in subsequent analyses. A further limitation concerns safety, particularly the hearing impairment in 12–15% of patients, which may be irreversible in some cases.

The evidence base is methodologically limited and rated as having low to very low reliability. Beyond the substantial economic uncertainties, implementation challenges must also be considered, including the need for specialised centres, comprehensive monitoring, and potential supply difficulties.

An ongoing phase 3b/4 post-marketing study is investigating the safety and tolerability of various teprotumumab dosing periods. Currently, no completed Health Technology Assessment for teprotumumab in TED is available, though evaluations by both NICE and NIHR are underway. Nevertheless, direct comparisons with standard therapies remain absent. Due to the limitations mentioned, a valid assessment of teprotumumab's value in treating active moderate-to-severe TED is not conclusively possible, and its use should be subject to defined criteria and structured documentation.

1 Medical condition and treatment options

1.1 Disease

Classifications and overview

TED: Autoimmunerkrankung, des retrobulbären Gewebes

Thyroid eye disease (TED) or Graves' orbitopathy (GO) is an autoimmune disease of the retro-ocular tissues that occurs in patients with Graves' disease and, less commonly, in Hashimoto's thyroiditis [1]. This condition can lead to visual disability, permanent disfigurement, and loss of vision, thereby dramatically impacting patients' quality of life (QoL) [2]. TED develops when autoantibodies over-activate the insulin-like growth factor 1 receptor (IGF-1R), triggering proinflammatory cytokines and tissue remodelling in orbital fat and extraocular muscles. IGF-1R overexpression by orbital fibroblasts and immune cells contributes to orbital soft tissue hypertrophy, while disrupted IGF-1 receptor signalling influences disease development [3].

Risiko- & begünstigende Faktoren für TED

There are several risk- and predisposing factors that may increase the risk of TED in patients with Grave's disease, e.g. sex (Grave's eye disease is more common in females than in males), genetic predisposition (HLA B8 on chromosome 6), smoking and radioiodine therapy [1, 2, 4, 5].

Clinical manifestations

3 Schweregrade: mild, moderat-schwer und visusbedrohend

The European Group on Graves' Orbitopathy (EUGOGO) classifies TED into three grades of severity: mild (minimal impact on daily activities), moderate-to-severe (affecting daily life, with ≥2 symptoms: lid retraction ≥2mm, moderate/severe soft tissue involvement, proptosis ≥3mm, or diplopia), and sight-threatening (compressive optic neuropathy and/or corneal breakdown) [5, 6]. The consulted clinical experts reported that diabetic patients are often affected by the moderate-to-severe form [7].

2 Phasen: aktive akute Phase mit Entzündungen & inaktive Phase mit bleibenden Veränderungen

TED progresses through two distinct phases. The initial active inflammatory phase is characterised by acute inflammation with several characteristic symptoms [3]. Following this active phase, the disease transitions into an inactive chronic phase as inflammation subsides. However, permanent changes may persist due to the transformation of inflamed tissue into scar tissue or fatty tissue deposits [3, 4]. The whole process is believed to last 18–24 months in untreated patients [5].

milde Form am häufigsten, bildet sich von selbst zurück

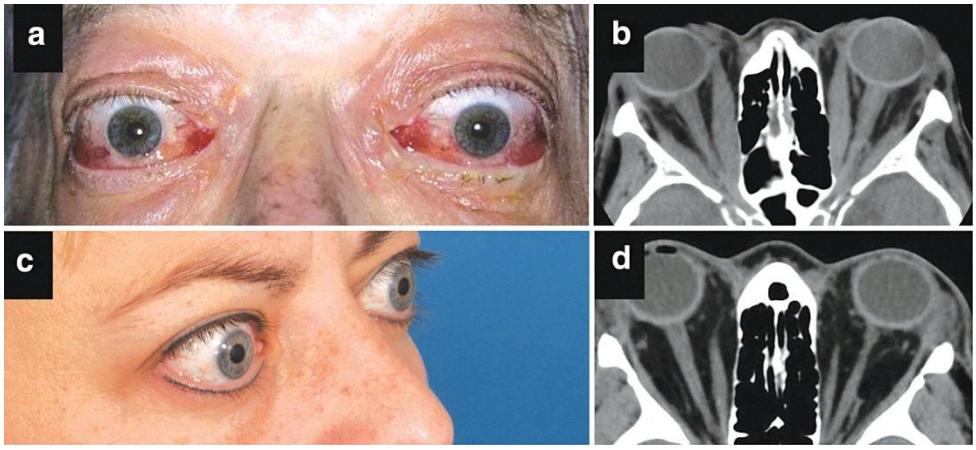
Most TED patients have mild disease that resolves spontaneously. About five percent develop severe complications like compressive optic neuropathy [3]. Prognosis for patients diagnosed after age 50 is worse [8]; and treatment initiated during the early months of the active inflammatory phase is most effective [8].

charakteristische Anzeichen von TED

The characteristic signs of TED include proptosis (exophthalmos), conjunctival inflammation, periorbital oedema and extraocular muscle dysfunction resulting in a dysconjugate gaze. These findings typically occur in the setting of current or past Graves' hyperthyroidism [1], although eye changes can precede Graves' disease [9]. Proptosis severity depends on orbit depth and enlargement of orbital muscles, fibrous and fatty tissue. Periorbital oedema may mask proptosis. Severe cases rarely develop corneal ulceration from overexposure [1, 10].

Significant symptoms include gritty sensation, excessive tearing (worsened by cold air, wind, and bright lights), eye/retro-ocular discomfort, blurred vision, diplopia, colour vision changes and/or periorbital swelling. In severe cases, there is a risk of vision loss [1]. Figure 1-1 shows some of the main symptoms of TED.

Fremdkörpergefühl, überschießende Tränenbildung, Schmerzen, in schweren Fällen Erblindung möglich



Note: extracted and adapted from Burch [11]. (a, b) extraocular muscle enlargement causing periorbital soft tissue congestion, ocular motility restriction, and optic nerve compression with dysthyroid optic neuropathy; (c, d) proptosis in a patient with TED and predominant retroocular fat compartment expansion.

Figure 1-1: Clinical and radiographic image correlations of main symptoms in patients with TED

1.2 Diagnosis

The assessment of disease activity and severity is crucial for determining the appropriate treatment while considering the individual burden of the disease. Within Europe, the clinical activity score (CAS) by Mourits has become the standard tool for evaluating disease activity. At the time of first manifestation, the assessment focuses on subjective and objective signs of activity; disease progression markers are monitored throughout the disease. An active TED is present when ≥3 points on the CAS are observed (for further information, refer to Chapter 1 in the Appendix) [1]. Austrian clinicians confirm the use of CAS as standardised diagnostic tool and add that determining the acute inflammatory phase can be challenging as clinical presentation isn't always definitive [7].

CAS zur Bestimmung der Krankheitsaktivität

The age of onset of TED shows some variation across studies. A median age of 43 years at diagnosis has been reported [8]. Recent evidence suggests TED predominantly manifests in middle adulthood, with a peak incidence between 40 and 65 years [4, 5]. Austrian clinical experts report most patients diagnosed are between 50 and 70 years old [7].

Durchschnittsalter bei Diagnose: 43 Jahre lt. Literatur, 50–70 Jahre lt. Ö klinischen Expert:innen

Additional diagnostic tests for TED include thyroid function tests (thyroxine FT4, TSH), evaluation of Thyrotropin receptor antibodies (TRAbs), and imaging studies. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) for assessing extraocular muscle involvement when optic nerve compression is suspected. Ultrasound can be useful when performed by experienced practitioners [1].

Diagnostik: Schilddrüsenfunktionstest, Bestimmung der Schilddrüsenantikörper, bildgebende Verfahren

Differential diagnoses of TED must be considered, particularly in cases of unilateral exophthalmos. Key differential diagnoses include Carotid-cavernous sinus fistula, tumours (e.g., sphenoid wing meningioma, lymphoma), sinus infections, allergic conjunctivitis and myasthenia gravis (M. gravis) [1].

Differentialdiagnosen: Karotis-Sinus-cavernosus-Fistel, Tumore, Nasennebenhöhlen-infektionen, allerg. Konjunktivitis, Myasthenia gravis

According to the ICD-11 classification system, TED and related conditions are coded as follows [12]: 5A02.0 Thyrotoxicosis with diffuse goitre.

ICD-11: 5A02.0

1.3 Epidemiology

TED represents a relatively rare disease, with reported incidence rates varying by gender – between 0.54 and 0.9 cases per 100,000 per year in men and 2.67 to 3.3 cases per 100,000 per year in women [5]. Most TED cases manifest in a mild form that does not progress to more severe stages [5]. The proportion of patients affected by moderate-to-severe TED is as follows:

Inzidenz Männer: 0,54–0,9 Fälle pro 100.000/Jahr; Inzidenz Frauen: 2,67–3,3 Fälle pro 100.000/Jahr

- A small proportion of patients, approximately 0.161 per 10,000 persons, is newly diagnosed each year with moderate-to-severe TED and need standard therapy [13].
- 20–40% of patients undergoing standard therapy need a second therapy of corticoid [11].

A previous EUGOGO report (2017[3]) indicates a prevalence rate of 0.09% to 0.15% of the total population [14]. It is not explicitly specified whether the mentioned incidence and prevalence rates are based on European countries or represent a more global perspective.

Prävalenz: 0.09–0.15 % der Gesamtbevölkerung

According to the consulted clinicians, approximately 148 new cases per year in Austria require treatment, representing moderate-to-severe TED cases [7]. This is consistent with the reported 150 patients per year in Austria with moderate-to-severe TED, as mentioned by the manufacturer [4]. Due to TED's variable disease duration and highly individual clinical progression, clinicians face difficulties estimating the prevalence rate [7].

Einschätzung Ö: ca. 150 neue moderate-bis-schwere TED-Fälle/Jahr

Notably, over the past three decades, studies have documented a significant decline in the incidence and severity of TED in patients with Graves' disease, as confirmed by recent meta-analyses and meta-regression [5]. This declining trend is particularly important to consider when evaluating older literature and research in this field.

signifikanter Rückgang von Inzidenz und Schwere der TED in den letzten 3 Jahrzehnten

1.4 Treatment guidelines

No specific guideline for moderate-to-severe TED was found for Austria. According to experts, the management of moderate-to-severe TED in Austria is guided by the recommendations of the EUGOGO 2021 clinical practice guidelines for the medical management of Graves' orbitopathy, published by the European Journal of Endocrinology [5]. In addition, there is a consensus statement of the American and European Tyroid Association (ATA and ETA) from 2022 about the management of TED [11].

keine eigene Ö. Leitlinie; lt. Expert:innen Orientierung an EUGOGO-Leitlinie (2021)

[3] The most recent EUGOGO report (2021) does not provide prevalence data.

1.5 Clinical treatment pathways

General recommendations

Übersicht der allgemeinen Behandlungsempfehlungen für TED gemäß der EUGOGO-Leitlinie (2021)

The EUGOGO guideline (2021) provides several evidence-based recommendations for the treatment of TED [5]. In general, treatment decisions are based on clinical activity, severity and duration of TED. The EUGOGO recommends the following:

- CAS is the best validated scoring system and should be used for assessing activity.
- TED should be classified using EUGOGO criteria (mild, moderate-to-severe, sight-threatening) and should include GO-QoL questionnaire.
- Patients should be referred to specialised centres providing both endocrine and ophthalmic expertise.
- Patients should be informed about smoking risks and advise cessation.
- Rapid correction of hyperthyroidism caused by Graves' disease with antithyroid drugs (ATD) and stable maintenance of euthyroidism is beneficial for TED and, therefore, strongly recommended.
- Careful monitoring of thyroid levels is essential to prevent iatrogenic hypothyroidism.
- Oral glucocorticoid prophylaxis is recommended for patients undergoing RAI therapy for Graves' hyperthyroidism.
- Application of local treatments such as artificial tears, gels and ointments is advised, with possible lid taping at night.
- Botulinum toxin injection in the levator muscle may reduce the palpebral aperture.
- A watchful approach with local treatments is typically sufficient for mild GO as spontaneous resolution often occurs [5].

First- and second-line treatment for moderate-to-severe TED

Behandlung erfolgt schrittweise basierend auf Krankheitsaktivität & individuellem Pat.-Ansprechen

Erstlinienbehandlung in Ö: Methylprednisolon-Monotherapie

direkter Übergang in inaktive Phase: Operation nach Bedarf

For the management of moderate-to-severe TED, both first-line treatments and second-line approaches are available as outlined in the EUGOGO guidelines. The approach follows a stepwise protocol with decisions based on disease activity and individual patient response [5].

For active TED, first-line treatment in Austria currently involves methylprednisolone monotherapy [7]. However, the EUGOGO guidelines recommend either combination therapy of methylprednisolone with mycophenolate or a higher dose of methylprednisolone alone. The opinions on the new recommended combination therapy are divided, as some experts have concerns about possible complications due to increased immunosuppression [7]. Treatment response is regularly monitored, and therapy is continued or adjusted accordingly. If the disease progresses directly to an inactive status, surgery can be performed as needed or required by the patient [5].

If patients show inadequate response to first-line therapy, treatment advances to second-line options. In Austria, the preferred second-line treatment is higher-dose methylprednisolone. Teprotumumab would also be considered as a second-line treatment option if available. Rituximab (off-label) is only used when the second cycle of methylprednisolone or the treatment with teprotumumab proves ineffective. Orbital decompression and orbital radiotherapy are used in specific clinical scenarios. In particular, orbital decompression is implemented for TED patients experiencing deterioration in visual acuity. While the EUGOGO guidelines also recommend tocilizumab, and prednisone/prednisolone combined with cyclosporin/azathioprine, these approaches are not commonly used in Austria [7].

Zweitlinienbehandlung in Ö: höher dosiertes Methylprednisolon; Teprotumumab wird erwogen, falls verfügbar

According to the ETA/ATA consensus paper [11], teprotumumab is recommendet as preferred option for patients with active, moderate-to-severe TED and significant propthosis.

Konsensuspapier der ETA/ATA: Teprotumumab bevorzugte Therapie für acitve, moderate bis schwere TED bei signifikanter Proptose

Once the disease progresses to an inactive status (directly or after first- or second-line treatment), rehabilitative surgery or orbital radiotherapy is recommended as needed or requested by the patient [5]. These treatment options are presented in Figure 1-2 in more detail.

inaktive Phase: rehabilitative Chirurgie oder orbitale Strahlentherapie werden nach Bedarf empfohlen

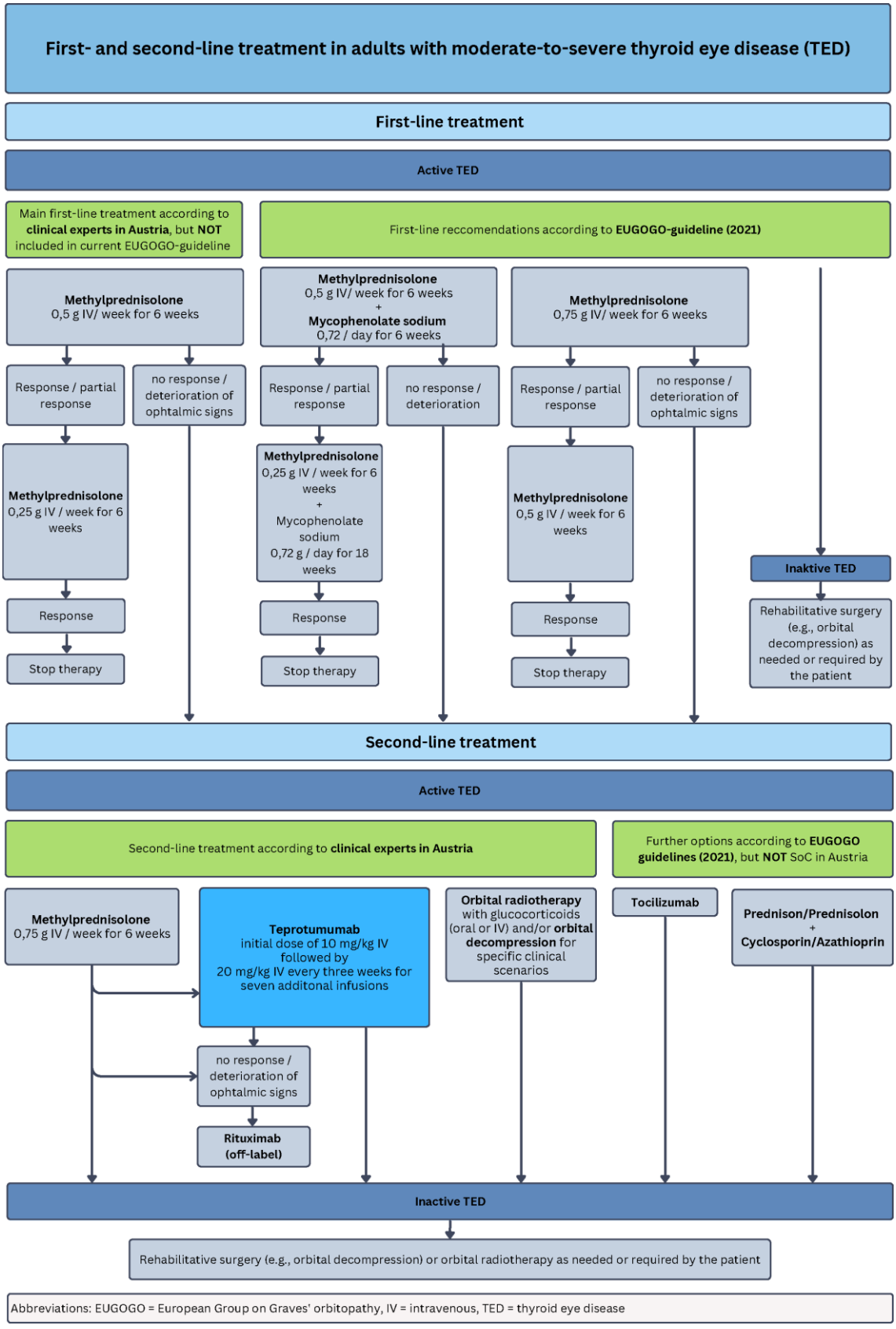


Figure 1-2: First- and second-line treatment in adults for moderate-to-severe TED

2 Medicinal product under review

2.1 Drug description

The medicinal product under evaluation in this health technology assessment (HTA) is teprotumumab (TEPEZZA®), a first-in-class, causal treatment option for patients with TED [4]. Table 2-1 summarises the most important information of this product.

