HTA Austria
Austrian Institute for
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GmbH

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

HTA-Appendix

Appendix

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1 Medical condition and treatment options

Table 1-1: Clinical activity score (CAS) according to Mourits [1]

Symptoms/findings		Single score
Subjective signs of activity	Spontaneous retrobulbar pain or pressure sensation	1
	Bulbar motion pain	1
Objective signs of activity	Eyelid redness	1
	Conjunctiva redness	1
	Oedema of the eyelids	1
	Oedema of the conjunctiva (chemosis)	1
	Oedema of caruncle and/or plica semilunaris	1
Sign of disease progression	Increase in exophthalmos (proptosis) >2 mm within 1-3 months	1
	Reduction in eye mobility in any direction >8° within 1-3 months	1
	Reduction in visual acuity >1 visual acuity level within 1-3 months	1
CAS total score	**An active thyroid eye disease is present when ≥ 3 points are observed**	**10**

Abbreviations: CAS: Clinical activity score, TED: thyroid eye disease

4 Methods

4.1 Search strategy

4.1.1 Cochrane (04.02.2025)

ID	Search
#1	(teprotumumab*) (Word variations have been searched)
#2	(teprotumumab*) (Word variations have been searched)
#3	(hzn NEXT 001*) (Word variations have been searched)
#4	(hzn?001*) (Word variations have been searched)
#5	(rg NEXT 1507*) (Word variations have been searched)
#6	(rg?1507*) (Word variations have been searched)
#7	(ro NEXT 4858696*) (Word variations have been searched)
#8	(ro?4858696*) (Word variations have been searched)
#9	(rv NEXT 001*) (Word variations have been searched)
#10	(rv?001*) (Word variations have been searched)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	English:la
#13	German:la
#14	#12 OR #13
#15	#11 AND #14
#16	(conference proceeding):pt
#17	(abstract):so
#18	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#19	#16 OR #17 OR #18
#20	#15 NOT #19

4.1.2 Embase (04.02.2025)

No.	Query	Results
#15.	#13 NOT #14	485
#14.	#13 AND 'Conference Abstract'/it	150
#13.	#12 AND ([english]/lim OR [german]/lim)	635
#12.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	649
#11.	rv$001*	32
#10.	'rv 001*'	8
#9.	ro$4858696*	
#8.	'ro 4858696*'	2
#7.	rg$1507*	5
#6.	'rg 1507*'	21
#5.	hzn$001*	
#4.	'hzn 001*'	2
#3.	teprotumumab*	45
#2.	teprotumumab*	615
#1.	'teprotumumab'/exp	593

4.1.3 International HTA database (04.02.2025)

11 ((rv001*) AND (monoclonal)) OR (("rv 001") AND (monoclonal)) OR (ro4858696*) OR ("ro 4858696") OR (rg1507*) OR ("rg 1507") OR (hzn001*) OR ("hzn 001") OR (teprotumumab*) OR (teprotumumab*),"0","2025-02-04T15:46:41.000000Z"
10 (rv001*) AND (monoclonal),"0","2025-02-04T15:45:59.000000Z"
9 ("rv 001") AND (monoclonal),"0","2025-02-04T15:45:15.000000Z"
8 ro4858696*,"0","2025-02-04T15:39:25.000000Z"
7 "ro 4858696","0","2025-02-04T15:39:02.000000Z"
6 rg1507*,"0","2025-02-04T15:38:39.000000Z"
5 "rg 1507","0","2025-02-04T15:38:22.000000Z"
4 hzn001*,"0","2025-02-04T15:37:56.000000Z
3 "hzn 001","0","2025-02-04T15:37:39.000000Z"
2 teprotumumab*,"0","2025-02-04T15:36:14.000000Z"
1 teprotumumab*,"0","2025-02-04T15:35:59.000000Z"

4.1.4 Medline (04.02.2025)

1 teprotumumab*.mp. (334)
2 teprotumumab*.mp. (23)
3 hzn 001*.mp. (0)
4 hzn?001*.mp. (0)
5 rg 1507*.mp. (1)
6 rg?1507*.mp. (1)
7 ro 4858696*.mp. (1)
8 ro?4858696*.mp. (1)
9 rv 001*.mp. (3)
10 rv?001*.mp. (19)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (352)
12 limit 11 to (english or german) (349)
13 remove duplicates from 12 (345)

4.3 Study selection – PRISMA flow chart

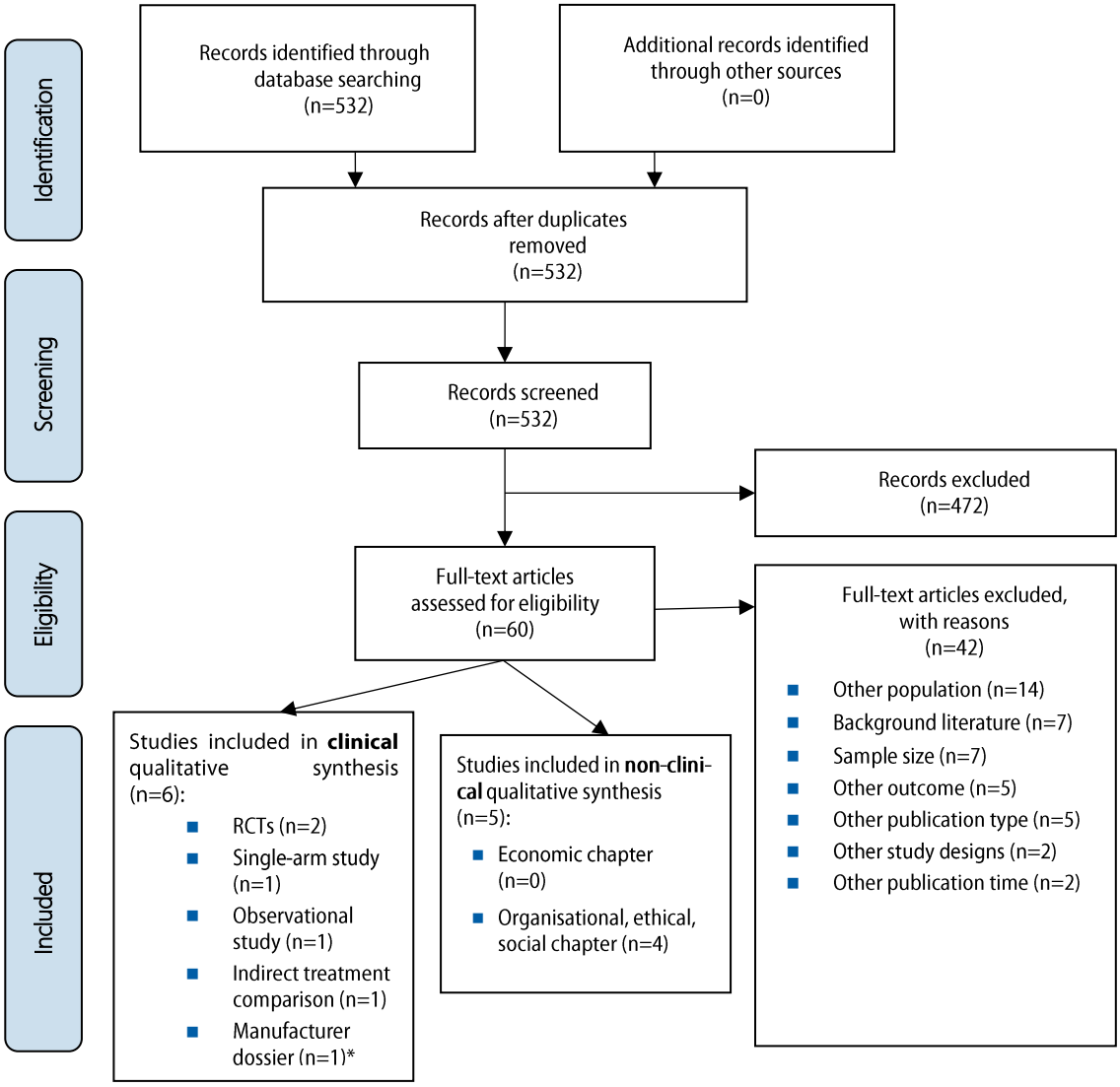

*Figure 4-1: Flow chart of study selection (PRISMA Flow Diagram); * The dossier was submitted to the AIHTA by the health technology developer on 20 February 2025.*