HTA-Bericht zu Teprotumumab (TEPEZZA®): monoklonaler Antikörper

Table 2-1: Characteristics of the medicinal product

INN	Teprotumumab
Product name	TEPEZZA®
Active substance(s)	teprotumumab
ATC Code	L04AG13
Pharmacologic class	Monoclonal antibody
Manufacturer/MAH	Amgen

Abbreviations: ATC … Anatomical Therapeutic Chemical, INN … International non-proprietary name, MAH … marketing authorisation holder

The mechanism of action of teprotumumab in patients with TED has not been fully characterised. Teprotumumab is a fully human IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO-DG44) cells; it binds to insulin-like growth factor 1 receptor (IGF-1R) and blocks its activation and signalling [15].

Wirkmechanismus: monoklonaler Antikörper blockiert IGF-1-Rezeptor

2.2 Regulatory status

Regarding the European regulatory status, teprotumumab is currently undergoing the European Medicines Agency (EMA) approval process. The manufacturer submitted the application on 25 April 2024, with expected European Commission authorisation in July 2025. The planned indication is "Treatment of patients with moderate-to-severe thyroid eye disease" [4]. At the time of completion of the report, there has been no positive recommendation from the Committee for Human Medicinal Products (CHMP) or granting of marketing authorisation for teprotumumab in the EU. Table 2-2 provides EMA regulatory information on teprotumumab.

Antrag auf EMA-Zulassung vom Hersteller eingereicht (April 2024)

In the United States, the FDA approved TEPEZZA® (teprotumumab-trbw) on 21 January 2020 for the treatment of TED. The FDA granted this application Priority Review, Fast Track- and Breakthrough Therapy Designation. Additionally, teprotumumab-trbw received Orphan Drug designation [15]. Notably, the label information published at the same time, as well as all later published label information documents, does not include an age restriction [15].

FDA-Zulassung seit 2020, Unklarheit bezüglich Altersangabe

In March 2024, Amgen expanded its regulatory submissions globally. The company submitted a Marketing Authorisation Application to the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain, a New Drug Submission to Health Canada, and an application to the Therapeutic

weitere Zulassungen beantragt (GB, Kanada, Australien, Japan)

Goods Administration (TGA) in Australia. Teprotumumab is also under review by the Ministry of Health, Labour and Welfare (MHLW) in Japan [16].

Table 2-2: EMA regulatory information on TEPEZZA®

Orphan medicinal product	No
Conditional marketing authorisation	No
Specific obligations of the conditional Marketing Authorisation	No
Additional monitoring	No
Accelerated approval	No
Exceptional circumstances	No
ATMP	No
PRIME	No
First approved indication	Not approved
Details of ongoing early access programs in the EU (as provided by the MAH)[a]	Early Access programs or Named Patient Programme are not provided in Austria (Status February 2025)

Abbreviations: ATMP … Advanced Therapy Medicinal Product, EU … European Union, MAH … Marketing Authorisation Holder, PRIME … Priority Medicines

Notes: [a] further detail on ongoing early access programs from unpublished information from the manufacturer

2.3 Posology[4]

Teprotumumab is administered as an intravenous (IV) infusion; the recommended dose is 10mg/kg for the initial dose, followed by an IV infusion of 20mg/kg every three weeks for seven additional infusions. The diluted solution should be administered intravenously in a clinical setting over 90 minutes for the first two infusions. If this is tolerated well, the minimum time for subsequent infusions can be reduced to 60 minutes [15]. According to clinicians, an extended hospital stay for administration is not expected [7].

insgesamt 8 intravenöse Infusionen, alle 3 Wochen

Use in specific populations

The safety and effectiveness of teprotumumab have not been established in pregnant women and paediatric patients. No overall difference was observed between patients older than 65 years and younger patients [15].

keine Daten zur Anwendung bei Schwangeren & Kindern

Requirements for companion diagnostics and/or monitoring

Patients treated with teprotumumab should be monitored for the following:

- infusion-related reactions (occur in approximately 4% of patients)
- exacerbation of pre-existing inflammatory bowel disease (IBD)
- hyperglycaemia or increased blood glucose
- hearing impairment/hearing loss (hearing should be assessed before, during, and after treatment with teprotumumab) [15].

Monitoring von: Infusionsreaktionen, möglicher Exazerbation entzündlicher Darmerkrankungen, Blutglukose & Hörfunktion

[4] Since there is no EMA EPAR available, this chapter refers to the FDA label information.

3 Scope of assessment

3.1 Research question

The following research questions will be answered in the present report:

1. **Clinical domain:**
   In adult and elderly patients with active moderate-to-severe thyroid eye disease (TED), is teprotumumab more effective and safer compared to current standard treatment regarding patient-relevant outcomes?
2. **Non-clinical domains:**
   What are the economic, ethical, organisational and social consequences of implementing teprotumumab into the Austrian healthcare system? What were the key contributions of publicly funded research institutions and private companies in discovering and developing teprotumumab as a therapy for TED, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

Fragestellungen

klinische Domäne: Wirksamkeit von Teprotumumab vs. Standardtherapie bei Pat. mit moderater-schwerer TED zu pat.- und systemrelevanten Endpunkten

nicht-klinische Domänen: ökonomisch, ethisch, organisatorisch, sozial & Entwicklungskosten

The assessment's focus was deliberately limited to patients with active moderate-to-severe TED based on input from Austrian clinical experts who emphasised that this represents the most relevant clinical scenario in local practice. While teprotumumab has demonstrated efficacy in chronic TED patients in clinical studies, our research questions were specifically tailored to the Austrian healthcare context, which may not necessarily align with the broader indication in regulatory approvals. The methodological decision to concentrate on active disease therefore provides decision-makers with evidence that is most relevant to current Austrian clinical practice patterns.

aktive moderate-bis-schwere TED als primäres Szenario durch klinische Expert:innen in Österreich identifiziert → Fokus des HTA auf aktive Phase der TED

3.2 Inclusion criteria

Inclusion criteria for relevant clinical studies are summarised in Table 3-1.

Regarding the non-clinical domains, relevant literature for the economic domain was included with information about teprotumumab prices and drug costs, as well as health economic evaluations. Relevant literature for the ethical, social and domain aspect on public investment, including information on public grants, funding and contributions, was included.

Einschlusskriterien für relevante klinische Studien

Einschlusskriterien für Literatur zu nicht-klinischen Aspekten

Table 3-1: Assessment scope including the PICO question for the clinical domain

Description of PICO elements	PICO
P	Adult and elderly patients with active moderate-to-severe[5] thyroid eye disease (TED)
I	Teprotumumab (TEPEZZA®, Amgen)
C	1st line treatment of moderate-to-severe and active TED: Monotherapy of methylprednisolone IV Methylprednisolone IV in combination with oral mycophenolate sodium or mycophenolate mofetil 2nd line treatment of moderate-to-severe and active TED: Methylprednisolone IV (second course) Rituximab (off-label) Non-pharmaceutical interventions: Surgeries, e.g. orbital decompression Orbital radiotherapy
O	Efficacy: ■ Proptosis response ■ Overall response ■ CAS ■ Mean change in proptosis ■ Diplopia response Durability of the effect: ■ Reactivation of TED PROs: e.g. QoL Safety: ■ AEs ■ AEs of special interest ■ SAEs
Studies	Effectiveness and safety: randomised controlled trials, non-randomised controlled trials and observational and single-arm studies (n≥40)
Languages	English and German

Abbreviations: AE … adverse event, CAS … Clinical activity score, IV … intravenous, QoL … quality-of-life, PICO … population-intervention-comparator-outcome, PRO … patient-reported outcomes, SAE … serious adverse event, TED … thyroid eye disease

Notes: outcomes in bold *indicate critical efficacy and safety endpoints based on clinical expert consultation.*

[5] According to the 2021 European Group on Grave's orbitopathy (EUGOGO) guideline.

4 Methods

The methods section of this report outlines a comprehensive approach across multiple domains. This report was conducted between January 29th 2025 and April 16th 2025.

Multi-Methoden-Ansatz; Bericht zwischen 29.01. und 16.04.2025 erstellt

Systematic literature search and study selection

A systematic literature search was conducted on February 4, 2025, across four databases: Medline via Ovid, Embase, The Cochrane Library, and INAHTA. The search was limited to English and German sources, excluding conference abstracts (see detailed search strategies in Chapter 4 in the Appendix). After deduplication, 532 citations were identified. Additional searches in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielded 32 potentially relevant hits. The manufacturer also submitted a dossier on February 20, 2025, though no new citations were identified from this source. Overall, the data cut-off for this report was February 21 2025, when the manufacturer sent the dossier.

1 systematische Literatursuche in vier Datenbanken: 532 Treffer

& Suche nach laufenden Studien

Daten Cut-off: 21.02.2025

The study selection process followed a structured approach where one researcher initially screened references at the abstract level, with a second reviewer checking included abstracts and those with uncertainty. Full texts were screened independently, with third-researcher arbitration when disagreements occurred. Four studies and the manufacturer dossier were ultimately included for clinical qualitative synthesis, along with five additional references for non-clinical domains. The study selection process is presented in the form of a PRISMA flow diagram in Chapter 4 in the Appendix.

Literaturauswahl:

klinische Domäne (n=4)

nicht-klinische Domäne (n=5)

Clinical effectiveness and safety assessment

For clinical effectiveness and safety assessment, the study quality was evaluated using different tools based on study design:

- Randomised controlled trials were assessed with the Cochrane Risk of Bias 2 tool
- Single-arm case series were evaluated with the Institute of Health Economics (IHE) checklist
- Risk of bias appraisal was conducted in duplicate with consensus resolution

Bewertung der Studienqualität im 4-Augenprinzip mit verschiedenen Tools abhängig vom Studiendesign

Data extraction was systematically performed by one reviewer and cross-checked by a second reviewer. An indirect treatment comparison (ITC) was critically reviewed using the ISPOR Guideline 2011 [17] and the PRISMA extension statement [18].

ITC bewertet nach ISPOR Guideline & PRISMA Statement

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scheme for each critical endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [19].

GRADE Framework für Einschätzung der Vertrauenswürdigkeit der Evidenz

Economic evaluation methods

Price information was collected by the Austrian National Public Health Institute (GÖG) and through a survey of the Pharmaceutical Pricing and Reimbursement Initiative (PPRI) network.

Preis-Infos von GÖG & zusätzlich Umfrage im PPRI-Netzwerk

The budget impact analysis incorporated several approaches (see detailed description in Chapter 4 in the Appendix):

- A placeholder price of €13,662.59 per 500mg powder was established for budget impact analysis (BIA) based on converted US pricing.
- Patient population estimates were derived from published epidemiological data and Austrian clinical expert input.
- Cost calculations incorporated outpatient sector prices from the Austrian refund code (Erstattungskodex, EKO) and inpatient treatment costs from DRG data (Leistungsorientierte Krankenanstaltenfinanzierung, LKF).
- According to the implementing regulation §4 (2), a three-year budget impact analysis included gross drug budget impact, net drug budget impact (including cost offsets), and additional costs related to administration.
- The analysis presents an optimistic scenario where teprotumumab potentially eliminates the need for further treatments, e.g. rituximab (off label) or surgical interventions. Minor cost categories and additional treatments were excluded from the analysis.

Platzhalter-Preis Teprotumumab: € 13.662,59 pro 500 mg Pulver

Pat.-Populationen basierend auf Expert:innen-Einschätzungen & publizierten Inzidenzzahlen; Unit Costs: EKO- und LKF-Daten

optimistisches Szenario präsentiert

We also screened the literature identified through systematic and additional manual searches via Google to identify existing economic evaluations of teprotumumab. However, no published economic evaluation has been identified.

keine publizierten ökonomischen Evaluationen

Organisational, ethical, and social assessment

The assessment of organisational, ethical and social aspects utilised the European Network for Health Technology Assessment (EUnetHTA) Core Model®. Data was gathered from three sources:

nach dem EUnetHTA CoreModel® 3 Quellen:

- Structured patient questionnaires (completed by four female patients and one carer with moderate-to-severe TED, see Chapter 4 in the Appendix for details).
- Expert consultations with three leading clinicians (see Chapter 4 in the Appendix).
- Systematic literature review findings.

Expert:innen-Konsultationen, schriftliche Patient:innen-Befragungen & Literaturquellen

Development costs and public contributions

The methodology for assessing development costs and public contributions involved several steps (see Chapter 4 in the Appendix for details):

- Identifying product origins through searches for generic/ non-proprietary names and trade names.
- Searching for earliest references to identify basic research and developement support and research grants.
- Exploring databases on clinical trials and research funding.
- Examining company websites for information on funding rounds, sponsors, mergers, and acquisitions.

Identifizierung von: generischer oder (nicht) geschützter Bezeichnungen

Produktherkunft & Grundlagenforschung

Finanzierungsrunden, Fusionen & Übernahmen

- Reviewing business news sources for additional information.

In addition, a landscape overview of therapies under development for TED was compiled using the International Horizon Scanning Initiative (IHSI) database.

zusätzlicher Überblick zu TED-Therapien in Entwicklung

5 Clinical effectiveness and safety

5.1 Characteristics of included studies

Three clinical phase 3 studies [20-22] and one cohort study [23] were identified for the clinical and safety assessment. Two of the four studies were randomised, double-masked, placebo-controlled multicentre studies, one from the USA and Europe (OPTIC) [20] and one from Japan (OPTIC-J) [22]. The third study was an open-label extension of the OPTIC study (OPTIC-X) [21], and the fourth study by Chen et al. was a single-centre longitudinal cohort study from the USA investigating reactivation of TED after initial teprotumumab therapy [23]. In the interventional studies, the patients with thyroid eye disease (TED) received intravenous infusions of either teprotumumab (10mg per kilogram of body weight for the first infusion and 20mg per kilogram for subsequent infusions) or placebo once every three weeks for 21 weeks for a total of eight infusions [20-22]. In the study by Chen et al., the observed patients received the same dosing regimen of teprotumumab [23]. See details in Table 5-1.

Evidenzbasis:
3 klinische Phase-3-Studien (OPTIC, OPTIC-J, OPTIC-X) + 1 Kohortenstudie – einheitliches Dosierungsschema von Teprotumumab über 21 Wochen

Table 5-1: Characteristics of included studies

Reference / ID	Study type and design	Study population	Study arms	Study duration, data cut off(s) and locations	Study endpoints	Available documentation
OPTIC [19]	Randomised, double-masked, placebo-controlled, phase 3 multicentre trial	Patients 18 to 80 years of age, with a diagnosis of Graves' disease, and active, moderate-to-severe thyroid eye disease.	■ Teprotumumab group (N = 41) ■ Placebo group (N = 42)	Study duration: 24 weeks with a total follow-up of 72 weeks. Completiondate: 30/11 2020 Data cut-off:unknown Numberofcentresby continent: 13 (United States and Europe)	Primary endpoint: 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. Key secondary outcomes: An overall response (defined as a reduction of ≥2 points in the clinical activity score plus a reduction in proptosis of ≥2 mm without a corresponding increase [of ≥2 points or ≥2 mm] in the fellow eye) at week 24. Clinical activity score (CAS) of 0 or 1 at week 24. Mean change in proptosis from baseline through week 24. Diplopia response (defined as a reduction in diplopia of ≥1 grade from baseline) at week 24. Mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QoL) questionnaire from baseline through week 24.	CSR:not provided Registry entry[a]: NCT03298867 Sponsoring status: sponsored
OPTIC-X [20]	Single-arm open-label clinical extension of the OPTIC study	Proptosis non-responder (<2 mm reduction in proptosis in the study eye) at week 24 of OPTIC OR proptosis responder at week 24 who flares during the follow-up period of study OPTIC.	■ 1st course OPTIC Placebo (N = 37) ■ 2nd course/ Retreatment OPTIC Teprotumumab (N = 14)	Study duration: 24 weeks with a total follow-up of 72 weeks. Completiondate: 17/02 2021 Data cut-off:unknown Numberofcentresby continent: 12 (United States and Europe)	Primary endpoint: proptosis responder rate at week 24 from entry into this trial. Secondary efficacy endpoints: Percentage of patients with a CAS of 0 or 1 at week 24. Mean change to week 24 in proptosis. Diplopia responder rate. Mean change to week 24 in GO-QoL questionnaire aggregate score. Exploratory endpoints: Overall responder rate (reduction of ≥2 points in the CAS and reduction in proptosis of ≥2 mm). Mean change to week 24 in the GO-QoL questionnaire visual functioning and appearance subscale scores.	CSR:not provided Registry entry[a]: NCT03461211 Sponsoring status: sponsored
OPTIC-J [21]	Randomised, double-masked, placebo-controlled trial	Age 20–80 years; Patients with Graves' disease and a moderate-to-severe TED.	■ Teprotumumab group (N = 27) ■ Placebo group (N = 27)	Study duration: 24 weeks with additional follow-up of 30 days. Completion date: 11/2023 Data cut-off: unknown Numberofcentresby continent: 1 (Japan)	Primary Endpoint: Proptosis responder rate at week 24 (defined as the percentage of patients with ≥2mm reduction from baseline in proptosis in the study eye, without deterioration [≥2mm increase] of proptosis in fellow eye). Key secondary endpoints: Overall responder rate (≥2-point CAS reduction AND ≥2mm proptosis reduction). CAS categorical response (percentage with CAS ≤1). Change from baseline in proptosis measurement. Diplopia responder rate (percentage with ≥1 grade improvement). Complete diplopia responder rate (percentage achieving score of 0). Change in GO-QoL overall score. Change in GO-QoL visual function and appearance subscale scores.	CSR:not provided Registry entry[b]: jRCT2031210453 Sponsoring status: sponsored

Reference / ID	Study type and design	Study population	Study arms	Study duration, data cut off(s) and locations	Study endpoints	Available documentation
OPTIC-J [21] *(cont.)*					Exploratory Endpoints: MRI assessments of: orbital fat/muscle volumes, inflammation/oedema, ocular motility changes. Safety Endpoints: Adverse events Laboratory evaluations Vital signs Visual acuity assessments	
Chen et al. [22]	Single-centre longitudinal cohort study	Patients with active TED treated with teprotumumab (age 24–81 years)	■ Patients with active TED (N = 42)	Study duration: 32 months (mean duration of follow-up 14 months) Completion date: 08/2023 Data cut off: Unknown Number of centres by continent: 1 (USA)	Reactivation of TED after initial teprotumumab therapy. The treatment response of second course of teprotumumab therapy vs IV steroids. Changes in proptosis measurements. Changes in CAS. Diplopia assessment. Response to second course of teprotumumab vs. IV steroids in reactivated cases.	CSR: not applicable Registry entry: not applicable Sponsoring status: sponsored

Abbreviations: CAS: clinical activity score, CSR … clinical study report, GO-QoL … Graves' Ophthalmopathy Quality of Life, MRI … magnetic resonance imaging, N … number of included patients, NCT … national clinical trial, IV … intravenous, TED … thyroid eye disease

Notes:

[a] *Study registry entry, number (NCT-Number, EudraCT-Number),*

[b] *Japan Registry for Clinical Trials*

5.1.1 Study population

Inclusion criteria

Einschlussktiterien

OPTIC trial [20]

- Male and female patients aged 18–80 years.
- Ocular symptoms onset within nine months before baseline and a CAS of at least 4 in the affected eye.

OPTIC:
Pat. 18–80 J., aktive moderate-schwere TED (CAS ≥4), Symptombeginn <9 Mo.

OPTIC-X trial [21]

- Patients who did not achieve adequate proptosis reduction during the initial OPTIC trial.
- Patients who initially had successful proptosis reduction but experienced a relapse during the follow-up period in the OPTIC trial.

OPTIC-X:
Nachbehandlung bei unzureichender Exophthalmusreduktion/ Rezidiv

OPTIC-J trial [22]

- Japanese male and female patients aged 20–80 years.
- Disease onset within seven months before screening and a CAS of at least 3, a slightly different threshold than the OPTIC study.

OPTIC-J:
japanische Population, 20–80 J., Krankheitsbeginn <7 Mo., CAS ≥3

Chen et al. [23]

- Patients who received initial teprotumumab treatment for active TED.

Chen-Studie:
Erstbehandlung mit Teprotumumab bei aktiver TED

Exclusion criteria

Ausschlusskriterien

OPTIC trial [20]

- Prior orbital treatments for TED and recent optic nerve complications.
- Previous use of specific biologics, glucocorticoid therapy.
- Specific medical conditions.

OPTIC:
vorherige Orbita-Behandlungen, Nervus-opticus-Komplikationen, Biologika-Vorbehandlung, Glukokortikoid-Therapie

OPTIC-X trial [21]

- Based on OPTIC criteria; no TED treatment between trials.
- Modified stability requirements, simplified medication restrictions.

OPTIC-X:
neue Stabilitätskriterien und vereinfachten Medikationsrichtlinien

OPTIC-J trial [22]

- Based on OPTIC criteria with lenient prior treatment restrictions.
- Different laboratory thresholds.

OPTIC-J:
weniger strenge Vorbehandlungs-Restriktionen, andere Laborwerte

Chen et al. [23]

- Incomplete teprotumumab dosing, lack of initial response, follow-up <6 months

Chen-Studie:
Ausschluss bei unvollständiger Dosierung, fehlendem Ansprechen oder Follow-up <6 Mo.

The in- and exclusion criteria of the OPTIC-related trials are depicted in Chapter 5 in the Appendix in more detail.

5.1.2 Baseline characteristics

The baseline characteristics varied across the four included studies (see Table 5-2). While the mean follow-up was not reported in the OPTIC, OPTIC-X, and OPTIC-J study, the mean follow-up duration was 14 (SD±7) months in the Chen et al. study [20-23]. For more detailed information, see Chapter 5 in the Appendix.

Baseline-Unterschiede & versch. Follow-up Zeiträume

Table 5-2: Baseline demographics of participants in the included studies

Characteristic	OPTIC [20]		OPTIC-X [21]		OPTIC-J [22]		Chen et al. [23]
Parameter	Teprotumumab (N=41)	Placebo (N=42)	1st Course (OPTIC Placebo) (N=37)	2nd Course/Retreatment (OPTIC Teprotumumab) (N=14)	Teprotumumab (N=27)	Placebo (N=27)	Teprotumumab retreatment (N=42)
Age [years], mean (SD)	51.6±12.6	48.9±13.0	48.5 (13.5)	56.1 (11.5)	46.6 (14.2)	50.0 (13.4)	56 (13)
Sex, n (%)							
Female	29 (71)	31 (74)	27 (73.0)	11 (78.6)	18 (67)	20 (74)	-
Male	12 (29)	11 (26)	10 (27.0)	3 (21.4)	9 (33)	7 (26)	-
Race, n (%)							
White	35 (85)	37 (88)	33 (89.2)	11 (78.6)	-	-	-
Black	4 (10)	2 (5)	1 (2.7)	1 (7.1)	-	-	-
Asian	2 (5)	1 (2)	1 (2.7)	2 (14.3)	-	-	-
Japanese	-	-	-	-	27 (100)	27 (100)	-
Other	0	2 (5)	2 (5.4)	0	-	-	-
Duration of Disease							
Duration of thyroid eye disease (TED) [months]	6.2±2.3[a]	6.4±2.4[a]	12.9 (7.01-15.86)[b]	16.5 (8.52-22.50)[b]	4.24 (1.94-6.83)[b]	5.22 (3.02-6.80)[b]	13 (11)[a]
Duration of Graves' disease [years]	3.5±6.1[a]	2.2±3.2[a]	1.4 (0.98-15.29)[b]	1.7 (0.79-28.78)[b]	-	-	-
Smoking Status, n (%)							
Non-smoker	32 (78)	34 (81)	29 (78.4)	11 (78.6)	10 (37)	11 (41)	-
Current smoker	9 (22)	8 (19)	8 (21.6)	3 (21.4)	4 (15)	4 (15)	-
Former smoker	-	-	-	-	13 (48)	12 (44)	-
Clinical Measures (SD)							
Proptosis measurement [mm], mean	22.62±3.32	23.20±3.21	23.0±3.1	21.0±4.2	21.07 (2.46)	20.39 (2.42)	-
Clinical activity score (CAS), mean	5.1±0.9	5.3±1.0	3.6±1.7	3.5±1.6	4.5 (1.3)	4.0 (0.8)	-
Thyroid Hormone Levels							
Free triiodothyronine (FT3) [pmol/L], mean (SD)	5.1±1.8	5.3±1.7	5.0±1.0	4.7±0.8	4.60 (4.00-5.20)[c]	4.90 (3.80-5.50)[c]	-
Free thyroxine (FT4) [pmol/L], mean (SD)	16.5±5.3	16.2±4.8	16.0±3.8	16.5±3.2	15.40 (12.90-16.70)[c]	14.20 (12.90-16.70)[c]	-
Thyrotropin (TSH) [mIU/L], mean (SD)	1.75±4.16	1.42±2.17	2.6±1.54	2.47±2.46	0.43 (0.01-2.81)[c]	0.77 (0.04-2.82)[c]	-

Abbreviations: CAS … clinical activity score, FT3 … free triiodothyronine, FT4 … free thyroxine, SD … standard deviation, TED … thyroid eye disease, TSH … thyroid stimulating hormone.

Note: [a] mean, [b] median, [c] median interquartile range

5.1.3 Sample size

The four teprotumumab studies demonstrated varying completion rates and discontinuation patterns (Table 5-3). In general, the number of withdrawn/dropout was low across all studies. For more detailed information, see flowcharts in Chapter 5 in the Appendix for the OPTIC [20], OPTIC-X [21, 22] and OPTIC-J [22] study. The study by Chen et al. was retrospective. Thus, no flowchart exists for it [23].

Unterschiede in Studienabbrüchen und -abschlüssen

Table 5-3: Distribution of patients of the included studies

Parameter	OPTIC [20]		OPTIC-X [21]		OPTIC-J [22]		Chen et al. [23]
	Teprotumumab	Placebo	First time teprotumumab	Retreatment	Teprotumumab	Placebo	Teprotumumab retreatment
Number Screened	107		40	15	64		66
Number Randomised	41	42	37	14	27	27	42
Number Witdrawn/Dropout (%)	2 (4.9)	2 (4.8)	1 (2.7)	2 (14.3)	1 (3.7)	1 (3.7)	N/A
Number for Efficacy Analysis (%)	41(100)	42 (100)	37 (100)	13 (92.9)	27 (100)	27 (100)	N/A
Number for Safety Analysis (%)	41 (100)	42 (100)	37 (100)	14 (100)	27 (100)	27 (100)	N/A
Duration of Follow-up	72 wk		72 wk		24 wk		32 mo

Abbreviations: mo … months; N/A … not available; wk … weeks

5.1.4 Outcomes

For the purpose of this HTA , four studies investigated teprotumumab treatment in active, moderate-to-severe TED werde considered: three clinical trials (OPTIC [20], OPTIC-X [21], and OPTIC-J [22]) evaluated initial treatment efficacy or retreatment in case of the OPTIC-X, while Chen et al. [23] investigated disease reactivation and retreatment outcomes.

OPTIC, OPTIC-X und OPTIC-J: Wirksamkeit der Erstbehandlung; Chen-Studie: Reaktivierung von TED und Wiederbehandlung

In this section, all outcomes defined as critical for evaluating clinical efficacy and safety are marked in **bold**.

Definitions and reporting of critical and important efficacy outcomes

Proptosis response: In the studies, the proptosis response was defined as a reduction in proptosis of ≥2mm from baseline in the study eye without a corresponding increase of ≥2mm in the fellow eye at week 24. The most severely affected eye was defined as the "study eye" at the baseline. Proptosis was measured using a Hertel exophthalmometer provided by the Sponsor to ensure consistency. The same Hertel instrument and observer were used throughout the study duration to maintain measurement reliability, except when strictly unavoidable. The same intercanthal distance (ICD) was maintained for all measurements. Observers were given instructions for the measurement of proptosis. This endpoint was measured in the OPTIC, OPTIC-X, and OPTIC-J trials.

Exophthalmus-Ansprechrate: Reduktion ≥2 mm im Studien-Auge ohne Verschlechterung des anderen Auges, standardisierte Messung mittels Hertel-Exophthalmometer über gesamte Studiendauer

Clinical activity score (CAS) response: The CAS was completed at screening, day 1, and weeks 6, 12, 18, and 24 during the treatment period and at weeks 28, 36, 48, 60, and 72 during the follow-up period using the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS [24]. 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). A CAS Score of 0 or 1 indicates no or minimal inflammation. A change of at least two points is considered clinically meaningful [25]. This endpoint was measured in the OPTIC, OPTIC-X, and OPTIC-J trials. Chen et al. only documented the mean CAS in patients with TED reactivation.

klinischer Aktivitäts-Score: 7-Punkte-EUGOGO-Score zur Entzündungsaktivität (0-7), klinisch relevant ab 2-Punkte-Änderung

Messung in allen Studien, bei Chen-Studie nur bei TED-Reaktivierung

Reactivation of TED: Based on the OPTIC-X study [21], the reactivated TED was defined as an increase in proptosis in the study eye of ≥2mm, an increase in CAS of ≥2 points or more with a total CAS score of ≥4 or more in the study eye, or both. This endpoint was measured in the studies of OPTIC and Chen et al.

Reaktivierung der TED: Exophthalmus-Zunahme & CAS-Anstieg untersucht in OPTIC und Chen-Studie

Quality-of-Life Assessment: The GO-QoL is a 16-item self-administered questionnaire divided into two subsets and used to assess the perceived effects of TED by the subjects on their daily physical activity as it relates to visual function and psychosocial functioning [26]. This endpoint was measured in the OPTIC, OPTIC-X, and OPTIC-J trials.

GO-QoL-Fragebogen: 16 Items, 2 Untergruppen, Endpunkt in den OPTIC-Studien gemessen

Changes in proptosis: The mean change in proptosis was measured from baseline to week 24 in OPTIC, OPTIC-X, and OPTIC-J trials. Chen et al. documented the mean change in proptosis in patients with TED reactivation.

Exophthalmus-Veränderung: mittlere Änderung nach 24 Wochen

Diplopia: Changes in diplopia grade were assessed with the use of the Gorman subjective diplopia score (range 0 to 3), which includes four categories: no diplopia (absent, scored as 0), diplopia in the primary position of gaze when the patient is tired or awakening (intermittent, scored as 1), diplopia at extremes of gaze (inconstant, scored as 2), and continuous diplopia in the primary or reading position (constant, scored as 3). A reduction of at least one grade was considered clinically meaningful [25]. This endpoint was measured in the OPTIC, OPTIC-X, and OPTIC-J trials. Chen et al. documented the diplopia score in patients with TED reactivation.

Diplopie: Gorman-Score (0–3), klinisch relevant ab 1-Grad-Reduktion; in OPTIC-Studien vollständig erfasst, bei Chen nur bei TED-Reaktivierung

Overall response: The overall response, a composite endpoint, was defined in both OPTIC and OPTIC-J studies [20, 22] as a ≥2-point reduction in CAS from baseline and ≥2mm reduction in proptosis from baseline. Additionally, there must be no corresponding deterioration in the fellow eye, specifically, no ≥2-point increase in CAS in the fellow eye and no ≥2mm increase in proptosis in the fellow eye. This endpoint was measured in the OPTIC, OPTIC-X, and OPTIC-J trials.

Gesamtansprechrate: CAS-Reduktion ≥2 Punkte + Exophthalmus-Reduktion ≥2 mm ohne Verschlechterung des anderen Auges, in allen OPTIC-Studien

Definitions and reporting of critical and important safety outcomes

The safety profile of teprotumumab was actively investigated in the OPTIC, OPTIC-X, and OPTIC-J studies, which reported adverse events, including serious adverse events. The study by Chen et al. reported the adverse events only superficially, not specifying any grades.

Sicherheit von Teprotumumab in allen Studien jedoch in Chen-Studie nur oberflächlich

Adverse events (AEs) and **serious adverse events (SAEs):** Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Pre-existing conditions that worsened during a study were to be reported as AEs.

unerwünschte Ereignisse (UE) nach CTCAE

Adverse events of special interest (AESIs): In the OPTIC study [20], the following AESIs were measured: infusion reactions (e.g., nausea, vomiting, facial flushing, warmth, dyspnoea, dizziness, hypertension, hypotension, pruritus), hyperglycaemia, muscle spasms, and diarrhoea. In the OPTIC-J study [22], the AESIs included infusion-related reactions, hyperglycaemia, hearing impairment, new onset inflammatory bowel disease and its exacerbation.

UEs in OPTIC vs. OPTIC-J: Unterschiedliche Erfassung unerwünschter Ereignisse mit teilweiser Überlappung (und studienspezifischen Schwerpunkten)

Study protocol amendments

The OPTIC-J study [22], underwent three protocol amendments, none of which affected the study endpoints. Complete details of these amendments and all study endpoints are documented in Chapter 5 in the Appendix. For the OPTIC-X and Chen et al. studies, no protocol could be identified.

OPTIC Studienprotokoll: 3 Amendments; kein Protokoll für OPTIC-X und Chen

5.2 Results on effectiveness and safety

The evidence for the relative effectiveness and safety of teprotumumab for the treatment of moderate-to-severe TED is derived from two RCTs (OPTIC [20] and OPTIC-J [22]), one single-arm trial (OPTIC-X) [21] and one observational study by Chen et al. [23]. For each outcome assessed, results are presented first from the two randomised controlled trials, followed by OPTIC-X and Chen et al.'s observational study findings.

2 RCTs, 1 einarmige-, 1 Beobachtungsstudie zur Wirksamkeit & Sicherheit von Temprotumumab

5.3 Clinical efficacy outcomes

Proptosis response

The critical outcome, proptosis response, showed comparable results in the OPTIC and OPTIC-J [20, 22] RCTs at week 24 (i.e., 83% to 89% for teprotumumab versus 10% to 11% in the placebo group). See Table 5-4.

RCTs: signifikant höhere Exophthalmus-Ansprechrate

In the OPTIC-X [21] study, patients who received the first course of teprotumumab, 89.2% were proptosis responders, whereas 40% of initial non-responder patients were proptosis responders at week 24. Patients who were re-treated but experienced disease flare, 62.5% were proptosis responders at week 24 (Table 5-5).