4.5 Methods economic domain

4.5.1 Budget impact analysis – placeholder price

1. Input cost estimate (value) reported in original study (e.g. 123.45)	16382 Recalculate
2. Select source dataset for PPP values	IMF
3. Select currency (country) reported in original study (e.g. United States)	United States
4. Select target currency (country) (e.g. United Kingdom)	Austria
5. Select price year reported in original study (e.g. 1997)	2024
6. Select target price year (e.g. 2010)	2024

Currency (country)	Price year	PPP values	ICF**	GDPD values	IIF***	Results
United States	2024	1		134.889999389648 | 134.889999389648	1.00	
Austria	2024	0.833999991416931	0.83			
						13662.59

* Cost estimate in original study is reported in a pre-Euro currency. Further information on the IMF website (see FAQs '3) Specific Data Series > For the countries that adopted the euro, how did you convert the series expressed in national currency?'). Irrevocable Euro conversion rates apply to both IMF and OECD PPP values.
** ICF = Implied Conversion Factor
*** IIF = Implied Inflation Factor

Figure 4-2: CCEMG - EPPI-Centre Cost Converter [5]

4.5.2 Budget impact analysis –assumptions for calculation

Information on the number of patients with TED in Austria was, on the one hand, calculated based on prevalence and incidence rates of the EUGOGO 2021 and, on the other hand, based on assumptions from Austrian clinical experts. Key assumptions presented the following:

- 90% of TED patients in Austria can be cured with thyroid treatments and do not need further treatments [2].
- Patients with moderate-to-severe TED (0,161/10,000 persons/year) receive SoC corticosteroid treatments [3].
- And 20-40% of these patients need further treatments, e.g. new monoclonal antibodies like Rituximab, teprotumumab or surgeries [4].
- The clinical experts estimated the market share of the different SoC treatments based on published data and their experience.
- The manufacturer estimated teprotumumab's market uptake based on expert consultations (1. year: 40; 2. year: 90; 3. year: 115).

For calculating expenditures for SoC treatments in the outpatient sector, we used the spot prices listed in the refund code (Erstattungskodex, EKO) provided by the Austrian Federation of Social Insurances. We used DRG data to calculate inpatient treatment expenditures (Leistungsorientierte Krankenanstaltenfinanzierung, LKF). We used average values in case more than one unit cost information was available for a single cost item.

Cost categories with a minor contribution to the overall costs were excluded (e.g., costs of eligibility and monitoring and treatments for adverse events). In addition, the analysis did not include additional treatments, such as local agents, supportive treatments, like pain therapy, or treatments of comorbidities.

We calculated the three-year gross drug budget impact (drug acquisition costs based on the eligible population and predicted market share), the net drug budget impact (drug acquisition costs and cost-offsets anticipated from the increased utilisation and/or displacement of other drugs) and additional costs, such as inpatient costs due to the application of the therapy and re-treatment costs. Due to limited data on post-teprotumumab treatment requirements and lacking experience in clinical practice, the BIA presents an

optimistic scenario where teprotumumab therapy could potentially eliminate the need for rituximab treatments or surgical interventions.

Table 4-1: Unit cost data

	(Average) unit costs	Range	Reference
A: Teprotumumab			
A1: Drug acquisition	€13,662.59 per 500 mg powder for IV	-	Converted US-price submitted by manufacturer $16,382 (2024)
A2: Hospital daycare clinic stay for IV			No cost information available for AT
A3: Hospital inpatient stay after IV-reactions	€1,571.40 per stay	-	Average LKF data for AT
B: SoC for moderate-to-severe TED in Austria			
B1: Thyroid treatments			
Methimazole oral	€3.25 per 20 mg tabl. 20 pieces	-	EKO
Euthyrox, oral	€1.50 per 100 mg tabl. 20 pieces	-	EKO
Thyroidectomy	€7,483.70 per intervention	-	Average LKF data for AT
B2: First- and second-line corticosteroid treatment			
Methylprednisolone (Urbason®/Metasol®) IV	€35.25 per 250 mg powder for IV	-	EKO
Oral mycophenolate sodium	€131.25 per 500 mg tabl. Mycophenolatmofetil 0,5 = Mycophenolsäure 0,36 150 pieces	-	EKO
B3: Further treatments after corticosteroids			
Rituximab (off-label)	€4,762,80 (costs for oncological indication)		Average LKF data for AT
Orbital decompression	€7,214.80 per intervention	-	Average LKF data for AT
MRT	€253.48 per intervention	€106.26 - €414.20	LKF data of different federal states
Excluded because not (cost) relevant based on clinical expert optionion			
Checks on contra indications before teprotumumab therapy			
Monitoring after teprotumumab or SoC treatment			
Treatment of adverse events			
Not considered because retrospective information			
Orbital radiotherapy after corticosteroids instead of surgical options			

Abbreviations: AT: Austrian, EKO: Erstattungskodex, IV: infusion; LKF: Leistungsorientierte Krankenanstalten-finanzierung; pat: patient, SoC: standard of care; TED: thyroid eye disease

4.6 Methods organisational, etcial and social domain

4.6.1 Patient survey

Table 4-2: Questions asked to TED patients

Question 1	Rolle des Ausfüllenden (einzelne/ Patient/Angehörige/Andere)
Question 2	Hauptwohnsitz
Question 3	Mitglied einer Patient:innenorganisation Wenn ja, bitte nennen Sie die Patient:innenorganisation Wenn ja, welche Rolle haben Sie in der Patient:innenorganisation? Wenn ja, welche Erkrankung(en) wird/werden von der Organisation vertreten?
Question 4/1	Krankheitsstadium/ Schweregrad
Question 4/2	Krankheitsgeschichte Wie lange leben Sie schon mit der Krankheit/dem Leiden? Bitte beschreiben Sie Ihre Behandlungsgeschichte
Question 4/3	Zusätzliche Informationen, die Ihrer Meinung nach für die Ersteller des HTA-Berichtshilfreich wären
Question 5	Falls zutreffend, wo haben Sie Informationen über die Erfahrungen der Patient:innen eingeholt? Falls zutreffend, wie haben Sie Informationen über die Erfahrungen der Patient:innen gesammelt?
Question 6	Wie wirkt sich die moderate bis schwere TED auf Ihr tägliches Leben (eines Patienten/einer Patientin) aus?
Question 7	Wie wirkt sich TED auf Angehörige aus?
Question 8	Wie gut bewältigen Patient:innen mit moderater bis schwerer TED ihre Erkrankung mit den derzeit verfügbaren Therapien?
Question 9	Was erwarten diejenigen Patient:innen, die keine Erfahrung mit Teprotumumab haben, von neuen Therapien im Allgemeinen?
Question 10	Für diejenigen, die Erfahrung mit Teprotumumab haben: Welche Auswirkungen hatte/hat es auf Ihr Leben?
Question 11	Bitte geben Sie alles an, was Ihrer Meinung nach für das für die gemeinsame Bewertung zuständige HTA-Team wissenswert sein könnte.
Question 12	Bitte fassen Sie Ihren Beitrag in maximal zehn Kernaussagen zusammen und listen Sie die wichtigsten Punkte auf.