OPTIC-X: 89,2 % bei Erstanwendung, 40 % Non-Responder-Pat., 62,5 % Re-Therapie

Clinical activity score (CAS) response

The critical outcome, CAS response, showed comparable statistically significant results in the OPTIC and OPTIC-J [20, 22] RCTs at week 24 (i.e., 59% in both for teprotumumab versus 21% to 22% in the placebo group). See Table 5-4.

OPTIC/OPTIC-J: CAS-Ansprechen Teprotumumab 59% vs. Placebo 21–22%

In the OPTIC-X [21] study, the CAS response was achieved in 65.6% of patients who received the first course of teprotumumab, none of the initial non-responder patients and 57.1% of re-treated patients with disease flare at week 24 (Table 5-5).

OPTIC-X:
65,6 % Erstbehandlung, 57,1 % bei Wiederbehandlung

In the study by Chen et al., the mean CAS was 4±1 (range: 3–7) in the eleven patients with TED reactivation (Table 5-6) [23].

Chen-Studie:
mittlere CAS (n=11) 4 ± 1

Reactivation of TED

The critical outcome of TED reactivation was assessed in the OPTIC study [20, 23] during the 48-week follow-up period (concluding at study week 72). Results showed that 29.4% of patients who received teprotumumab experienced disease reactivation (Table 5-4).

OPTIC:
TED-Reaktivierung während Follow-up 29,4 %

In the study by Chen et al. [23], 26% of patients experienced reactivation of TED (Table 5-6).

Chen-Studie:
TED Reaktivierung 26 %

Graves' ophthalmopathy-specific quality-of-life (GO-QoL) questionnaire

The critical patient-reported outcome, GO-QoL score showed in both the OPTIC-X: GO-QoL OPTIC [20] and OPTIC-J [22] study statistically significant results in the teprotumumab group compared to the placebo group (i.e., between-group difference, 9.36 to 11.01) (Table 5-4).

OPTIC/OPTIC-J:
GO-QoL statistisch signifikante Verbesserung

In the OPTIC-X study, in the first-course teprotumumab patients, GO-QoL scores improved in visual functioning (+11.7±22.5) and appearance (+15.1 ±20.3) subscales. Re-treated patients with disease flare demonstrated clinically significant improvements in the visual functioning (+28.0±28.0) and appearance (+7.8±11.5) subscales (Table 5-5) [21].

OPTIC-X:
Erstbehandelte: moderate Effekte;
Wiederbehandelte: sig. visuelle & moderate Erscheinungsbild-verbesserung

The overall response

The important outcome, the overall response, showed similar statistically significant results at week 24 in the OPTIC [20] and OPTIC-J [22] RCTs (i.e., 78% in both for teprotumumab versus 7% and 4% respectively in the placebo group) (Table 5-4).

Gesamtansprechrate
OPTIC: 78 % vs. 7 %
OPTIC-J: 78 % vs. 4 %

Mean change in proptosis

The important outcome, mean change in proptosis, showed comparable statistically significant results in the OPTIC [20] and OPTIC-J [22] study (i.e., −2.82 to −2.36mm for teprotumumab versus −0.54 to −0.37mm in the placebo group) (Table 5-4).

Exophthalmus:
sig. Reduktion
OPTIC- & OPTIC-J

In the OPTIC-X study [21], mean proptosis reduction at week 24 varied across patient subgroups: first-course teprotumumab patients demonstrated a –3.5mm reduction, initial non-responders showed a –1.5mm reduction, and disease flare re-treated patients exhibited a –1.9mm reduction (Table 5-5).

In the study by Chen et al. [23], the mean increase in proptosis was +3mm in the eleven patients with TED reactivation (Table 5-6).

OPTIC-X und Chen-Studie: Reduktion durch Teprotumumab-Behandlung vs. Zunahme bei TED-Reaktivierung

Diplopia response

Diplopie-Ansprechrate

The important outcome, diplopia response, showed comparable results in the OPTIC [20] and OPTIC-J [22] studies.

OPTIC: 68 % vs. 29 %
OPTIC-J: 64 % vs. 45 %

At week 24, the diplopia responder rates were notably higher in the teprotumumab groups (68% and 64%, respectively) compared to the placebo groups (29% and 45%) in both RCTs. Statistical significance was achieved in the OPTIC trial; however, the OPTIC-J trial did not demonstrate statistically significant differences between treatment groups [20, 22] (Table 5-4).

OPTIC-X:
Erstbehandelte: 60.9 %;
Non-Responder-Pat.: 20 %; Wiederbehandelte: 33 %

In the OPTIC-X study [21], diplopia response rates varied across patient subgroups. Among first-course teprotumumab patients, 60.9% achieved diplopia response. Initial non-responders demonstrated a 20% diplopia response rate, while disease flare patients who received retreatment exhibited a 33% response rate (Table 5-5).

Chen-Studie: 45 %

In the study by Chen et al. [23], 45% of patients had diplopia with a mean Bahn-Gorman score of 2 (Table 5-6).

Table 5-4: Efficacy results – primary and secondary efficacy endpoints of the two included RCTs (OPTIC and OPTIC-J [20, 22])

Outcome Measure	Teprotumumab (N=41)	Placebo (N=42)	Treatment Difference (95% CI)	P-value	Teprotumumab (N=27)	Placebo (N=27)	Treatment Difference (95% CI)	P-value
Study reference/ID	OPTIC [20]				OPTIC-J [22]			
The primary outcome of proptosis response								
Proptosis Response Rate (%), ITT population	83 (34/41)	10 (4/42)	73 (59 to 88)	<0.001	89 (24/27)	11 (3/27)	78 (61-95)	<0.0001
Proptosis Response Rate (%), PP population	88 (29/33)	12 (4/34)	76 (61 to 92)	<0.001	n.r.			
Secondary outcomes (in the ITT population)								
Overall Response Rate (%)	78 (32/41)	7 (3/42)	71 (56 to 86)	<0.001	78 (21/27)	4 (1/27)	74 (57-91)	<0.0001
Clinical activity score of 0 or 1 (%)	59 (24/41)	21 (9/42)	36 (17 to 55)	<0.001	59 (16/27)	22 (6/27)	37 (13-62)	0.0031
Mean Proptosis Change (mm)	−2.82±0.19	−0.54±0.19	−2.28 (−2.77 to −1.80)	<0.001	−2.36	−0.37	−1.99 (−2.75 to −1.22)	<0.0001
Diplopia Response Rate[a] (%)	68 (19/28)	29 (8/28)	39 (16 to 63)	0.001	64 (14/22)	45 (9/20)	17 (-11 to 45)	0.24
Complete Diplopia Resolution[a] (%)	n.r.				50 (11/22)	20 (4/20)	29.1 (1 to 57)	0.043[b]
Mean change in **GO-QoL** score from baseline through wk 24[c]	13.79±2.07	4.43±2.10	9.36 (4.08 to 14.64)	<0.001	17.39 (10.67 to 24.11)	6.39 (–0.33 to 13.10)	11.01 (2.65 to 19.36)	0.011
Mean change in **GO-QoL**: Visual Function[c]	n.r.				16.22 (8.29 to 24.14)	4.39 (–3.55 to 12.33)	11.83 (1.82 to 21.83)	0.022
Mean change in **GO-QoL**: Appearance[c]	n.r.				19.35 (11.48 to 27.23)	8.69 (0.83 to 16.56)	10.66 (1.04 to 20.28)	0.031
Reactivation of TED								
Reactivation of TED (%)	29.4%[d]	-	-	-	n.r.	-	-	-

Abbreviations: CI … confidence interval, GO-QoL … Graves' Orbitopathy Quality of Life, ITT … intention to treat, N … number of patients, n.r. … not reported, PP … per protocol, TED … thyroid eye disease, wk … week.

Notes:

[a] *In the OPTIC-J study, diplopia analyses were conducted on patients with diplopia at baseline (teprotumumab n=22, placebo n=20).*

[b] *Nominal P-value (statistical significance cannot be claimed due to hierarchical testing).*

[c] *The least squares mean values were used to compare the average changes in QoL scores over time between the treatment groups.*

[d] *Based on the extension study; OPTIC-X. Calculated from 34 patients that entered follow-up. The time of the reactivation was not reported for individual patients.*

Critical outcomes are marked in **bold**.

Table 5-5: Efficacy results – primary and secondary efficacy endpoints of the included single-arm trial OPTIC-X [21]

Outcome Measure Study reference/ID	First Course (Previous Placebo) N=37	Retreatment (Non-responders) N=5	Retreatment (Disease Flare) N=9 (8 evaluable at wk 24)
OPTIC-X [21]			
Median TED Duration	12.9 months	-	16.5 months
Proptosis Response Rate	33/37 (89.2%)	2/5 (40%)	5/8 (62.5%)
Mean Proptosis Reduction	−3.5 ± 1.7 mm	−1.5 ± 0.9 mm	−1.9 ± 1.2 mm
Median Time to Proptosis Response	6.4 weeks	-	-
Diplopia Response Rate	14/23 (60.9%)	1/5 (20%)*	3/9 (33%)
Complete Diplopia Resolution	13/23 (56.5%)	-	3/9 (33%)
CAS 0/1 Response Rate	21/32 (65.6%)	0/3 (0%)	4/7 (57.1%)
Mean change in **GO-QoL** score at wk 24 (visual functioning subscale)	11.7 ± 22.5	-	28.0 ± 28.0
Mean change in **GO-QoL** score at wk 24 (appearance subscale)	15.1 ± 20.3	-	7.8 ± 11.5
Response Maintenance at Week 48			
■ Proptosis	29/32 (90.6%)	-	-
■ CAS 0/1	20/21 (95.2%)	-	-
■ Diplopia	12/14 (85.7%)	-	-
Reactivation of TED	Not reported.		

Abbreviations: CAS … clinical activity score; TED … thyroid eye disease; GO-QoL … Graves' Ophthalmopathy Quality of Life, N … number of patients, wk … week.

Notes: ± values are SD, (*) This patient responded at weeks 6, 12, and 18 but did not undergo measurements at week 24, (-) Data not reported in the study. Critical outcomes are marked in **bold**.

Table 5-6: Efficacy results – primary and secondary efficacy endpoints of the included observational study by Chen et al. [23]

Chen et al. (N=42)	
TED reactivation	N=11/42 (26%)
Mean age of reactivated cases ± SD (n=11)	57 ± 11 years (range: 42-81)
Mean time to reactivation ± SD (n=11)	9 ± 5 months (range: 2-20)
Mean increase in proptosis ± SD (n=11)	3 ± 1 mm (range: 2-6)
Mean CAS at reactivation ± SD (n=11)	4 ± 1 (range: 3-7)

Abbreviations: CAS … clinical activity score, N … number of patients, SD … standard deviation, TED … thyroid eye disease. Critical outcomes are marked in **bold**.

5.3.1 Safety outcomes

Adverse Events (AEs) and serious adverse events (SAEs)

Adverse and serious adverse events (AEs & SAEs) were reported in all four included trials [20-23].

UEs & SUEs in allen 4 Studien aufgetreten

In the OPTIC study, 85% of teprotumumab versus 69% of placebo patients had at least one AE. The teprotumumab group had two SAEs (unrelated pneumothorax; infusion reaction causing withdrawal). The placebo group had one SAE (visual-field defect causing withdrawal). Hearing impairment affected 12% of teprotumumab patients and were resolved in all [20].

OPTIC: mehr UEs, z. B.: reversible Hörprobleme (12 %), selten schwerwiegende

In the OPTIC-J study, 93% of patients in the teprotumumab group and 78% in the placebo group experienced at least one AE. Two patients experienced grade 3 AEs unrelated to the study drug. Treatment adherence issues (>2 missed infusions) occurred in one teprotumumab patient (4%) and two placebo patients (7%), with hearing loss being the cause in one patient from each group. Hearing impairment occurred in four teprotumumab patients (15%) versus one placebo patient (4%). Three teprotumumab patients had only mild audiogram changes without subjective symptoms, and two of the four had pre-existing hearing issues [22] (Table 5-7).

OPTIC-J:
höhere Inzidenz an UEs (93 % vs. 78 %),
häufigste UEs bei Teprotumumab:
Hörbeeinträchtigung 15 %, teilweise asymptomatisch oder bei Vorerkankungen

In the OPTIC-X study, muscle spasms were less frequent in re-treated patients (28.6%) compared to treatment-naïve patients (48.6%). A re-treated smoker discontinued the study after experiencing an intracerebral hemorrhage, and another study participant discontinued due to hearing AE. Six patients developed mild hearing issues, with three resolved cases and three cases persisting beyond the study period. Four were first-time teprotumumab recipients, two were re-treated with recurring hearing AEs. Overall, AE frequency was similar between OPTIC and OPTIC-X trials (Table 5-8) [21].

OPTIC-X:
Muskelspasmen bei Re-Therapie 28,6 % vs. Ersttherapie 48,6 %;
6 Pat. leichte Hörbeeinträchtigung, teilweise reversibel;
Wiederauftreten auch bei Re-Therapie

In the study by Chen et al., four of the eleven patients with reactivated TED experienced AEs, including nausea, muscle spasms, hair loss, brittle fingernails, hyperglycaemia, and diarrhoea [23].

Chen-Studie:
4 Pat. berichten von UEs

Table 5-7: Safety results of the two included RCTs (OPTIC and OPTIC-J [20, 22])

Adverse Event	Teprotumumab (N=41)	Placebo (N=42)	Teprotumumab (N=27)	Placebo (N=27)
Study reference/ID	OPTIC [20], no. (%)		OPTIC-J [22], no. (%)	
Muscle spasms	13 (32)	4 (10)	3 (11)	0
Alopecia	8 (20)	5 (12)	5 (19)	0
Diarrhea	4 (10)	5 (12)	3 (11)	1 (4)
Hyperglycaemia	2 (<5)	0	3 (11)	1 (4)
Upper abdominal pain	2 (5)	3 (7)	2 (7)	0
Dysgeusia	4 (10)	0	NR	NR
Amenorrhea	3 (7)	0	NR	NR
Dizziness	3 (7)	0	NR	NR
Cough	2 (5)	3 (7)	NR	NR
Influenza	1 (2)	3 (7)	NR	NR
Fatigue	5 (12)	1 (2)	NR	NR
Nausea	6 (15)	4 (10)	NR	NR
Seasonal allergy	NR	NR	4 (15)	0
COVID-19 infection	NR	NR	4 (15)	3 (11)
Contact dermatitis	NR	NR	2 (7)	0
Eczema	NR	NR	2 (7)	0
Stomatitis	NR	NR	2 (7)	0
Increased gamma-glutamyl transferase	NR	NR	2 (7)	0
Diabetes mellitus	NR	NR	2 (7)	0
Dry eye	NR	NR	2 (7)	0
Hearing-Related Events				
Hypoacusis	2 (5)	0	2 (7)	0
Deafness	1 (2)	0	NR	NR

Adverse Event	Teprotumumab (N=41)	Placebo (N=42)	Teprotumumab (N=27)	Placebo (N=27)
Autophony	1 (2%)	0	NR	NR
Patulous eustachian tube	1 (2%)	0	1 (4%)	0
Tinnitus	NR	NR	3 (11%)	0
Ear discomfort	NR	NR	2 (7%)	0
Neurosensory hypoacusis	NR	NR	2 (7%)	1 (4%)

Abbreviations: N … number of participants, NR … not reported.

Table 5-8: Safety results of the included single-arm trial OPTIC-X [21]

Study OPTIC-X		
Adverse Events	Second Course (OPTIC Teprotumumab) N = 14 no. (%)	First Course (OPTIC Placebo) N = 37 no. (%)
Any serious adverse events	1 (7.1)	0 (0)
Cerebral hemorrhage	1 (7.1)	0 (0)
Any adverse event	11 (78.6)	32 (86.5)
AEs in >10% of patients		
Muscle spasm	4 (28.6)	18 (48.6)
Arthralgia	2 (14.3)	0 (0)
Back pain	2 (14.3)	0 (0)
Nasal dryness	2 (14.3)	0 (0)
Alopecia	2 (14.3)	4 (10.8)
Dry skin	2 (14.3)	4 (10.8)
Hearing impairment	2 (14.3)	4 (10.8)
Diarrhea	1 (7.1)	5 (13.5)
Fatigue	0 (0)	4 (10.8)
Dysgeusia	0 (0)	4 (10.8)
Onychoclasis	0 (0)	4 (10.8)
Any AEs of special interest <10%		
Potential infusion-related reaction	1 (7.1)	3 (8.1)
Anaphylactic reaction	0 (0)	0 (0)
Hyperglycaemia	0 (0)	3 (8.1)

Abbreviations: AEs … adverse events, N … number of patients, no … number.

5.4 Quality of the evidence

Risk of Bias

Several risks of bias were identified in the two RCTs, OPTIC and OPTIC-J [20, 22] (see Chapter 5 in Appendix). The baseline patient characteristics were incompletely reported, with missing information on comorbidities and previous therapies. Neither trial clearly specified whether patients were permitted anti-thyroid therapy such as thiamazol and propylthiouracil. The administration protocol for maintaining euthyroid state was not disclosed, making it unclear if there were differences between groups. Furthermore, certain adverse events could have potentially unmasked the true intervention.

OPTIC/OPTIC-J:
Risk of Bias
(RoB, Verzerrungsrisiken)
→ unvollständige
Baseline Daten
und Informationen zur
Schilddrüsentherapie

Variabilität zw. Beobachtern bleibt trotz Standardisierung problematisch; beide RCTs mit „einigen Bedenken"

Inter-observer variability remained a potential concern despite implementing standardised measures for proptosis measurement across sites (including standardised equipment, observers, and measurement methods). The study protocol specified using the same Hertel instrument and observer "except when strictly unavoidable", but the impact of any between-site measurement variations remains unknown. According to the Cochrane RoB 2.0 tool [27], both the OPTIC and OPTIC-J studies were assessed as having "some concerns" for the total risk of bias.

OPTIC-X: RoB durch offenes Design; selektive Rekrutierung, unzureichende Baseline-Daten

The OPTIC-X extension study [21] demonstrated additional sources of bias (see Chapter 5 in Appendix). Its primary limitation was its open-label design. Patient recruitment was non-consecutive, with varying entry points depending on when participants experienced flares during follow-up. The baseline characterisation lacked details regarding concomitant and previous therapy and comorbidities. The disease stage at study entry showed considerable variation, evidenced by wide standard deviations in both the median months since TED diagnosis and years since Graves' disease diagnosis. Information about permitted concomitant therapies was insufficient, and the use of additional disease management treatments was not reported. While appropriate proptosis measurement methods were employed, inter-observer variability across sites remained a potential concern.

methodische Limitationen: moderater RoB, kein Signifikanztest, fehlende Power-Berechnung und Unklarheit bei Langzeitdaten

The OPTIC-X study [21] also had several methodological limitations: no significance testing was performed for comparing baseline and post-treatment endpoints, no power or sample size calculations were conducted, and no adjustments were made for multiple comparisons. Additionally, while patients were followed-up to week 72, the number of patients following beyond this time point was not reported. According to the Risk of Bias tool Institute of Health Economics (IHE) checklist for single-arm case series [28], these collective factors compromise the study's internal validity, resulting in a moderate risk of bias [28].

Chen Studie: moderater RoB; retrospektiv, unverblindet, unzureichende Baseline-Charakteristika

Similarly, the study by Chen et al. [23] had methodological limitations that resulted in a moderate risk of bias. The study was an unblinded, retrospective, single-centre longitudinal cohort study. The baseline characteristics of patients lacked detailed information on the concomitant and previous therapy, comorbidities, thyroid eye and Graves' disease diagnosis, race, smoking status, clinical activity score, and proptosis measurement. There was no information on the accepted concomitant therapy, and it was not clear whether additional treatments were used for disease management. Additionally, it is unknown if the proptosis was measured in a standardised way among the patients (see Chapter 5 in the Appendix).

Inconsistencies in statistical analysis

statistische Ansätze der einzelnen Studien variieren

Due to varying study designs, statistical approaches differed across studies. OPTIC [20] and OPTIC-J [22] used power calculations and predefined analytical hierarchies. For more information, see Chapter 5 in the Appendix.

For OPTIC, no apparent analysis plan changes occurred, though the final protocol (v4.0, January 31, 2019) was possibly completed near data unblinding time [20].

OPTIC-J made two amendments to their analysis plan, including updating methods for primary efficacy and responder endpoints [22].

No protocols or analysis plans were available for OPTIC-X [21] and Chen et al. [23] studies. Chen et al. used descriptive statistics.

External validity and applicability

Anwendbarkeit der Teprotumumab-Studienergebnisse: Bewertung der Generalisierbarkeit für klinische Praxis

The applicability of evidence from the OPTIC, OPTIC-X, OPTIC-J and Chen et al. studies of teprotumumab in moderate-to-severe thyroid eye disease are addressed in Chapter 5 of Appendix. For each domain, key characteristics of the trial are described and evaluated regarding their impact on the generalisability of results to routine clinical practice.

Quality of evidence according to GRADE

Vertrauenswürdigkeit der Evidenz → GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scheme for each critical endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of the applied criteria can be found in the recommendations of the GRADE Working Group [19].

Vertrauenswürdigkeit der Evidenz: RCTs → niedrig

The ranking according to the GRADE scheme for the research question can be found in the summary of findings tables below (Table 5-9 & Table 5-10) as well as in the evidence profile and the classification of evidence strength in Chapter 5 of the Appendix.

Beobachtungsstudie → sehr niedrig

Overall, the strength of evidence for the effectiveness and safety of the two included RCTs [20, 22] for teprotumumab in comparison to placebo is low. The strength of evidence for the effectiveness and safety of the included observational study [23] was very low.

Table 5-9: Summary of findings table for the two included RCTs [20, 22]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Efficacy			
Proptosis response assessed with: Hertel exophthalmometer follow-up: range 24 weeks to 72 weeks	OPTIC Study: ■ Teprotumumab response rate: 83% (34/41) ■ Placebo response rate: 10% (4/42) OPTIC-J Study: ■ Teprotumumab response rate: 89% (24/27) ■ Placebo response rate: 11% (3/27)	137 (2 RCTs) [20, 22]	⨁⨁◯◯ Low[a,b]
Clinical activity score (CAS) assessed with: physician follow-up: range 24 weeks to 72 weeks	Events (CAS 0/1): ■ OPTIC: 24/41 vs 9/42 ■ OPTIC-J: 16/27 vs 6/27 Confidence Intervals: ■ OPTIC: 17–55% difference ■ OPTIC-J: 13–62% difference	(2 RCTs) [20, 22]	⨁⨁◯◯ Low[a,c]
Reactivation – not reported	The outcome reactivation was only reported in the extension study which is a single arm study.	-	-
Patient reported outcome – Graves' ophthalmopathy-specific quality-of-life (GO-QoL) assessed with: questionnaire follow-up: range 24 weeks to 72 weeks	OPTIC: ■ Mean change: 13.79 points (vs 4.43 placebo) ■ Difference: 9.36 points (CI: 4.08 to 14.64) OPTIC-J: ■ Mean change: 17.39 points (vs 6.39 placebo) ■ Difference: 11.01 points (CI: 2.65 to 19.36)	(2 RCTs) [20, 22]	⨁⨁◯◯ Low[a,d]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Safety			
Serious adverse events (SAE) follow-up: range 24 weeks to 72 weeks	Point estimates: OPTIC: ■ Teprotumumab: 2/41 (4.9%) ■ Placebo: 1/42 (2.4%) OPTIC-J: ■ Teprotumumab: 1/27 (3.7%) ■ Placebo: 0/27 (0%)	(2 RCTs) [20, 22]	⨁⨁◯◯ Low[a,e]

Abbreviations: CI … confidence interval, GRADE … Grading of Recommendations Assessment, Development and Evaluation

Notes:

[a] *Insufficient detail on randomization process; potential unblinding due to higher adverse event rates in teprotumumab group; potential inter-observer variability in the measurement of proptosis affecting outcome assessment reliability;*

[b] *Studies enrolled fewer than 50 participants per arm (our pre-specified threshold), increasing risk of chance findings and potentially overestimated treatment effects;*

[c] *Small sample size, wide confidence intervals, and limited events in control groups affect precision of estimated treatment effect*

[d] *Small sample sizes, wide confidence intervals, lower CI bounds close to minimal important difference;*

[e] *Very few events overall prevent reliable estimation of safety risks, resulting in imprecise risk estimates.*

Table 5-10: Summary of findings table of the one included observational study [23]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Efficacy			
Proptosis follow-up: range 6 months to 32 months	Teprotumumab retreatment (n=4): ■ Mean reduction: 4mm (SD: 2mm) Steroids (n=6): ■ Mean reduction: 0mm (SD: 1mm)	(1 non-randomised study) [23]	⨁◯◯◯ Very low[a,b]
Clinical activity score (CAS) assessed with: physician follow-up: range 6 months to 32 months	Final CAS: 0 in all patients IV Steroids: ■ Mean final CAS: 2 (SD: 1) ■ Range: 1-4	(1 non-randomised study) [23]	⨁◯◯◯ Very low[a,c]
Reactivation follow-up: range 6 months to 32 months	■ 11/42 patients (26%) experienced reactivation ■ Mean time to reactivation: 9 months (SD: 5) ■ Range: 2-20 months	(1 non-randomised study) [23]	⨁◯◯◯ Very low[a,d]
Patient Reported Outcomes – not measured	-	-	-
Safety			
Serious adverse events (SAEs) follow-up: range 6 months to 32 months	No serious adverse events were reported for either retreatment group ■ 4/11 patients had mild side effects during retreatment (nausea, muscle spasms, hair loss, hyperglycaemia)	(1 non-randomised study) [23]	⨁◯◯◯ Very low[a,e]

Abbreviations: CI … confidence interval, GRADE … Grading of Recommendations Assessment, Development and Evaluation, IV … intravenous, SD … standard deviation

Notes:

[a] *Missing detailed information on the concomitant and previous therapy. Missing comorbidities in the baseline characteristics. No information on the time of thyroid eye and Graves' disease diagnosis.*

[b] *Very small sample size (4 teprotumumab vs 6 steroids for retreatment), large variations in effects, wide confidence intervals not reported but likely wide given sample size.* [c] *Very small sample sizes (4 vs 6 patients), limited number of events, confidence intervals not reported.*

[d] *Relatively small sample size and wide variability in timing (2-20 months)*

[e] *Very few events reported, Small sample size (n=42), Limited power to detect rare events, No confidence intervals provided*

5.5 Published indirect treatment comparison

5.5.1 Methods

Douglas et al. [29] have published a meta-analysis and Matching-Adjusted Indirect Comparison (MAIC) of teprotumumab versus active comparator, intravenous methylprednisolone (IVMP). Data for patients receiving teprotumumab or placebo were obtained from a phase 2 trial [30] and a phase 3 trial (OPTIC) [20]. Given the similar inclusion and exclusion criteria, data were pooled. The aim was to evaluate improvements in proptosis and diplopia with the IVMP and to compare these results with teprotumumab and placebo in patients with moderate-to-severe active TED. The MAIC analysed the change from baseline in proptosis and diplopia.

Metaanalyse mit indirektem Vergleich (MAIC) von Teprotumumab vs. IVMP: Daten aus Phase-2- und Phase-3-Studie (OPTIC), Untersuchung der Exophtalmus- & Diplopie-Veränderung

5.5.2 Results

The review for the indirect treatment comparison (ITC) identified twelve IVMP studies and two teprotumumab studies. The IVMP studies comprised seven RCTs and five observational studies, no placebo-controlled, conducted in China (n=6) and European countries (n=6). The teprotumumab studies were placebo-controlled, double-masked, multicentre trials conducted in Europe and the US. Study characteristics meeting PICOs criteria are presented in Chapter 5 in the Appendix.

Identifikation von 12 IVMP-Studien (7 RCTs, 5 Beobachtungsstudien) vs. keine placebokontrollierte, Teprotumumab-Studien

Results from the meta-analyses for IVMP show a change from the baseline in proptosis and the proportion of diplopia responders, as shown in Table 5-3. These unadjusted analyses demonstrated that IVMP treatment resulted in a reduction of 0.80mm (95% CI, −1.37 to −0.23mm) in proptosis and a 50% (95% CI, 38% to 63%) diplopia response rate from baseline to week twelve [29].

Metaanalyse IVMP: Exophthalmus-Reduktion von 0,80 mm und Diplopie-Ansprechrate von 50 % nach 12 Wochen

The MAIC analysis, adjusted for mean age, proportion of women, and proportion of smokers, showed that teprotumumab was associated with a statistically significantly greater change from baseline in proptosis compared with IVMP (mean difference, −2.31mm; 95% CI, −3.45 to −1.17mm; effective sample size: n=56). The difference in proptosis change from baseline between the IVMP group and placebo group was not statistically significant (mean difference, −0.16mm; 95% CI, −1.55 to 1.22; effective sample size: n=37). Furthermore, IVMP was associated with increased odds of diplopia response compared with placebo (odds ratio, 2.69; 95% CI, 0.94 to 7.70; effective sample size: n=24), while statistically not significant. The teprotumumab diplopia response was greater when compared with IVMP (odds ratio, 2.32; 95% CI, 1.07 to 5.03; effective sample size: n=44) and was statistically significant. For details, see Chapter 5 in the Appendix [29].

Teprotumumab vs. IVMP: statistisch signifikant bessere Ergebnisse bei Exophthalmus (−2,31 mm) und Diplopie

IVMP vs. Placebo: kein Unterschied bei Exophthalmus

5.5.3 Limitations

The methodological evaluation of the ITC revealed limitations identified by both the MAIC authors and HTA evaluators.

The MAIC authors identified inherent methodological constraints of the unanchored MAIC approach. A fundamental assumption of this method requires a balanced distribution of prognostic factors and treatment-effect modifiers across studies; however, this assumption was potentially violated due to the

MAIC: methodische Einschränkungen und „Confounding-Faktoren" …

limited availability of reported characteristics in the included studies. Additionally, the adjustment for relevant characteristics in the IVMP-placebo comparison resulted in reduced effective sample size, potentially increasing inter-study heterogeneity and yielding wide confidence intervals, thus introducing potential confounding factors.

... durch ungleiche Verteilung von Prognosefaktoren

The HTA evaluators identified additional methodological limitations in the analytical approach. These comprised the absence of formal validity assessment, which was particularly significant given the substantial heterogeneity in geographical distribution and study designs. Furthermore, the evaluation noted methodological gaps, including the absence of individual study quality assessment, insufficient documentation of bias risk management, limited sensitivity analysis for outlier detection, lack of model fit evaluation and comparative model assessment, and inadequate internal and external validity verification (documented in Chapter 5 of Appendix).

HTA: methodische Defizite in Validität, Bias-Management und Modellbewertung

5.6 Indirect treatment comparison (unpublished data)

This part includes confidential information!

5.7 Ongoing Studies

Three ongoing clinical studies evaluating teprotumumab treatment in patients with TED and one expanded access protocol were identified via ClinicalTrials.gov [32]. The marketing authorisation holder sponsors two of the trials and the expanded access protocol; the Walter Reed National Military Medical Center sponsors the observational study. For details on ongoing trials, please see Chapter 5 in the Appendix.

derzeit 3 laufende Studien und 1 erweitertes Studienprotokoll

As of 3 February, 2025, no complete HTA reports for teprotumumab in TED are available. However, two HTA assessments are currently in progress. The National Institute for Health and Care Excellence (NICE) in the United Kingdom has an ongoing evaluation scheduled for completion in August 2025 [33]. Additionally, the National Institute for Health Research (NIHR) has issued an initial technology briefing but has not yet completed a full assessment [34].

2 HTA-Berichte aktuell in Bearbeitung: NICE & NIHR

6 Price comparisons, treatment costs and budget impact

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) found no official price information for teprotumumab in moderate-to-severe active thyroid eye disease (TED) in 15 member states of the EU countries and the United Kingdom (UK), as teprotumumab is not approved by the European Commission (EC) yet.

keine offiziellen Preisinfos zu Teprotumumab vorhanden

This part includes confidential information!

For Austria, the pharmaceutical company also reported no official price for teprotumumab until completion of the report (April 16th 2025).

Angaben des Unternehmens: kein Preis für Ö verfügbar

6.1 Pharmacoeconomic model(s)

6.1.1 Submitted pharmcoeconomic model

The manufacturer has not submitted a model as requested as part of the dossier.

kein Modell vom Unternehmen eingereicht

6.1.2 Economic evaluation based on pharmacoeconomic models

We could not identify any (international) pharmacoeconomic evaluation or HTA report with a pharmacoeconomic evaluation for teprotumumab through the systematic literature search or additional manual searches.

keine gesundheits-ökonomischen Evaluationen vorhanden

6.2 Budget impact analysis for the Austrian context before negotiation

Eligible population and market share in years 1-3

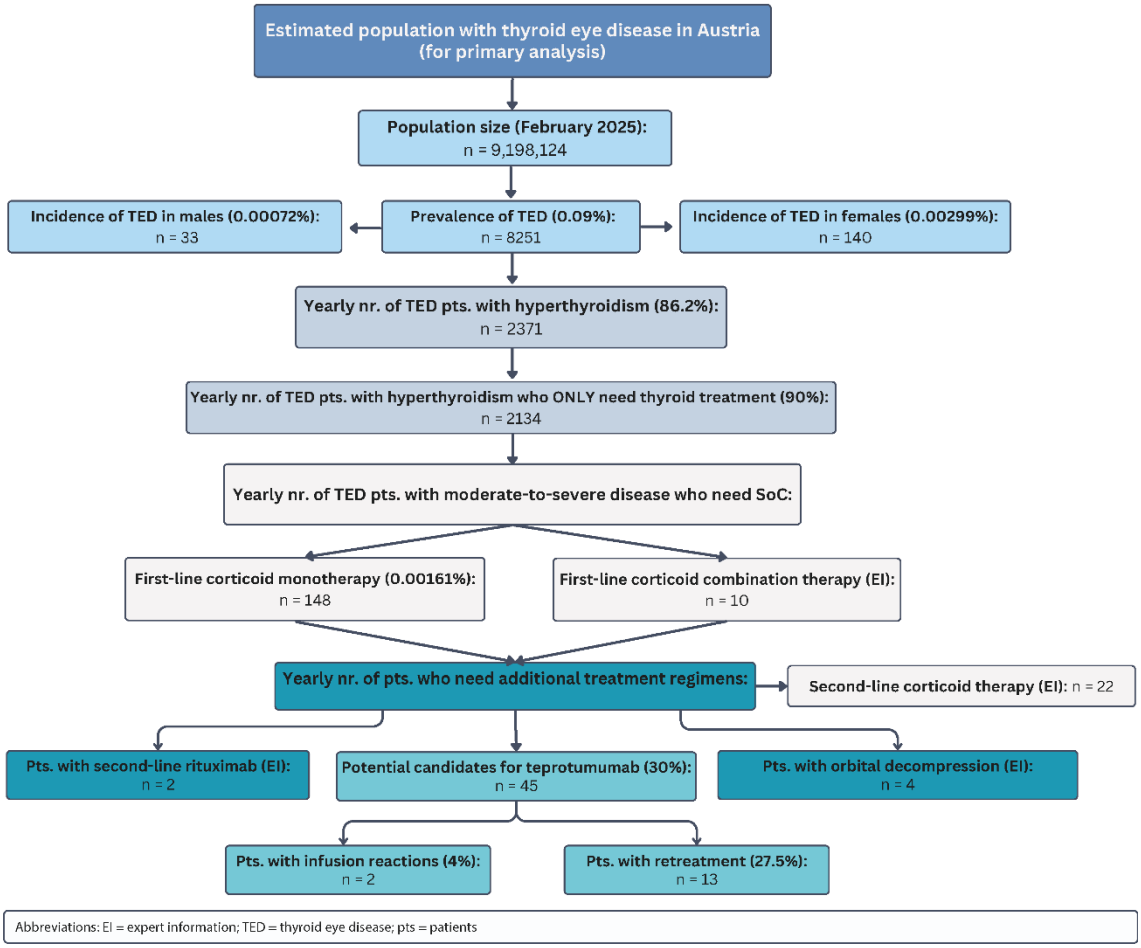
According to published data, there are currently around 8,251 persons living with TED in Austria. This number is anticipated to remain constant over three years, as most patients achieve a cure within one year. According to Austrian clinical expert information, 90% of the patients can be cured with thyroid treatments or thyroidectomy due to a mild form of TED.