4.6.2 Expert consultation

Table 4-3: Questions for clinical experts

Questions about epidemiological data in Austria	
Question 1	Wie würden Sie die Prävalenz und Inzidenz von TED in der österreichischen Bevölkerung einschätzen?
Question 2	Wie hoch sind nach Ihrer klinischen Erfahrung die Prävalenz und Inzidenz schwerer bis moderater TED-Fälle in Österreich?
Questions 3	Wie hoch schätzen Sie die jährliche Anzahl an TED-Patient*innen in Österreich ein, für die Teprotumumab als Therapieoption in Frage kommt?
Question 4	In welchem Lebensalter erfolgt typischerweise die Diagnose einer TED?
Questions about standard of care in Austria	
Question	Was sind die aktuellen Standardtherapien für moderat-schwere TED in Ö (Erstlinie & Zweitlinie)?
Question	Wird ADT immer zeitgleich zur Behandlung der EO gegeben (laut EUGOGO)? Wenn ja, in welcher Dosis?
Question	Was sind die Marktanteile der Standardtherapien bzw. welches wird am häufigsten/wenigsten häufig verwendet? % der Pat?
Question	Welche Arzneimittel werden verschrieben? In welcher Dosierung?
Question	Welche kostenrelevanten Nebenwirkungen haben diese Arzneimittel?
Question	Wie schaut das Monitoring der jeweiligen SoC-Behandlungen aus? Welche Aspekte sind kostenrelevant?
Questions about teprotumumab	
Question	Wird Teprotumumab im stationären oder ambulanten Setting verabreicht?
Question	Wird Teprotumumab als Erstlinien- und/oder Zweitlinientherapie eingesetzt (laut EUGOGO 2021 Zweitlinientherapie)? Welche Standardtherapien sind die richtigen Vergleichtstherapien?
Question	Welche kostenrelevanten Nebenwirkungen hat TEPROTUMUMAB®?
Question	Welches Monitoring ist nach der Therapie mit Teprotumumab notwendig, für wie lange? Ist es kostenrelevant?
Question	Ist das Follow-up der Studie ausreichend lange gewählt (24 Wochen)?
Question	Erfolgreiche TEPROTUMUMAB®-Therapie bedeutet, dass keine Standardtherapie zusätzlich mehr notwendig ist bzw. welche begleitenden Therapien sind dennoch notwendig, z.B. ADT?
Questions about organisational, ethical and social aspects	
Question	Gibt es besondere organisatorische Strukturen, die für die Verabreichung von Teprotumumab notwendig sind (z. B. spezielle Zentren, spezielles Personal, Schulungen für medizinisches Personal, Infrastruktur)
Question	Welche ethischen und sozialen Herausforderungen sehen Sie für Patientinnen mit endokriner Orbitopathie, insbesondere im Hinblick auf Diagnose, Krankheitsbewältigung und psychosoziale Belastungen?
Question	Inwiefern könnte der Einsatz von Teprotumumab ethische oder soziale Fragen aufwerfen, beispielsweise in Bezug auf den Zugang zur Therapie oder mögliche Auswirkungen auf ihre Lebensqualität?

4.7 Methods public funding domain

We started our research on product origins by thoroughly searching for product identifiers, including initial numbers and character combinations, generic or non-proprietary names of active ingredients, and trade or brand names usually given later in development. This search was conducted using AdisInsight. This ensures that we start the product search as early as possible for its history before the company gives the product a final brand name for marketing's sake.

Next, we searched for the earliest reference of these generic or non-proprietary names in publications to identify the origins of the products. Medline was searched to identify early basic R&D support, and the corresponding publications were searched for affiliations with academic institutions and research grants mentioned. Then, databases on clinical trials (https://clinicaltrials.gov/, https://eudract.ema.europa.eu/) and supranational institutions for research funding (https://cordis.europa.eu/; https://reporter.nih.gov/) were searched. Sponsor details, type of funding and amounts were extracted. This was followed by searching the European Commission Competition website (https://competition-cases.ec.europa.eu/search) to determine whether any EU member states provided funds to the companies developing gene therapies for TED. Company-specific research was conducted using the official websites of the originators and collaborators to find additional information on funding rounds, sponsors, mergers, and acquisitions (M&A). We complimented our findings by extracting information on employee numbers, revenues and shareholders from 10-K reports.

Finally, we used Google, Forbes, and Reuters to identify news articles about the products. We finished the search using various investor news sources (Statnews, BusinessInsider, Business Wire, FiercePharma, Pharmafile, Pharmatimes, Pharmaphorum, BioPharma Drive, BioWorld, Biospace, etc.). If the products or the knowledge that led to a product were acquired through an M&A, we also analysed the originator company if they received public contributions.

5 Clinical effectiveness and safety assessment

5.1 Inclusion and exclusion criteria

Table 5-1: In- and exclusion criteria of the OPTIC trial [5]

Inclusion criteria	Exclusion criteria
Eligible patients must meet/provide all of the following criteria: ■ Written informed consent. ■ Patients between the ages of 18 and 80 years, inclusive, at screening. ■ Clinical diagnosis of Graves' disease associated with active TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at screening and baseline. ■ Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia. ■ Onset of active TED symptoms (as determined by patient records) within 9 months prior to baseline. ■ Patients must be euthyroid with the thyroid function under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels <50% above or below the normal limits) at screening. Every effort should be made to correct mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the duration of the clinical trial. ■ Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study. ■ Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3 times the upper limit of normal (ULN) or serum creatinine <1.5 times the ULN according to age at Screening. ■ Diabetic patients must have HbA1c <9.0% with no new diabetic medication [oral or insulin] or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to screening). ■ Women of childbearing potential (including those with an onset of menopause <2 years prior to screening, non-therapy-induced amenorrhea for <12 months prior to screening, or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and through week-48 of the follow-up period); patients who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate less than 1% per year), when used consistently and correctly, includes implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner.	Patients will be ineligible for study participation if they meet any of the following criteria: ■ Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or colour defect secondary to optic nerve involvement within the last 6 months. ■ Corneal decompensation unresponsive to medical management. ■ Decrease in CAS of ≥2 points in the study eye between screening and baseline. ■ Decrease in proptosis of ≥2 mm in the study eye between screening and baseline. ■ Previous orbital irradiation or surgery for TED. ■ Any steroid use (intravenous [IV] or oral) with a cumulative dose equivalent to ≥1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to screening. ■ Corticosteroid use for conditions other than TED within 4 weeks prior to screening (topical steroids for dermatological conditions and inhaled steroids are allowed). ■ Selenium and biotin must be discontinued 3 weeks prior to screening and must not be restarted during the clinical trial; however, taking a multivitamin that includes selenium and/or biotin is allowed. ■ Any previous treatment with rituximab (Rituxan® or MabThera®) or tocilizumab (Actemra® or Roactemra®). Use of any other non-steroid immunosuppressive agent within 3 months prior to screening. ■ Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial. ■ Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude study participation or complicate interpretation of study results. ■ Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial. ■ Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin). ■ Pregnant or lactating women. ■ Current drug or alcohol abuse, or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the patient.