In Austria, around 148 patients are diagnosed with moderate-to-severe TED annually, summing up to 444 patients over three years. These patients usually receive standard-of-care (SoC) first-line monotherapy corticosteroids. Only a small proportion receive combination therapy with oral mycophenolate sodium and 15% require an additional corticosteroid cycle. On average, 30% (45 patients annually, 135 patients over three years) need subsequent treatments following corticosteroid therapy, rituximab (off-label, 5%) or orbital decompression (9%). These patients also represent potential candidates for teprotumumab treatment.

ca. 444 erwachsene Pat. mit moderater-schwerer TED in den kommenden 3 Jahren in Ö erwartet, davon potenziell 135 für Teprotumumab Behandlung

Based on clinical evidence, approximately 4% of patients receiving teprotumumab experience IV reactions that may necessitate dosage adjustments or treatment discontinuation. Furthermore, a mean of 27.5% of patients are expected to require a second eight-infusion course of teprotumumab due to disease reactivation. For the following budget impact analysis, an optimistic scenario based on expert expectations assumes that treatments with rituximab and surgical interventions like orbital decompressions can be avoided through teprotumumab treatment. The detailed patient numbers are displayed in Figure 6-1.

Budgetfolgenanalyse mit optimistischem Szenario: Teprotumumab ersetzt Rituximab-Behandlungen und chirurgische Eingriffe



Note: Figure based on Chapter 6 in the Appendix.

Figure 6-1: Estimated population with thyroid eye disease and potential candidates for teprotumumab

Treatment costs of teprotumumab per patient and gross budget impact year 1-3

Kosten Teprotumumab erster Zyklus (135 Pat.): € 42,4 Mio. für 3 Jahre

erneute Behandlung bei 27,5 % der Pat.: weitere € 12,3 Mio. für 3 Jahre

gesamt € 54,7 Mio. für 3 Jahre

Currently, no official price is available for teprotumumab in Europe. Based on a US price of $16,382 submitted by the manufacturer, the converted price was around €13,663 per 500mg powder solution for infusion. Given that every patient receives eight infusions, the cost for teprotumumab for a 75kg patient is €314,240. For the estimated patient population of 45 patients annually, the total drug acquisition cost for the first course would be approximately €14.1 million annually, resulting in around €42.4 million over the next three years. The drug acquisition costs for the retreatment of 27.5% of the patients add another €4.1 million annually and around €12.3 million over three years. In sum, the total drug costs are €18.2 million annually and €54.7 million for three years (see Table 6-2).

Standard of care costs

gesamte Standardtherapiekosten für die nächsten 3 Jahre: ca. € 19,4 Mio.

Schilddrüsenbehandlungen machen den größten Anteil aus (98,34 %)

The SoC includes thyroid treatments and corticosteroids. The latter is used as both first-line and second-line therapy. Alternative second-line treatments such as rituximab (off-label) and surgical interventions like orbital decompression are employed when necessary. The thyroid treatments in TED patients account for the most significant SoC costs (98.34%), with €7,600 per patient, €6.4 million annually and €19.1 million over three years. In contrast, the costs for first-and second-line pharmacological treatments represent only 1.20% of the total costs, at €20,004 per patient and approximately €233,134 over three years, while orbital decompressions account for merely 0.46%, at €7,468 per patient and €89,619 over three years. The total SoC treatment costs amount to €19.4 million over three years. Table 6-1 presents the SoC treatment costs in more detail.

Table 6-1: Cost of SoC scenario

Cost categories SoC	Per patient	Year 1	Year 2	Year 3	Total	%
A: Total costs of thyroid treatments in TED patients	€7,600	€6,369,523	€6,369,523	€6,369,523	€,19,108,569	98,34%
B: Total costs of TED SoC first- and second-line treatments	€20,044	€77,711	€77,711	€77,711	€233,134	1,20%
C: Total costs of surgeries in patients with TED	€7,468	€29,873	€29,873	€29,873	€89,619	0,46%
A-C: Total direct medical costs of SoC scenario WITHOUT temprotumumab*	€35,113	€6,477,107	€6,477,107	€6,477,107	€19,431,322	100,00%

Abbreviation: SoC … standard of care, TED … thyroid eye disease

*Note: * One clinic retrospectively reported that they also use orbital radiotherapy instead of surgical options in a few patients. These costs are not included in the total direct medical costs of the SoC scenario.*

Net drug-budget impact in years 1-3

ca. € 222.978 Einsparungen bei Standardtherapie innerhalb von 3 Jahren durch Einführung von Teprotumumab (optimistisches Szenario)

In an optimistic scenario, which was selected based on input from Austrian clinical experts due to missing long-term data, no further treatments with rituximab or surgeries such as orbital decompressions are necessary after one or two treatment cycles with teprotumumab. If this assumption holds in real-world practice, the net budget impact (drug acquisition cost of the first cycle and retreatment cycle and cost offsets anticipated from the displacement of SoC treatments) would be €18.2 million annually and €54.5 million over three years. In contrast, the savings in SoC would only be minimal, at

€74,326 annually and €222,978 over three years. In the case of the long-term effectiveness of teprotumumab, these savings would affect the inpatient sector, while the first- and second-line treatments funded by the outpatient sector would remain the same.

Additional costs in the teprotumumab scenario

The additional costs in the teprotumumab scenario consist of the inpatient stay for patients with IV reactions concerning the first treatment cycle, resulting in a budget impact of around €67,884 over three years. In addition, costs arise as a result of retreatment with teprotumumab in a mean of 27.5% of patients due to reactivation of the disease. The additional costs for retreatment again involve inpatient stays for patients with IV reactions, which accounts for another €19,611 over three years. Additional costs would also involve the daycare clinic stay for the therapy application; however, no data was available.

zusätzliche Kosten der Behandlung mit Teprotumumab erster Zyklus: ca. € 67.884 bzw. zweiter Zyklus € 19.611 über 3 Jahre; weitere Kosten für Standardtherapie vor Teprotomumab: € 19,2 Mio. über 3 Jahre

Before teprotumumab treatments, patients also receive thyroid treatments and first- and second-line corticoid treatments, resulting in around €8,593 per patient, €6.4 million annually and €19.2 million over three years.

The total direct medical costs of the teprotumumab scenario are around €662,215 per patient and €73.9 million over three years (see Table 6-2).

gesamte Kosten Teprotumumab Szenario: € 73,9 Mio. für 3 Jahre

Table 6-2: Cost of teprotumumab scenario

Cost categories	Per patient	Year 1	Year 2	Year 3	Total	%
A: Drug acquisition cost first cycle	€314,240	€14,140,781	€14,140,781	€14,140,781	€42,422,342	57,39%
B: Administration cost*	€12,571	€22,628	€22,628	€22,628	€67,884	0,09%
C: Drug acquisition cost retreatment	€314,240	€4,085,114	€4,085,114	€4,085,114	€12,255,343	16,58%
D: Administration cost retreatment*	€12,571	€6,537	€6,537	€6,537	€19,611	0,03%
E: TED-SoC before teprotumumab	€8,593	€6,385,060	€6,385,060	€6,385,060	€19,155,180	25,95%
A-E: Total direct medical costs of teprotumumab scenario	€662,215	€24,640,120	€24,640,120	€24,640,120	€73,920,360	100,00%

Abbreviation: SoC … standard of care, TED … tyroid eye disease

*Note: * Administration cost without daycare clinic cost as this data was not available.*

Comparison of teprotumumab scenario with current SoC in Austria

In summary, based on published data, the assumed number of patients potentially eligible for teprotumumab in Austria would be 45 per year. Considering these patients, total TED treatment costs would rise annually, summing up to €73.9 million over three years. The additional costs associated with the acquisition of teprotumumab and its administration and retreatment account for 74.05% of the total costs, while the treatment for the SoC before teprotumumab accounts for 25.95%. In contrast, if teprotumumab is not introduced, and patients continue receiving SoC as usual, only around one-fourth of the costs (€19.4 million) would be needed (Figure 6-2).

Teprotumumab-Szenario rund 4x teurer als das Standardtherapie-Szenario über die nächsten 3 Jahre

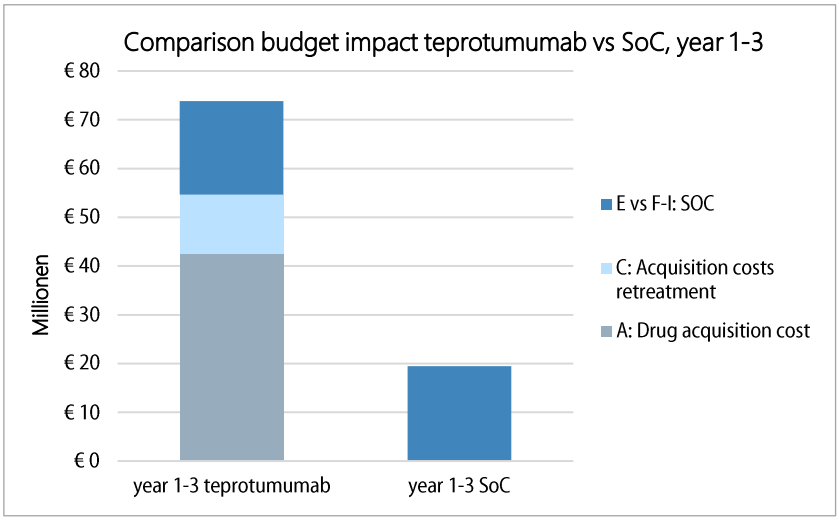


Figure 6-2: Comparison teprotumumab vs. SoC (primary analysis)

Scenario analysis: patient number assumptions from the manufacturer

In contrast to the published patient data, the manufacturer assumes an increasing market uptake of teprotumumab over the years (year 1: n=40; year 2: n=90; year 3: n=115). Stated reasons for this increase in patient numbers include an expected gradual establishment of the therapy in patients with moderate-to-severe TED and the additional consideration of patients in the chronic stage following expert consultations. However, the assumptions are highly uncertain, as firstly, the actual number of chronic patients is difficult to assess, and secondly, the label of the European Medicines Agency has not yet been determined. This means that the chronic patient population may not be considered in the approval process and may be excluded.

Szenario-Analyse: steigende Pat.-Anzahl für Teprotumumab (1. Jahr: 40 – 3 Jahr: 115)

Unsicherheiten der Annahme gegeben

The acquisition costs of the first teprotumumab-cycle are significantly higher in the scenario analysis resulting in annual costs between €12.6 million (year 1) and 36.1 million (year 3), totaling to roughly €77 million over three years. Overall, the total TED treatment costs would rise from €22.4 million in the first year to €52.7 million in the third year, summing up to €117.7 million over three years. The additional costs associated with the acquisition of teprotumumab, and its administration and retreatment would increase to 83.73% of the total costs, while the treatment for the SoC before teprotumumab would account for 16.27%. In contrast, if teprotumumab is not introduced, and patients continue receiving SoC as usual, only around one-sixth of the costs would be needed (€6.4 million annually; €19.4 million over three years). However, this comparison between the teprotumumab scenario and the SoC scenario is highly uncertain because this scenario analysis only accounted for the change in potential patients for teprotumumab, whilst all other patient numbers (e.g. for SoC) remained unchanged (Figure 6-3).

mehr Pat. für Teprotumumab führt zu deutlich höheren Gesamtkosten: € 117,7 Mio. für 3 Jahre

Annahme Pat.-Anzahl für SoC unverändert → neues Teprotumumab-Szenario 6x teurer

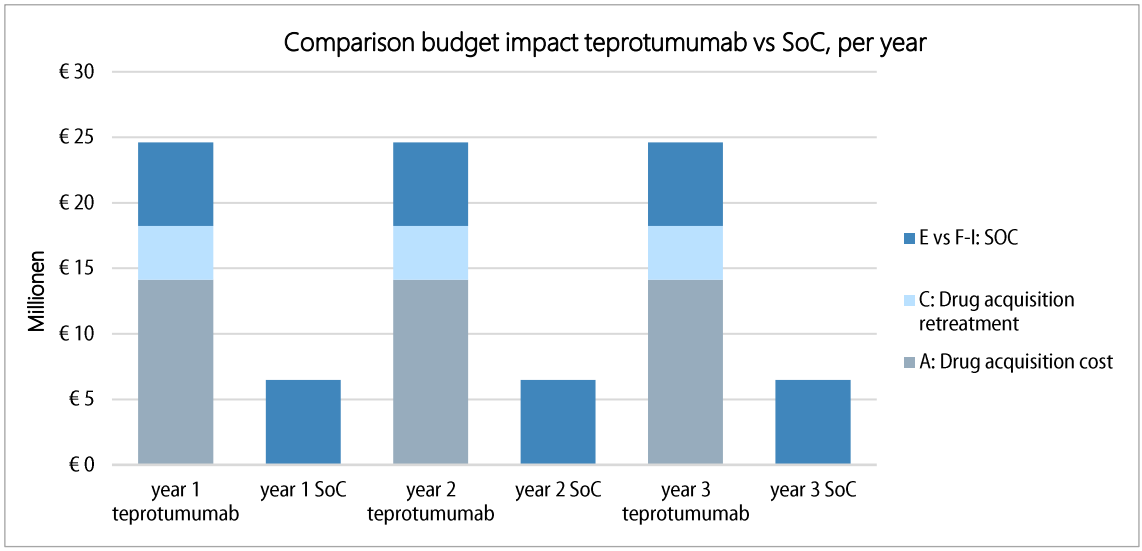


Figure 6-3: Comparison teprotumumab vs. SoC (scenario analysis)

Indirect costs

keine indirekten Kosten berücksichtigt

In Austria, standardised and widely accepted data on indirect healthcare costs are unavailable. Therefore, we followed the healthcare perspective for the analysis and did not consider indirect costs, which represents a limitation of the analysis.

7 Extended perspective

7.1 Stakeholder perspectives

Teprotumumab was included as a second-line therapy option in the 2021 EUGOGO guideline [5]. In a subsequent 2022 consensus report, ETA/ATA described teprotumumab (if available) as a preferred therapy for patients with active moderate-to-severe TED with significant proptosis and/or diplopia [11].

Teprotumumab bevorzugt bei aktiver moderat-schwerer TED mit sign. Exophthalmus und/oder Diplopie

The manufacturer cites the EUGOGO and ETA/ATA consensus and claims no established treatment specifically targeting TED's underlying pathophysiological mechanisms is currently available. The manufacturer argues there is a substantial need for a new therapy with proven efficacy against inflammation, proptosis, and diplopia, as well as improved tolerability [4].

laut Hersteller: Bedarf an neuer Therapie

Clinicians in Austria predominantly utilise glucocorticoid administration as a first-line treatment based on its efficacy profile and favourable safety outcomes in most patients. According to the clinicians, teprotumumab might be considered as a potential therapeutic option for severe cases demonstrating inadequate response to glucocorticoid therapy. However, the absence of direct comparative studies between teprotumumab and current first-line treatments remains a significant limitation in establishing its precise therapeutic positioning. Consequently, based on current evidence, clinical opinion in Austria positions teprotumumab primarily as a second-line therapeutic intervention within the established treatment pathway for active TED [7].

Expert:innen in Ö verwenden Glukokortikoide als Erstlinientherapie

Teprotumumab optional als Zweitlinientherapie

According to the manufacturer, early access or named patient programs are not planned in Austria as of February 2025 [4].

Early Access- oder Named Patient-Programme nicht vorgesehen

Organisational aspects

The administration of teprotumumab requires pre-treatment assessments and ongoing monitoring protocols, e.g. before initiating treatment, several essential examinations must be conducted, including fasting blood glucose, haemoglobin A1C, baseline vision testing, hearing tests and pregnancy testing for premenopausal females. An ophthalmologist, ear nose throat (ENT) specialist, neuro-ophthalmologist, or endocrinologist should oversee the primary management of patients receiving teprotumumab [35]. However these assessments do not significantly differ from other systemic treatments and are generally recommended for the management of TED.

Teprotumumab erfordert gängige Voruntersuchungen & Nachbeobachtungen

Medical staff must brief patients and caregivers on the procedure before infusion therapy. Scheduled for every three weeks, any changes require physician approval. Laboratory values, especially glucose levels, must be within acceptable ranges before each treatment [36]. Regular monitoring during treatment involves reviews by an ophthalmologist, an ENT specialist, and/or endocrinologist every six to twelve weeks, with the frequency depending on disease severity and in general recommended for the management of TED. Patients with compressive optic neuropathy require more frequent monitoring at the physician's discretion to assess their response to therapy. These comprehensive monitoring requirements are designed to ensure appropriate patient response while minimising adverse events during treatment [35].

regelmäßige Überwachung: 3-Wochen-Rhythmus, Laborkontrollen & fachärztliche Begleitung alle 6-12 Wochen abhängigig von der Krankheitsschwere

keine TED-Register in Österreich

Currently, Austria has no existing registry, making it difficult to accurately record patient numbers, to estimate regional distribution, and to plan care. To minimise existing problems, experts recommend the establishment of an official patient forum or information platform monitored by healthcare authorities or relevant medical organisations to provide patients and relatives with reliable information and help them avoid misinformation. They also reiterate that new therapies such as teprotumumab should be restricted to specialised centres with the appropriate expertise. The clinical rationale supporting these recommendations is elaborated in the subsequent section [7].

Health delivery process and management

Behandlung durch spezialisiertes Personal essenziell

laut Expert:innen besteht Mangel an spezialisierten Zentren

Fichter et al. (2012) recommended that patients with TED (except those with very mild disease) should be referred to a specialist centre for clarification and further treatment planning [37], an opinion also shared by the experts interviewed. Many years of experience are important for treatment to recognise which form of therapy is the most appropriate. Teprotumumab should only be prescribed by specialised physicians, primarily as a second-line treatment when cortisone therapy is ineffective. These specialists determine when alternative treatments are appropriate, as cortisone remains the first-line therapy [7]. However, Austrian clinical experts currently see one of the biggest problems in the lack of specialised centres for the treatment of TED, a problem that remains also with the introduction of teprotumumab [7].

überlastete Ambulanzen, Personalfluktuation & erschwerter Zugang zu spezialisierten Zentren

This also raises the question of fair distribution for experts. Hospital outpatient clinics are generally overcrowded, and specialist thyroid centres operate on an elective basis, which means that access to rapid care can present financial hurdles. In addition to hospitals' limited capacity, the constant staff turnover in outpatient clinics is also a problem. This means that patients are treated by different doctors, which makes targeted and standardised treatment difficult and can create an additional burden for those affected [38].

7.2 Patient's perspective

5 Pat./Angehörige haben Fragebögen ausgefüllt

A total of five participants completed the patient questionnaire (from 4 patients and one carer). Three participants stated that they were members of a patient organisation. The characteristics of the participants in this study are described in Table 7-1.

Table 7-1: Characteristics of participants of the structured patient questionnaires

Patient characteristics	Total number of patients (n=5)
Sex	
Female	4
Male	1
Indication	
severe TED	3
moderately severe TED	1
Role	
Patient	4
Carer	1
Member of patient organisation	
Yes	3

späte Diagnosestellung & Symptomatik: erhebliche Belastung für die Pat.

According to the patients and the carer, moderate-to-severe TED is a major burden for patients in both the first phase (active phase) and the second phase (inactive phase). Furthermore, the path to diagnosis is already the first hurdle; the disease diagnosis is often late when it is already in an inflammatory stage. However, even after the diagnosis, the patient's condition only improved slowly. The physical symptoms reported by the patients include severe eye pain, dry and irritated eyes, double vision, a restricted field of vision and deterioration of vision and colour vision [38].

psychische Belastung kann Lebensqualität reduzieren und zu Arbeitsunfähigkeit führen → zusätzliche indirekte Kosten

In addition to the physical symptoms, patients reported severe psychological stress characterised by panic, depression and personality changes, leading to a reduction in QoL associated with TED. Several hospital stays and restrictions on everyday life can lead to an inability to work and a reduction in independence. One of the patients also mentioned that with her current medication, there are often delivery problems in Austria – which can have a further impact on the results of the medication [39]. A study revealed that approximately one-third of patients with TED experienced work limitations or were unable to work. Among these affected individuals, half experienced these limitations during the active disease phase, while one-fifth reported permanent work disability. Both the inability to work and the changes in QoL caused by TED have an impact on the indirect costs incurred by the state and the healthcare system [40].

langanhaltende Einschränkungen trotz Therapie

All patients reported that both the treatments and their associated restrictions and burdens have persisted for several years, spanning both active and inactive disease phases. While patients acknowledged some improvements in their condition, they indicated that their everyday lives remain significantly restricted [39].

Expectations and wishes regarding the new therapy

Pat. erhoffen sich schnellere und verbesserte Behandlung durch Teprotumumab

The patient survey also revealed diverse expectations regarding teprotumumab among patients with TED. Foremost among these expectations was the desire for improved treatment outcomes: patients expressed hope for more rapid and less complicated symptom relief, wished to avoid burdensome decompression therapies and anticipated a shorter disease course with reduced hospitalisation requirements [38].

Verbesserung von QoL essenziell

Pat.-Wissen über Teprotumumab gering

Respondents placed particular emphasis on QoL improvement. Primarily, they prioritised the prevention of visible changes in the orbital region and the alleviation of pain. These improvements would not only reduce psychological stress but also help to maintain social relationships. One patient described the burdensome side effects of her cortisone therapy, which particularly exacerbated her mental well-being. She expressed a desire for an effective alternative to SoC, as she felt the current treatment options are associated with overly severe side effects. However, it should be noted that only one of the three surveyed patients had prior familiarity with teprotumumab, having learned about it through participation in a self-help group [38].

Pat. würden orale Verabreichung bevorzugen

The patients also expressed hope for reduced sick leave duration and the possibility of home-based treatment administration. The mode of administration was identified as an important consideration, with patients demonstrating a clear preference for oral medication over injectable formulations. However, this preference appears incompatible with teprotumumab's administration protocol, which requires intravenous infusion therapy [38].

Bedenken zu Nebenwirkungen, Kosten und Anwendungsform

Regarding teprotumumab as a potential new therapy option, respondents expressed various concerns about the new drug. The main concerns were possible side effects and potential intolerances that could occur during treatment. Financial aspects were also a concern for those affected, particularly the potentially high cost of treatment. Finally, the need for medical supervision during use was mentioned as a potential uncertainty factor, as this could mean additional organisational and time expenditure [38].

7.3 Further ethical and social aspects

Social impact

soziale Isolation und psychische Belastung durch äußere Veränderungen & körperliche Einschränkung

TED can significantly impact patients' lives by altering their optical appearance and causing severe physical symptoms. This condition not only reduces QoL but also leads to negative socioeconomic consequences and increased mortality rates. Patients and carers report that those affected withdraw significantly from their social lives. The reasons for this are shame and insecurity about their appearance and restrictions on activities due to physical changes and required treatments. The loss of the ability to work in a profession and to participate in social activities increases the psychological burden of TED on patients [38].

Frauen häufiger betroffen, frühzeitige Intervention besonders bei jungen Pat. aus ästhetischen Gründen

Furthermore, TED is a disease that tends to affect women more often than men [5]. According to experts, there are differences in the timing of when treatment is started. Particularly younger women are treated at an earlier stage to prevent visible and aesthetic changes as soon as possible. Intervening too late in the case of moderate-to-severe complications can require additional surgery, which in turn can lead to optical changes in the facial area [38].

TED belastet Familiendynamik durch intensivere Betreuungsanforderungen

The disease also constitutes a significant burden for the patient's family ecosystem. Family members, particularly spouses or partners, frequently assume substantial caregiving responsibilities – ranging from coordinating medical appointments to aiding with activities of daily life. This dependency on family members fundamentally alters established relationship dynamics [38].

keine speziellen kulturellen oder ethischen Aspekte identifiziert

However, overall, no specific cultural or ethnic aspects could be identified.

Autonomy, justice and equity

Pat.-Aufklärung & Autonomie zentral für Therapieentscheidung

The ethical aspects of teprotumumab therapy for TED have several important dimensions. Douglas et al. (2022) [35] emphasise the fundamental importance of comprehensive patient education before starting therapy. Patients must be thoroughly informed about possible side effects to make an autonomous decision between treatment with teprotumumab and alternative therapeutic options. This emphasis on patient autonomy is supported by Perros (2023) [41], who highlights that individual patient characteristics and preferences should significantly influence therapy choice. Austrian clinical experts emphasised the critical importance of interdisciplinary collaboration in the management of TED [7].

Therapiewirksamkeit unabhängig von Pat.-Merkmalen; individuelle Anpassung möglich

From an equality perspective, the study data show encouraging results. Treatment efficacy was consistent across different age groups, genders, and even smokers [36]. While treatment protocols are standardised, they retain flexibility for adaptation to individual patient needs. Douglas (2022) emphasises the importance of implementing uniform monitoring protocols and safety

measures across all patient populations. Particular attention is directed toward specific patient subgroups, such as elderly individuals and those with diabetes mellitus, for whom specialised recommendations have been developed [36].

Kostenverantwortung & Setting: komplexe Ressourcenverteilung vs. ärztliche Einzelentscheidung

The ethical responsibility of managing costly treatments extends beyond individual physicians for several key reasons. While clinicians are obligated to use resources efficiently, evaluating the cost-effectiveness of new health technologies requires a more systemic perspective. Additionally, physicians' primary role as patient advocates can create conflicts of interest when balancing individual patient needs against utilitarian principles of resource allocation [41].

Gerechtigkeitsfragen: Kostenverteilung und Versorgungszugang

However, significant challenges arise in the context of justice. Perros (2023) points to the need for cost-benefit analyses and the question of fair distribution of this costly treatment [41]. A particular problem is the geographical distribution of care: Austrian clinical experts consulted for this report criticise the uneven distribution of specialised centres across regions, which particularly disadvantages patients in rural areas. This situation underscores the need for standardised evaluation processes and evidence-based guidelines to ensure fair and high-quality care for all patients [7, 38].

7.4 Registries and documentation of application

fehlende spezifische TED-Register in Europa; Daten evt. in breiteren Endokrinologie-Registern erfasst

Currently, no dedicated European registries specific to TED or Graves' orbitopathy exist [7]. Instead, information on these conditions may be captured within broader disease registries. As indicated by Orphanet, patients with euthyroid Graves' orbitopathy might be included in more comprehensive registries such as the European Register of Multiple Endocrine Neoplasia (EUROCRINE), or national registries like the German CATCH (Cooperative Approach to Thyroid Research), the Italian Thyroid Cancer Observatory, or the Spanish Registry of Endocrine System Tumours (REET) [42].

8 Development costs and public contributions

8.1 Own development costs, acquisitions and licences

Table 8-1 provides a short overview of teprotumumab. We were unable to find any information regarding the total development cost of teprotumumab.

Table 8-1: TEPEZZA® overview

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
TEPEZZA® – Active substance: teprotumumab				
Roche, Genmab, River Vision Development Corporation	Amgen; Horizon Therapeutics	2006: Developed by Genmab in cooperation with Roche but did not lead to a product n.a. but likely between 2010-2012: Licensing deal with River Vision Development Corporation 2017: River Vision Development Corporation acquired by Horizon Therapeutics 2023: Horizon Therapeutics acquired by Amgen	Basic research is publicly funded Early clinical development in cooperation with publicly funded research institutes and hospitals	Basic, applied and translational research support Early-stage research in SME and Biotech start-ups

Basic research and clinical development

Entwicklungsgeschichte von Teprotumumab

Teprotumumab was repurposed for the treatment of thyroid eye disease (TED) after its initial development as a cancer treatment proved unsuccessful. Originally investigated by Genmab and Roche for cancer therapy, it was later studied for both Ewing's sarcoma and diabetic macular oedema, as documented in Chapter 10 in the Appendix. Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center (henceforth: Lundquist Institute) started its research on TED in 1999 and continued it until 2010, when it licensed its patent to River Division Development Corporation. In 2013, the first clinical trial for teprotumumab for TED was conducted by River Division Development Corporation (NCT01868997), followed by Horizon Therapeutics in 2017 (NCT03298867 "OPTIC", NCT03461211 "OPTIC-X", NCT04583735, NCT05002998 (post-marketing, ongoing).

Grundlagenforschung: University of Michigan, University of Pisa und Cedars-Sinai Medical Center

Academic basic and pre-clinical research for the effect of teprotumumab on TED was mainly conducted at the University of Michigan Medical School, the University of Pisa, but also at Hospitals such as the Cedars-Sinai Medical Center (see tables in Chapter 10 in the Appendix). A better understanding of IGF-IR, PTX-3 and TED can be attributed to academic research. Several researchers made significant contributions to the development: Terry Smith (Ludquist Institute, University of Michigan Medical School), Raymond S. Douglas (Ludquist Institute, University of Michigan Medical School, Cedars-Sinai Medical Center) and Alon Kahana (University of Michigan Medical School) led many pivotal studies.

wichtigste Orte für die Entwicklung von Teprotumumab

The research sites included both public and private institutions, with a significant presence of academic medical centres and public hospitals mainly in North America (e.g. Cedars-Sinai Medical Center, Kellogg Eye Center at the University of Michigan) and Western Europe (e.g. University of Pisa, Johannes Gutenberg University Medical Center).

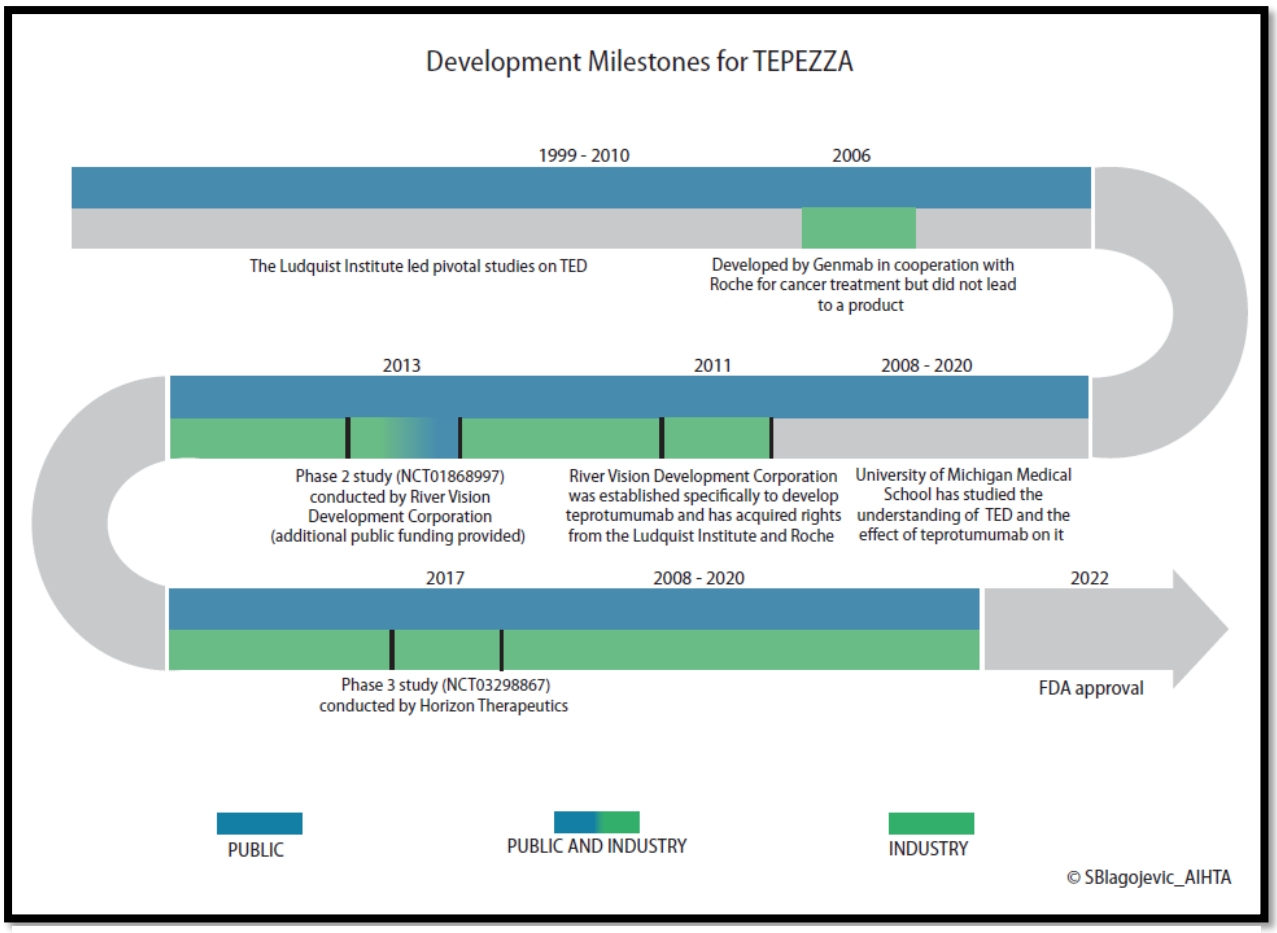


Figure 8-1: Developement Milestones for TEPEZZA

8.2 Public contributions to drug development

Chapter 10 in the Appendix demonstrates substantial public funding supporting TED-specific research, particularly from the US-state-funded National Eye Institute (NEI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The University of Michigan Medical School has received numerous grants between 2008 and 2020, with funding directed toward projects for understanding the disease and the effect of teprotumumab, accumulating a total funding of roughly $9.4 million. The Ludquist Institute has received roughly $8.6 million in grants from 1999 to 2010 for their research in TED. Additionally, the FDA has awarded River Vision Development Corporation grants of $1.2 million from 2014 to 2016 for a phase 2 study for teprotumumab. In total, we have found roughly $19.3 million of public support, the largest portion of which can be attributed to basic research (roughly $18.1 million).

University of Michigan Medical School erhielt mit $ 9.4 Mio. am meisten Förderung, gefolgt von Ludquist Insitute ($ 8,6 Mio.) und River Vision Development Corporation ($ 1,2 Mio.)