■ Male patients must be surgically sterile or, if sexually active with a female partner of childbearing potential, must agree to use a barrier contraceptive method from Screening through 180 days after the last dose of study drug. ■ Patient is willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.	■ Biopsy-proven or clinically suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus, or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis). ■ Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies. ■ Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study. ■ Previous enrollment in this study or participation in a prior teprotumumab clinical trial. ■ Human immunodeficiency virus (HIV), hepatitis C or hepatitis B infections.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CAS: clinical activity score, FT3: free triiodothyronine, FT4: free thyroxine; HbA1c: haemoglobin A1C, HIV: Human immunodeficiency virus, IV: intravenous, IUD: intrauterine devices, TED: thyroid eye disease, ULN: upper limit of normal

Table 5-2: Differences in the in- and exclusion criteria of the OPTIC-X [6] trial compared to the OPTIC trial [5]

Inclusion criteria	Exclusion criteria

Key Differences in Inclusion Criteria:
1. Patient Age:
■ **OPTIC**: Required patients between ages 18-80 years at screening.
■ **OPTIC-X**: No specific age requirement mentioned.
2. Disease Characteristics:
■ **OPTIC:** Required CAS ≥ 4 and onset within 9 months prior to baseline.
■ **OPTIC-X**: Must have completed the 24-week double-masked treatment period in OPTIC and either:
  ■ Be a proptosis non-responder (<2 mm reduction) at week 24, OR
  ■ Be a proptosis responder who flares during the follow-up period.
3. Diabetic Control:
■ **OPTIC:** Required HbA1c < 9.0% with no new diabetic medication or >10% dose change within 60 days.
■ **OPTIC-X**: Simply requires HbA1c < 9.0% at the most recent clinic visit.
	Key Differences in Exclusion Criteria:
	1. Prior Treatment:
	■ **OPTIC**: Excluded those with any previous orbital irradiation/surgery.
	■ **OPTIC-X**: Added criterion that the patient must not have received any treatment for TED since week 24 of OPTIC.
	2. Disease Stability:
	■ **OPTIC**: Excluded those with a decrease in CAS ≥ 2 points or proptosis ≥ 2 mm between screening and baseline.
	■ **OPTIC-X**: Does not include these stability requirements.
	3. Prior Medications:
	■ **OPTIC**: Had specific restrictions on prior steroid use, selenium/biotin use, and other immunosuppressive agents.
	■ **OPTIC-X**: Less specific about prior medication restrictions, focusing mainly on current disease status.
	4. Study Participation:
	■ **OPTIC**: Excluded previous enrolment in this study or prior teprotumumab trials.
	■ **OPTIC-X**: This criterion is not included since it's specifically for OPTIC study participants.

Abbreviations: CAS: clinical activity score, HbA1c: haemoglobin A1C, TED: thyroid eye disease.

Table 5-3: Differences in the in- and exclusion criteria of the OPTIC-J [7] trial compared to the OPTIC trial

Inclusion criteria	Exclusion criteria
Key Differences in Inclusion Criteria: 1. Age Requirements: ■ **OPTIC**: 18-80 years inclusive. ■ **OPTIC-J**: 20-75 years inclusive. 2. Disease Activity/Severity: ■ **OPTIC**: CAS ≥ 4 (on 7-item scale) and onset within 9 months. ■ **OPTIC-J**: CAS ≥ 3 (not specified if 7-item scale) and onset within 12 months. 3. Thyroid Status: ■ **OPTIC**: Euthyroid or mild hypo/hyperthyroidism (FT4 and FT3 <50% above/below normal limits). ■ **OPTIC-J:** Only specifies that thyroid function must be stable for 3 months.	Key Differences in Exclusion Criteria: 1. Prior Treatment Restrictions: ■ **OPTIC**: No prior orbital radiation/surgery for TED, cumulative steroid dose <1g methylprednisolone equivalent. ■ **OPTIC-J:** Less restrictive on prior treatments, allows previous steroid treatment if completed >4 weeks before. 2. Laboratory Requirements: ■ **OPTIC**: ALT/AST ≤3 times the upper limit of normal (ULN), serum creatinine <1.5 times the ULN, HbA1c < 9.0%. ■ **OPTIC-J:** AST/ALT < 5 times the ULN, serum creatinine ≤ 2.0 mg/dL, HbA1c ≤ 8.0%.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CAS: clinical activity score, FT4: free thyroxine, FT3: free triiodothyronine, HbA1c: hemoglobin A1C, TED: thyroid eye disease, ULN upper limit normal

5.2 Baseline characteristics

Table 5-4: Baseline demographics and disease characteristics of participants in the OPTIC study [5]

Study reference/ID Characteristics Category	Study intervention	
OPTIC	Teprotumumab N = 41	Placebo N = 42
Age [years], mean (SD)	51.6±12.6	48.9±13.0
Sex [f/m] (%)	29 (71)/12 (29)	31 (74)/11 (26)
Race, n (%)		
White	35 (85)	37 (88)
Black	4 (10)	2 (5)
Asian	2 (5)	1 (2)
Other	0	2 (5)
Duration of thyroid eye disease — mo.	6.2±2.3	6.4±2.4
Duration of Graves' disease — yr	3.5±6.1	2.2±3.2
Smoking status — no. (%)		
Smoker	9 (22)	8 (19)
Nonsmoker	32 (78)	34 (81)
Proptosis measurement — mm	22.62±3.32	23.20±3.21
Clinical activity score‡	5.1±0.9	5.3±1.0
Thyroid hormone level — pmol/liter		
Free triiodothyronine	5.1±1.8	5.3±1.7
Minimum–Maximum	3.3-13.0	3.3-11.1
Free thyroxine	16.5±5.3	16.2±4.8
Minimum–Maximum	6.3–34.2	8.8–32.2
Thyrotropin level — mIU/litre	1.75±4.16	1.42±2.17
Minimum–Maximum	0.01–25.77	0.01–7.99

*Abbreviations: f: female, m: male, **mo: months**, N: number of randomized patients, SD: standard deviation, yr: year.*

Table 5-5: Baseline demographics and disease characteristics of participants in the OPTIC-X study [6]

Study reference/ID Characteristics Category	Study intervention	
OPTIC-X	1st Course (OPTIC Placebo) N = 37	2nd Course/Retreatment (OPTIC Teprotumumab) N = 14
Age, Mean (SD)	48.5 (13.5)	56.1 (11.5)
Gender, n (%)		
Female	27 (73.0%)	11 (78.6%)
Male	10 (27.0%)	3 (21.4%)
Race, n (%)		
White	33 (89.2%)	11 (78.6%)
Black	1 (2.7%)	1 (7.1%)
Asian	1 (2.7%)	2 (14.3%)
Other	2 (5.4%)	0
Years since Diagnosis of Graves' Disease, Median (range)	1.4 (0.98 - 15.29)	1.7 (0.79 - 28.78)
Months Since Diagnosis of Thyroid Eye Disease, Median (range)	12.9 (7.01 - 15.86)	16.5 (8.52 - 22.50)
Smoking Status, n (%)		
Non-smoker	29 (78.4%)	11 (78.6%)
Smoker	8 (21.6%)	3 (21.4%)
Clinical activity score, mean ± SD	3.6 ± 1.7	3.5 ± 1.6
Proptosis measurement, mm, mean ± SD	23.0 ± 3.1	21.0 ± 4.2
Thyroid hormone level, pmol/L		
Free triiodothyronine (FT3), mean ± SD	5.0 ± 1.0	4.7 ± 0.8
Patients with Normal FT3	32 (86.5%)	14 (100%)
Patients with Low FT3	1 (2.7%)	0
Patients with High FT3	4 (10.8%)	0
Free thyroxine (FT4), mean ± SD	16.0 ± 3.8	16.5 ± 3.2
Patients with Normal FT4	32 (86.5%)	13 (92.9%)
Patients with Low FT4	3 (8.1%)	0
Patients with High FT4	2 (5.4%)	1 (7.1%)
Thyrotropin (TSH) level, mIU/L, mean ± SD	2.6 ± 1.54	2.47 ± 2.46
Patients with Normal TSH	22 (59.5%)	10 (71.4%)
Patients with Low TSH	14 (37.8%)	3 (21.4%)
Patients with High TSH	1 (2.7%)	1 (7.1%)

Abbreviations: FT3: triiodothyronine, FT4: Free thyroxine, mIU/L, milli-International units per litre, N: number of randomised patients, SD: standard deviation, TSH: Thyrotropin.

Table 5-6: Baseline demographics and disease characteristics of participants in the OPTIC-J study [7]

Study reference/ID Characteristics Category	Study intervention	
OPTIC-J	Teprotumumab N = 27	Placebo N = 27
Sex		
Female	18 (67%)	20 (74%)
Male	*9 (33%)*	*7 (26%)*
Age (years)	46.6 (14.2)	50.0 (13.4)
Race		
Japanese	27 (100%)	27 (100%)
Smoking status		
Former	13 (48%)	12 (44%)
Current	4 (15%)	4 (15%)
Non-smoker	10 (37%)	11 (41%)
Period from diagnosis of TED to screening, months	4.24 (1.94–6.83)	5.22 (3.02–6.80)
Free triiodothyronine, pmol/L	4.60 (4.00–5.20)	4.90 (3.80–5.50)
Free thyroxine, pmol/L	15.40 (12.90–16.70)	14.20 (12.90–16.70)

Study reference/ID Characteristics Category	Study intervention	
Thyrotropin, mIU/L	0.43 (0.01–2.81)	0.77 (0.04–2.82)
Proptosis in the study eye, mm	21.07 (2.46)	20.39 (2.42)
CAS in the study eye	4.5 (1.3)	4.0 (0.8)
Diplopia–Gorman score		
0—no diplopia	5 (19%)	7 (26%)
1—intermittent	5 (19%)	1 (4%)
2—inconstant	11 (41%)	9 (33%)
3—constant	6 (22%)	10 (37%)
GO-QOL transformed score		
Overall (total score)	68.3 (23.6)	74.9 (20.0)
Visual functioning subscale	70.5 (27.9)	80.1 (20.9)
Appearance subscale	66.4 (24.8)	69.9 (25.9)

Abbreviations: CAS: clinical activity score; GO-QOL, Graves' ophthalmopathy quality of life, mIU/L, milli-International units per litre, TED: thyroid eye disease.

5.3 Sample size

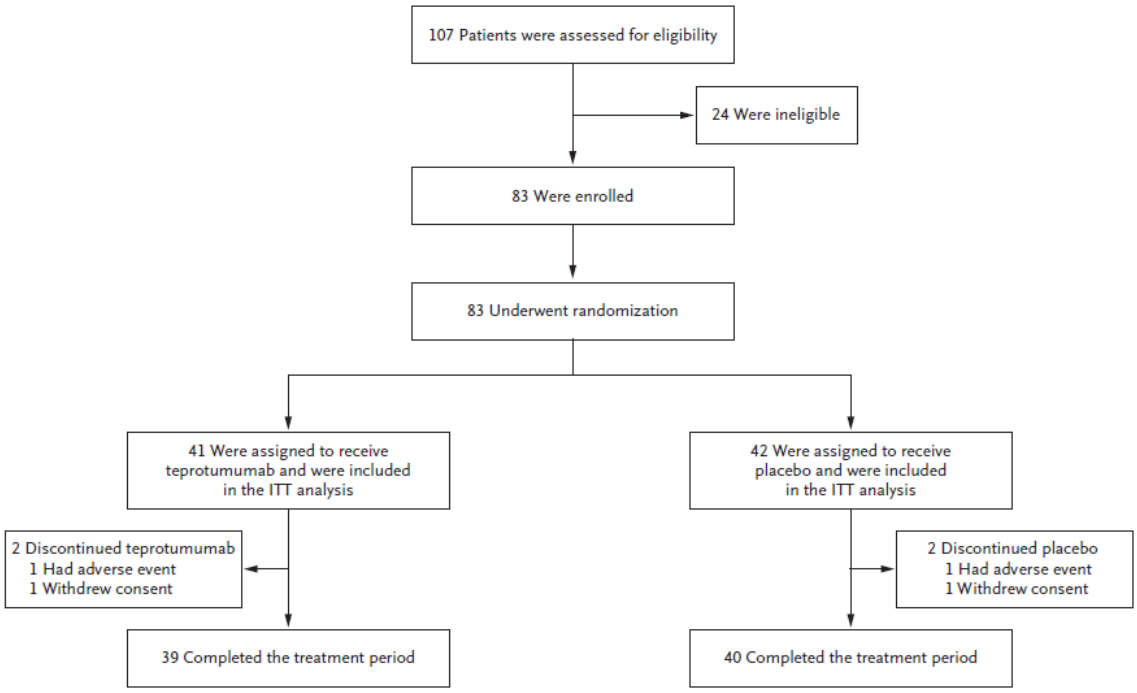

Figure 5-1: Diagram of patients in the OPTIC study (extracted from [1])

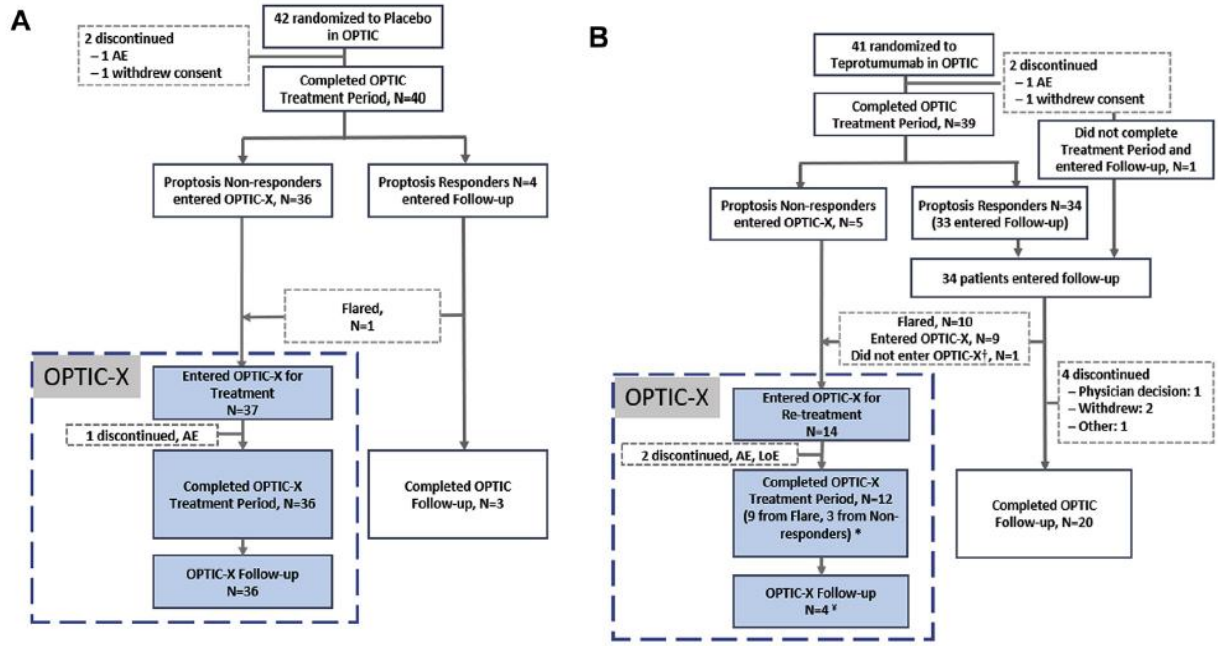

Figure 5-2: Diagram of patients in the OPTIC-X study (extracted from [2])

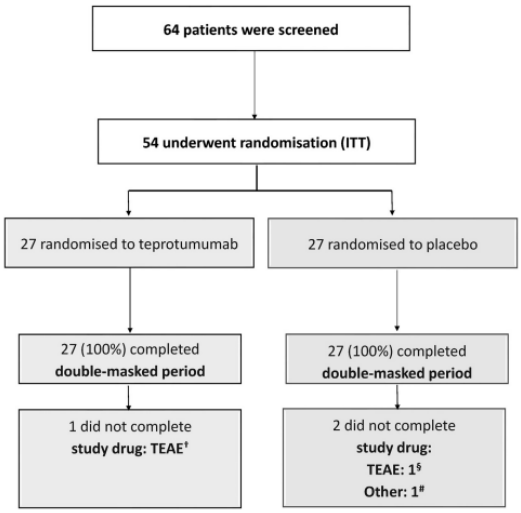

Figure 5-3: Diagram of patients in the OPTIC-Ƒ study (extracted from [3])

Notes: †Patient did not receive the study drug (teprotumumab) at weeks 15 and 21 due to an AE of neurosensory hypoacusis. § The patient did not receive the study drug (placebo) at weeks 18 and 21 due to an AE of neurosensory hypoacusis. #Patient did not receive study drug (placebo) at weeks 15, 18, and 21.

5.4 Study protocols and study endpoints

Table 5-7: Study protocol amendments in the OPTIC trial [5]

Version	Date and scope of amendment
OPTIC	
Original protocol	Approved on 10 July 2017.
Version 2.0	Approved on 24 October 2017.
Version 3.0	Approved on 16 April 2018.
Version 4.0	Approved on 31 January 2019. This amendment introduced a new secondary endpoint, the diplopia responder rate, defined as the percentage of subjects with baseline diplopia greater than zero in the study eye who experience a reduction of ≥1 grade without a corresponding deterioration (≥1 grade worsening) in the fellow eye at Week 24.

Table 5-8: Study protocol amendments in the OPTIC-J trial [7]

Version	Date of amendment
OPTIC-J	
Amendment 1	No information.
Amendment 2	Dated 31 October 2022.
Amendment 3	Dated 19 June 2023.

Table 5-9: Study endpoints for the study OPTIC as defined in the study protocol version 4.0 [5]

Study reference / ID Outcome category	Endpoints as defined in the study protocol
OPTIC	
Primary endpoint	Proptosis responder rate (percentage of subjects with a ≥2 mm reduction from baseline in the study eye without a deterioration (≥2 mm increase) in the fellow eye at week 24.
Key secondary efficacy endpoints	■ The overall responder rate (percentage of subjects with ≥2-point reduction in CAS AND ≥2 mm reduction in proptosis from baseline, provided there is no corresponding deterioration (≥2 mm increase) in CAS or proptosis in the fellow eye at week 24. ■ Percentage of subjects with a CAS value of 0 or 1 in the study eye at week 24. ■ Mean change from baseline to week 24 in proptosis measurement in the study eye. ■ Diplopia responder rate (percentage of subjects with baseline diplopia >0 in study eye who have a reduction of ≥1 grade with no corresponding deterioration (≥1 grade worsening) in the fellow eye at week 24. ■ Mean change from baseline to week 24 in the GO-QoL questionnaire overall score.
Exploratory efficacy endpoints	Clinical measures of severity individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to week 24. ■ Mean change from baseline to week 24 in the CAS. The overall responder rate at week 24 stratified by the level of response (high responders, responders, low responders, and non-responders; see Section 8.3.3 for definitions). ■ Mean change from baseline to week 24 in the GO-QoL questionnaire VF and A subscale scores. Mean change from baseline to week 24 on the motility component of the Clinical Measures of severity. ■ Mean percent change from baseline to week 24 in proptosis measurement. Time to relapse.

Study reference / ID Outcome category	Endpoints as defined in the study protocol
Exploratory pharmacokinetic and biomarker endpoints	■ Descriptive summaries of serum concentrations by time point. ■ Listing of serum concentrations by time point. Absolute concentrations for biomarkers at Day 1 and weeks 12 and 24. ■ Change from baseline for biomarkers at weeks 12 and 24.
Safety endpoints	■ Adverse events, including AE of special interest. Concomitant medication use monitoring. Descriptive summary of immunogenicity. Physical examination. Ophthalmic examination. Vital signs. ■ Clinical laboratory assessments (complete blood count, chemistry [including thyroid panel and HbA1C], and urinalysis). Pregnancy testing. Electrocardiogram.

Abbreviations: A: appearance, AE: adverse events, CAS. Clinical activity score, GO-QoL questionnaire: Graves' Ophthalmopathy Quality of Life Questionnaire, HbA1C: Hemoglobin A1C, VF: visual function.

Table 5-10: Study endpoints for the study OPTIC-J as defined in the study protocol version 4.0 [7]

Study reference / ID Outcome category	Endpoints as defined in the clinical trial protocol
OPTIC-J	
Primary endpoint	**Proptosis responder rate** (defined as the percentage of patients with a ≥ 2 mm reduction from baseline in proptosis in the study eye, without deterioration [≥ 2 mm increase] of proptosis in the fellow eye) at week 24.
Key secondary efficacy endpoints	■ The overall responder rate is defined as the percentage of patients with ≥ 2-point reduction in CAS AND ≥ 2 mm reduction in proptosis measurement from the Baseline in the study eye, provided there is no corresponding deterioration (≥ 2-point increase in CAS or ≥ 2 mm increase in proptosis in the fellow eye) at week 24. ■ The percentage of patients with a CAS value of 0 or 1 at week 24 in the study eye. ■ The mean change from baseline in proptosis measurement in the study eye at week 24. ■ The binocular diplopia responder rate is the percentage of patients with baseline diplopia grade >0 who have a reduction of ≥ 1 grade at Week 24. ■ The complete binocular diplopia responder rate (i.e., the percentage of patients with baseline binocular diplopia >0 and a score of 0 at Week 24). ■ The mean change from the baseline in the GO-QoL questionnaire overall score at week 24. ■ The mean change from the baseline in the GO-QOL questionnaire VF and A subscale scores at week 24.
Exploratory efficacy endpoints	MRI assessments: ■ Orbital fat and EOM volumes. T2 signal intensity ratios. Inflammation/edema grading. Ocular motility changes: ■ Adduction, abduction. ■ Supraduction, infraduction. ■ Using Hirschberg test.
Exploratory pharmacokinetic and biomarker endpoints	Not specified.

Study reference / ID Outcome category	Endpoints as defined in the clinical trial protocol
Safety endpoints	AEs of special interest (AESI): Infusion reactions. Hyperglycemia. Hearing impairment. IBD onset/exacerbation. Laboratory assessments: Fasting glucose. ■ Thyroid function tests (FT3, FT4). ■ HbA1c. Vital signs. Treatment discontinuations.

Abbreviations: AE: Adverse events, AESI: Adverse events of special interest, CAS. Clinical activity score, EOM: extra-ocular muscles, FT3: triiodothyronine, FT4: Free thyroxine, GO-QoL questionnaire: Graves' Ophthalmopathy Quality of Life Questionnaire, HbA1C: Haemoglobin A1C, IBD: irritable bowel disease, MRI: Magnetic resonance imaging, VF: visual function

5.5 Risk of Bias tables and GRADE evidence profiles

Table 5-11: Risk of bias of the study OPTIC (RCT at study outcome level (Cochrane RoB 2.0) [8]

Domain	Bias arising from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias	Comments
Study/ Outcome	Some concerns	Low	Low	Some concerns	Low	**Some concerns**	

Abbreviations: RCT: randomised controlled trial, RoB: risk of bias.

Table 5-12: Risk of bias of the study OPTIC-J (RCT at study outcome level (Cochrane RoB 2.0) [8]

Domain	Bias arising from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias	Comments
Study/ Outcome	Some concerns	Low	Low	Some concerns	Low	**Some concerns**	

Abbreviations: RCT: randomised controlled trial, RoB: risk of bias.

Table 5-13: Risk of bias of the OPTIC-X study (non-randomised studies other than uncontrolled trials, cross-sectional studies and case series) report at study level (IHE checklist) [9]

Risk of bias - study level (case series) according to IHE									
1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Was the hypothesis/ aim/ objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in more than one center?	Were patients recruited consecutively?	Were the characteristics of the patients included in the study described?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at a similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?
yes	yes	yes	partial[1]	partial[2]	yes	no[3]	yes	no[4]	yes
11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Were outcome assessors blinded to the intervention that patients received?	Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was follow-up long enough for important events and outcomes to occur?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by the results?	Were both competing interests and sources of support for the study reported?
no[5]	partial[6]	yes	unclear[7]	partial[8]	yes	yes	yes	yes	yes
Overall risk of bias: moderate									

[1] Patients may have entered the study at differing time points depending on when they experienced a flare during the follow-up period.

[2] Missing detailed information on the concomitant and previous therapy and missing comorbidities in the baseline characteristics.

[3] In the patients' baseline characteristics there was a wide SD in the median of the months since diagnosis of thyroid eye disease and also in the years since diagnosis of Graves' disease.

[4] Detailed information on the allowed concomitant therapy is missing and it is also not clear if additional treatments were used for disease management.

[5] The study was an extension study with an open-label design.

[6] Although appropriate methods for measurement were employed, an inter-observer variability can occur when measuring the proptosis.

[7] No statistical analysis plan was available. No statistical significance testing was conducted when comparing the endpoints at baseline and after treatment. No calculation of power or sample size was conducted and no adjustment for multiple comparisons was made.

[8] Patients were followed up to week 48. The study by Douglas et al, 2022 [6] includes a case of a patient from week 104, however it is not clear how many patients were followed beyond week 48.

Table 5-14: Risk of bias of the Chen et al. study (non-randomised studies other than uncontrolled trials, cross-sectional studies, and case series) report at study level (IHE checklist) [9]

Risk of bias - study level (case series) according to IHE									
1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Was the hypothesis/ aim/ objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in more than one center?	Were patients recruited consecutively?	Were the characteristics of the patients included in the study described?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at a similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?
yes	no[9]	no[10]	yes	no[11]	yes	no[12]	yes	no[13]	yes
11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Were outcome assessors blinded to the intervention that patients received?	Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was follow-up long enough for important events and outcomes to occur?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by the results?	Were both competing interests and sources of support for the study reported?
no[14]	partial[15]	yes	yes	yes	yes	yes	yes	yes	yes
Overall risk of bias: moderate									

[9] This was a retrospective single-center longitudinal cohort study.

[10] Single-center study.

[11] Missing detailed information on the concomitant and previous therapy, comorbidities, race, smoking status, clinical activity score and proptosis measurement in the baseline characteristics.

[12] No information on the time of thyroid eye and Graves' disease diagnosis.

[13] Detailed information on the allowed concomitant therapy is missing and it is also not clear if additional treatments were used for disease management.

[14] The study was not blinded.

[15] Not clear if the proptosis was measured in a standardised way.

5.6 Statistical analyses

Table 5-15: Statistical analyses in the OPTIC [5] and OPTIC-J [7] studies

Study	Statistical analysis
OPTIC	■ Primary analyses conducted on the intention-to-treat population. ■ Sensitivity analyses conducted on the per-protocol population. ■ Calculated sample size of 38 patients per group to achieve 90% power for detecting a 39 percentage-point difference between treatment groups at a two-sided alpha level of 0.05. This was adjusted upward to account for an anticipated 16% discontinuation rate.
OPTIC-J	■ Primary analyses conducted on the intention-to-treat population. ■ Determined a sample size of 50 patients to provide 83% power for detecting differences in proptosis responder rates between groups, using a two-tailed significance level of 0.05. ■ Hierarchical, sequential testing approach for efficacy endpoints.

5.7 Evidence profiles

A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group.

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Table 5-16: Evidence profile: efficacy and safety of the two included RCTs [5, 7] based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) [10]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Proptosis response (follow-up: range 24 weeks to 72 weeks; assessed with: Hertel exophthalmometer)									
2	randomised trials	seriousa	not serious	not serious	seriousb	none	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)	⨁⨁◯◯ Low[a,b]	CRITICAL
Clinical activity score (follow-up: range 24 weeks to 72 weeks; assessed with: physician)									
2	randomised trials	seriousa	not serious	not serious	seriousc	none	OPTIC: ■ 24/41 vs 9/42 ■ 17-55% difference OPTIC-J: ■ 16/27 vs 6/27 ■ 13-62% difference	⨁⨁◯◯ Low[a,c]	CRITICAL
Re-activation - not reported									
-	-	-	-	-	-	-	The outcome re-activation was only reported in the extension study which is a single arm study.	-	CRITICAL
Patient reported outcome - Graves' ophthalmopathy-specific quality-of-life (follow-up: range 24 weeks to 72 weeks; assessed with: questionnaire)									
2	randomised trials	seriousa	not serious	not serious	seriousd	none	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)	⨁⨁◯◯ Low[a,d]	CRITICAL
Mortality - not measured									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
-	-	-	-	-	-	-		-	CRITICAL
Serious adverse events (follow-up: range 24 weeks to 72 weeks)									
2	randomised trials	seriousa	not serious	not serious	seriouse	none	OPTIC: ■ Teprotumumab: 2/41 (4.9%) ■ Placebo: 1/42 (2.4%) OPTIC-J: ■ Teprotumumab: 1/27 (3.7%) ■ Placebo: 0/27 (0%)	⨁⨁◯◯ Low[a,e]	CRITICAL

Abbreviation: CI: *confidence interval.*

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 5-17: Evidence profile: efficacy and safety of the included observational study [11] based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) [10]

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Proptosis (follow-up: range 6 months to 32 months)									
1	non-rando-mised studies	serious[a]	NA*	not serious	very serious[b]	none	Teprotumumab retreatment (n=4): ■ Mean reduction: 4mm (SD: 2mm) Steroids (n=6): ■ Mean reduction: 0mm (SD: 1mm)	⨁◯◯◯ Very low[a,b]	CRITICAL
Clinical activity score (follow-up: range 6 months to 32 months; assessed with: physician)									
1	non-rando-mised studies	serious[a]	NA*	not serious	very serious[c]	none	Mean final CAS: ■ Teprotumumab (n=4): CAS 0 in all patients ■ IV Steroids (n=6): CAS 2 (SD: 1, range 1-4)	⨁◯◯◯ Very low[a,c]	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Re-activation (follow-up: range 6 months to 32 months)									
1	non-rando-mised studies	serious[a]	NA*	not serious	serious[d]	none	■ 11/42 patients (26%) experienced reactivation ■ Mean time to reactivation: 9 months (SD: 5) ■ Range: 2-20 months	⨁◯◯◯ Very low[a,d]	CRITICAL
Patient Reported Outcomes - not measured									
-	-	-	-	-	-	-		-	CRITICAL
Mortality - not measured									
-	-	-	-	-	-	-		-	CRITICAL
Serious adverse events (follow-up: range 6 months to 32 months)									
1	non-rando-mised studies	serious[a]	NA*	not serious	very serious[e]	none	No serious adverse events reported for either retreat-ment group ■ 4/11 patients had mild side effects during retreatment (nausea, muscle spasms, hair loss, hyperglycemia)	⨁◯◯◯ Very low[a,e]	CRITICAL

Abbreviation: CI: *confidence interval.*

*Notes: *NA: not applicable since it is an observational study without a control arm. 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*

5.8 Applicability

Table 5-18: Summary table characterising the applicability of the included study

Domain	Description of applicability of evidence
Population	OPTIC and OPTIC-X study included female and male patients (18 to 80 years of age) with moderate-to-severe thyroid eye disease. In the OPTIC study mean age of the patients was 51.6 (SD±12.6) years in the teprotumumab and 48.9 (SD±13.0) years in the placebo group with a White majority of 85% and 88% in the teprotumumab and placebo group respectively. The mean duration of the thyroid eye disease was 6.2 months (SD±2.3) and 6.4 months (SD±2.4) in the teprotumumab and placebo groups respectively.

	The OPTIC-X study enrolled both teprotumumab naïve patients and non-responders to teprotumumab together with patients who flared after the treatment. In the OPTIC-X study mean age of the patients was 48.5 (SD±13.65) years in the 1st Course (OPTIC Placebo) and 56.1 (SD±11.5) years in the re-treated patients with a White majority of 89% and 79% in these groups respectively. The mean duration of the thyroid eye disease was 12.9 and 16.5 months in the 1st Course (OPTIC Placebo) and in the re-treated patients respectively. The OPTIC-J study included Japanese female and male patients (20 to 80 years of age) with moderate-to-severe thyroid eye disease. The mean age of the patients was 46.6 (SD±14.2) years in the teprotumumab and 50.0 (SD±13.4) years in the placebo group. The Chen et al. study included female and male patients with moderate-to-severe thyroid eye disease from 1 USA centre. The mean age was 56 years (SD, 13) and the mean duration of active TED was 13 months. It is not clear how are these populations reflective of the population in the real world since the previous therapy of these patients has not been disclosed in either study. Additionally, the applicability of the results obtained in the Japanese population for the European population is questionable due to the differences in eye proptosis.
Intervention	In the case of OPTIC and OPTIC-J studies, interventions consisted of intravenous infusions of either teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks for a total of eight infusions. The same is applicable to OPTIC-X and Chen et al. study, only without the placebo. However, the studies did not adequately address how variations in body weight might affect dosing effectiveness throughout the treatment period. The timing of infusions in relation to thyroid function status was not comprehensively detailed, which could be important for understanding optimal treatment scheduling. Additionally, the studies did not describe how the infusion protocols might need to be adapted for different healthcare settings with varying resources and capabilities.
Comparators	The OPTIC and OPTIC-J studies implemented a placebo group. The OPTIC-X and Chen et al. studies were single-arm and had no comparator groups. In these studies, it is not clear if patients were allowed concomitant anti-thyroid therapy such as thiamazol and propylthiouracil. Additionally, the studies notably lacked active comparators such as corticosteroids or orbital radiotherapy, which are commonly used treatments. There was also limited information about how standard care varies across different regions, and no comparisons were made with surgical interventions for TED.
Outcomes	The primary endpoint was proptosis response defined as a reduction in proptosis of ≥2 mm from baseline in the study eye without a corresponding increase of ≥2 mm in the fellow eye at week 24. Inter-individual variability might have been present in the measurement of proptosis between the sites. Taking into account that some of the patients from the OPTIC and Chen et al studies have relapsed, the durability of the teprotumumab's efficacy is currently unknown. Furthermore, the studies provided limited data on patient-reported outcomes beyond GO-QOL and economic outcomes and cost-effectiveness were not assessed. Long-term outcomes beyond the study period were not systematically tracked, and the impact on quality of life in different cultural contexts was not fully explored.
Setting	The OPTIC trial was conducted at 13 sites in the United States and Europe. The OPTIC-X study was conducted in 7 States in the USA and 5 European sites. The OPTIC-J study was conducted in 1 Japanese centre. The Chen et al. study was conducted in 1 centre in the USA. However, differences in healthcare delivery systems across these regions were not addressed. The studies did not detail variations in diagnostic criteria and treatment protocols across centers. Resource availability and access to care differences were not fully discussed, and the impact of different levels of expertise and experience across centers was not analysed.

Abbreviation: CI: *confidence interval, GO-QoL questionnaire: Graves' Ophthalmopathy Quality of Life Questionnaire, SD: standard deviation, TED: thyroid eye disease.*

5.9 Indirect treatment comparison

Published indirect comparison

Table 5-19: Characteristics of the included ITC studies [4]

Characteristics of studies included in the ITC											
Source	Study Design	Sample Size	Single vs Multicentre	Age Range	CAS	Age (y)	Female %	Smokers %	Duration of TED (mo)	Baseline Proptosis (mm)	Diplopia at Baseline %
IV methylprednisolone											
Bartalena et al, 2012 (EU)	RCT	54	Multicentre	18-75	≥3/7	50.0	57.0	74.0	12.4	22.2	74.0
Kahaly et al, 2018 (Germany, Italy)	RCT	81	Multicentre	18-75	≥3/7	50.6	79.0	51.0	8.5	21.3	64.0
Aktaran et al, 2007 (Turkey)	RCT	25	