The University of Pisa made a significant contribution through their understanding of thyroid eye disease pathophysiology and teprotumumab's mechanism of action despite having less direct involvement in teprotumumab development. However, we could not quantify specific public funding allocated to their research efforts.

keine direkten Fördersummen für University of Pisa gefunden

Besitzverhältnisse und Ansprüche auf zukünftige Umsätze

The Ludquist Institute licensed its patents to River Vision Development Corporation between 2010 and 2012. Two venture capital investors, Lundbeckfonden and S.R. One, each initially held 35.66% rights to future teprotumumab payments. However, agreements reached in April 2020 reduced these rights significantly, decreasing the Company's (Horizon Therapeutics, now Amgen) payment obligations by 70.25%. Consequently, the two venture capital firms now collectively receive 29.75% of teprotumumab revenues, down from their original 71.32% share.

Meilensteinzahlungen von bis zu CHF 103 Millionen für Roche

Under their licensing agreement, River Vision Development Corporation is obligated to pay Roche milestone payments totalling up to CHF103.0 million for teprotumumab development, regulatory approvals, and sales targets. Of this amount, CHF2.0 million was paid in 2017, CHF3.0 million in 2019, and CHF5.0 million in Q1 2020. Additionally, Roche receives tiered royalties ranging from 9% to 12% on annual worldwide net sales.

Company Structure and Financials

Gründung River Vision Development für die Entwicklung von Teptrotumumab

River Vision Development Corporation was established in 2011 specifically to develop teprotumumab. The startup secured $17 million in Series A financing in 2012 with support from Narrow River (an investment management company and limited partner) and venture capital firms, including Vivo Capital, Lundbeckfonden BioCapital, and SR One Capital Management. Following promising results from clinical trial NCT01868997, Horizon Therapeutics acquired River Vision Development Corporation in 2017 for $145 million upfront. Subsequently, in 2023, pharmaceutical giant Amgen acquired Horizon Therapeutics for $27.8 billion, ranking as the second-largest pharmaceutical acquisition that year.

9 Landscape overview

8 Therapien für TED momentan in Entwicklung

We found eight different therapies in development for the treatment of TED (mostly moderate-to-severe). In order of estimated EC decision, the therapies are batoclimab, satralizumab, veligrotug, efgartigimod alfa/hyaluro-nidase-qvfc, VRDN-003 (one for active and one for chronic TED) and linsitinib. The earliest estimated EC decision is expected to be for batoclimab in July 2026, and the latest for linsitinib in December 2028 (see Chapter 10 in the Appendix for further information).

10 Discussion

Thyroid eye disease (TED) is an autoimmune condition affecting retro-ocular tissues primarily in patients with Graves' disease, characterised by overactivation of the insulin-like growth factor 1 receptor (IGF-1R) leading to inflammation and tissue remodelling [1, 3, 43]. The European Group on Graves' orbitopathy (EUGOGO) classifies it into three severity grades (mild, moderate-to-severe, sight-threatening) and approximately 25% of patients develop clinically apparent disease [5]. The current standard first- and second-line treatment for moderate-to-severe active TED is intravenous methylprednisolone (IVMP) monotherapy or combined with mycophenolate, though 20–40% of patients require additional interventions due to insufficient response [6]. Teprotumumab, a human IgG1 monoclonal antibody targeting IGF-1R, presents a potential future treatment option that, while FDA-approved since January 2020, still awaits European Commission approval (expected July 2025) for moderate-to-severe TED [16, 44].

TED:
Autoimmunerkrankung des retrobulbären Gewebes, die durch Überaktivierung des IGF-1-Rezeptors ausgelöst wird

Teprotumumab
→ humaner IgG1-monoklonaler Antikörper

noch keine EC-Zulassung

The development history of teprotumumab provides an interesting case of an active ingredient initially intended for cancer treatment that was subsequently pursued by both academia and industry for an entirely different indication, namely TED. A biotech start-up explicitly founded to develop teprotumumab was later acquired by a larger pharmaceutical company, which subsequently became part of one of the largest pharmaceutical companies worldwide. Throughout the entire development process, approximately $19.3 million came from public funding, with the majority (approximately $18.1 million) allocated to basic research worldwide.

Teprotumumab ursprüngl. für andere Indikation entwickelt

ein Großteil der öffentlichen Finanzierung für Grundlagenforschung (ca. $ 18,1 Mio.)

In this assessment, the evidence base for teprotumumab in active moderate-to-severe TED comprises two pivotal randomised controlled phase 3 trials ([RCTs] OPTIC and OPTIC-J), supplemented by a single-arm extension study (OPTIC-X) and one observational trial (Chen et al.)[20, 22, 23, 45]. These studies established teprotumumab's efficacy across multiple clinically relevant endpoints, including proptosis reduction, clinical activity score (CAS) improvement, and enhanced disease-specific quality of life (QoL) metrics.

Evidenzbasis:
2 Phase-3 RCTs,
1 einarmige- und
1 Beobachtungsstudie

The durability of teprotumumab's therapeutic effect represents an important clinical factor, with published follow-up data revealing variable disease reactivation rates ranging from approximately 25% to 29% across included studies. Additional published retrospective studies not included in the present report show more concerning outcomes, documenting "regression" in 65% of eyes within one year of initial treatment [46] and reactivation in 47% of patients with only 33% maintaining a sustained response at 24 months [47]. While the OPTIC-X extension trial demonstrated that retreatment can be effective for both initial non-responders and patients experiencing disease flares, the limited sample sizes in these subgroups, coupled with knowledge gaps regarding efficacy and safety of third or subsequent treatment cycles, warrant cautious interpretation and necessitate careful patient counselling about expectations and potential retreatment – considerations particularly relevant when weighing teprotumumab against established interventions like intravenous methylprednisolone or surgical decompression, which may offer different durability profiles with distinct risk-benefit considerations. Nevertheless, large real-world studies need to be considered in future, as they might give further insights on the reactivation rate in clinical practice.

fragliche Langzeitwirksamkeit:
Rückfallraten zwischen 25 % und 65 % in diversen publizierten Studien

in Zukunft sollten jedoch auch Daten aus der klinischen Praxis weitere Aufschlüsse bzgl. den Rückfallrate geben

Sicherheitsprofil: besondere Aufmerksamkeit hinsichtlich Hörprobleme, auch als FDA-Warning ergänzt

Teprotumumab's safety profile differs notably from conventional TED treatments, with its most common adverse events including muscle spasms and alopecia rather than hyperglycaemia, blood pressure fluctuations, and potential hepatotoxicity associated with intravenous methylprednisolone [48-50]. However, the potential hearing impairment associated with teprotumamuab, which was added to the FDA warning label in 2023, requires attention in patient selection and monitoring protocols, as this can significantly impact quality of life and functional status, even in cases where symptoms eventually resolve. The final decision regarding the use of teprotumumab in each specific case remains the responsibility of the treating physicians, in close consultation with their patients.

Therapieentscheidungen in enger Abstimmung zwischen Ärzt:innen und Pat.

Vertrauenswürdigkeit der Evidenz → GRADE: niedrig bis sehr niedrig

RoB: RCTs mit „einigen Bedenken"

Einarmige & Beobachtungsstudie mit moderaten RoB

The quality of the evidence from the included teprotumumab studies was assessed as low to very low according to GRADE methodology [19]. The risk of bias (RoB) of the OPTIC [21] and OPTIC-J [21] RCTs was evaluated using the Cochrane RoB 2.0 tool [27], showing "some concerns" for total RoB, while the OPTIC-X extension [23] and Chen et al. [23] observational studies were assessed via the IHE checklist [28], yielding moderate RoB designations. Key limitations included incomplete baseline reporting, unclear anti-thyroid therapy protocols, and potential unmasking due to adverse events [22]. Additional concerning was possible bias regarding inter-observer variability in proptosis measurement – a critical outcome – despite standardisation attempts. OPTIC-X lacked significance testing, and sample size calculations [21], while Chen et al. was limited by its retrospective, unblinded, single-centre design with inadequate baseline characterisation [23].

Metaanalyse & indirekter Vergleich → Überlegenheit von Teprotumumab gg. Methylprednisolone

Limitationen: Qualitätsbewertung & Sensivitätsanalyse

A published meta-analysis and matching-adjusted indirect comparison (MAIC) found teprotumumab superior to IVMP in proptosis reduction and diplopia response [29]. However, this indirect comparison has significant methodological limitations, including the absence of individual study quality assessment and limited sensitivity analysis. Additionally, six of the twelve methylprednisolone studies included were conducted in Chinese populations, raising questions about generalisability to European patients given known ethnic differences in proptosis manifestation [32]. Furthermore, an unpublished MAIC submitted by the marketing authorisation holder has shown similar results, comparing teprotumumab not only to IVMP, but also mycophenolate mofetil.

fehlende direkte Vergleichsstudien als kritische Evidenzlücke

direkte Vergleiche nur mit Placebo

While these indirect comparisons suggest potential superiority, a critical limitation in teprotumumab's evidence base remains the absence of direct comparative studies against SoC treatments. In fact, no head-to-head trials have been conducted comparing teprotumumab to established treatments such as corticosteroids, orbital radiotherapy, or surgical interventions. This comparison gap represents a significant barrier to definitively establishing teprotumumab's position within treatment algorithms.

laufende Studien & keine HTA-Berichte

Notably, an ongoing Phase 3b/4 post-marketing study is investigating the safety and tolerability of different teprotumumab dosing schedules, which may provide additional insights into optimal treatment protocols. While no completed health technology assessment (HTA) reports for teprotumumab in TED are currently available, evaluations by both the National Institute for Health and Care Excellence (NICE) and National Institute for Health Research (NIHR) are currently underway and the results are expected in August 2025.

fehlende TED-Register

Moreover, the absence of dedicated European registries for thyroid eye disease limits the systematic collection of real-world comparative effectiveness data, leaving considerable uncertainty about relative therapeutic value that must be resolved through targeted comparative research.

Implementierungshürden von Teprotumumab: multidisziplinäre Versorgung, spezialisierte Zentren, Register

From an organisational and implementation perspective, the implementation of teprotumumab would involve logistical adaptions. For example, the treatment requires preliminary assessments, including fasting blood glucose, haemoglobin A1C, vision and hearing testing, and pregnancy testing when applicable [35]. Delivery necessitates specialised centres with trained personnel and monitoring protocols, which may include implementation challenges given the limited availability of facilities with sufficient TED expertise [37, 51]. Adding complexity, TED diagnosis and management require collaboration among multiple specialists (endocrinologists, ophthalmologists, and others).

Teprotumumab mit hohen Kosten verbunden

Budgetfolgen hängen von tatsächlicher Pat.-Anzahl, die Teprotumumab bekommen & von Preis ab

Economic considerations surrounding teprotumumab present significant uncertainties for healthcare systems. Currently, no official European prices are available. Thus, a placeholder price of €13,662.59 per 500mg powder for infusion was derived from the US market price (manufacturer price: $16,382) for analytical purposes. The budget impact analysis conducted (BIA) is subject to considerable uncertainty due to several key factors. Firstly, the projected increasing market uptake of teprotumumab by the manufacturer (year 1: 40, year 2: 90, year 3: 115 patients) contrasts with an estimated 45 patients annually based on published incidence rates. Therefore, the total three-year budget impact for the teprotumumab scenarios ranges between €73.9 million and 117.7 million[6]. Given a three-year budget impact of €19.4 million of the SoC-scenario, the teprotumumab-scenarios are four to six-times higher. Overall, the eventually negotiated price and actual treated population size will substantially influence budgetary implications because the cost of teprotumumab marks the biggest share of the total budget impact.

BIA präsentiert optimistisches Szenario

keine Kosteneffektivitätsanalyse verfügbar

Furthermore, the analysis presents an optimistic scenario based on expert expectations where teprotumumab introduction generates minimal cost savings through the elimination of subsequent rituximab treatments or surgical interventions like orbital decompression. Notably absent is any cost-effectiveness evaluation for teprotumumab, with neither published international pharmacoeconomic assessments available nor manufacturer-supplied analyses. These economic uncertainties compound the decision-making complexity regarding teprotumumab's appropriate position within healthcare systems, particularly given its high per-patient cost relative to existing therapies.

Bewertung VOR EU-Zulassung, daher keine realen Daten aus Europa

Befragte Kliniker*innen nicht für ganz Ö repräsentativ; Pat.-Perspektive durch kleine Stichprobengröße eingeschränkt

This HTA report has several limitations that should be considered when interpreting its findings. From an economic perspective, the budget impact analysis relies on assumptions regarding market uptake and potential cost offsets that may not accurately reflect real-world implementation patterns. The assessment's timeline coincided with the pre-approval phase of teprotumumab in Europe (even before positive CHMP opinion), meaning that post-marketing surveillance data and real-world evidence from European healthcare settings were unavailable for consideration, creating uncertainty in the applicability of findings to local contexts. Regarding clinical perspectives, the expert consultations have not involved experts from all nine federal states, potentially limiting geographic representation in clinical practice insights. Additionally, patient perspective analysis was constrained by the small sample size, with only five patient questionnaires available for analysis, which may not fully capture the diversity of experiences, preferences, and

[6] Without orbital radiotherapy and daycare costs due retrospectively reported or missing data.

needs within the broader TED patient population, particularly regarding QoL impacts and treatment expectations.

Teprotumumab: Verbesserungen in relevanten Endpunkten, aber mit klinischen, organisatorischen und ökonomischen Unsicherheiten verbunden

Overall, whilst teprotumumab demonstrates promising efficacy for key outcomes in active moderat-to-severe TED, including proptosis reduction and improved QoL, substantial uncertainties exist across multiple domains that limit definitive assessment of its value proposition. From a clinical perspective, the evidence base is constrained by low to very low GRADE quality assessments, concerning durability questions from retrospective studies, and critically, the absence of direct comparative studies against standard treatments. Implementation considerations reveal logistical adpations through specialised infrastructure requirements and multidisciplinary care coordination needs. The economic evaluation highlights a considerable cost differential compared to existing therapies, whilst the absence of cost-effectiveness analyses raises important questions about sustainable resource allocation. Resolution of these uncertainties requires targeted comparative research, registry development, and comprehensive economic evaluation before teprotumumab's optimal position within the Austrian healthcare system can be fully established.

11 References

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12 List of abbreviations

AE..... adverse events
AESI..... adverse event of special interest
AIHTA ..... Austrian Institute of Health Technology Assessment
ATC..... Anatomical Therapeutic Chemical
ATD ..... antithyroid drugs
ATMP..... Advanced Therapy Medicinal Product
BIA ..... budget impact analysis
CAS ..... clinical activity score
CATCH..... Cooperative Approach to Thyroid Research
Cfb..... indicates change from baseline
Cfb_{raw} ..... raw change from baseline
CHMP..... Committee for Human Medicinal Products
CHO ..... Chinese hamster ovary
CI..... confidence interval
CT..... Computer tomography
COVID-19..... coronavirus disease 2019
CSR ..... clinical study report
DON..... dysthyroid optic neuropathy
EC..... European Commission
EKO..... Erstattungskodex
EMA ..... European Medicines Agency
EO ..... Graves' orbitopathy
EOM..... extra-ocular muscles
EU ..... European Union
EUGOGO..... European Group on Grave's Orbitopathy
EUnetHTA ..... European Network for Health Technology Assessment
EUROCRINE.. European Register of Multiple Endocrine Neoplasia
FDA..... Food and Drug Administration
FT3..... triiodothyronine,
FT4..... free thyroxine
GO ..... Graves' orbitopathy
GO-QoL ..... Graves' ophthalmopathy-specific quality-of-life
GÖG ..... Gesundheit Österreich GmbH
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
Gy ..... gray
HTA ..... health technology assessment
HbA1C ..... Haemoglobin A1C
IBD..... inflammatory bowel disease
ICD ..... International Statistical Classification of Diseases and Related Health Problems
IGF-1R..... insulin-like growth factor 1 receptor
IgG1..... immunoglobulin G1
IHE..... Institute of Health Economics
IHSI..... International Horizon Scanning Initiative Database
ITC ..... indirect treatment of comparison
INN ..... International non-proprietary name
ITT ..... intention to treat
IV..... intravenous
IVMP..... intravenous methylprednisolone
LKF..... Leistungsorientierte Krankenanstaltenfinanzierung
LSM ..... least squares mean
MAA..... Marketing Authorisation Application
MAH ..... Marketing Authorisation Holder
MAIC ..... Matching Adjusted Indirect Comparison
M.gravis ..... myasthenia gravis
MHLW..... Ministry of Health, Labour and Welfare
MHRA..... Medicines and Healthcare products Regulatory Agency
mIU/L..... milli-International units per litre
MMF ..... mycophenolate mofetil
MRI ..... magnetic resonance imaging
N..... number of patients
NCT ..... national clinical trial
NDS ..... New Drug Submission
NEI..... National Eye Institute

NICE ..... National Institute for Health and Care Excellence
NIDDK ..... National Institute of Diabetes and Digestive and Kidney Diseases
NIHR ..... National Institute for Health Research
n.r. ..... not reported
PICO ..... population-intervention-comparator-outcome
P.P ..... per protocol
PPRI ..... Pharmaceutical Pricing and Reimbursement Initiative
PRIME ..... Priority Medicines
PRO ..... patient-reported outcomes
PTX-3 ..... Pentraxin 3
QoL ..... quality of life
RAI ..... radioactive iodine
REET ..... Spanish Registry of Endocrine System Tumours
RCT ..... randomised controlled trial
RoB ..... Risk of Bias
SAE ..... serious adverse event
SD ..... standard deviation
SoC ..... standard of care
TED ..... thyroid eye disease
TGA ..... Therapeutic Goods Administration
TRAbs ..... thyrotropin receptor antibodies
TSH ..... thyroid stimulating hormone
TSH-R-Ab ..... TSH receptor antibodies
UK ..... United Kingdom
US ..... United States
VF ..... visual function
WHO ..... World Health Organisation

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH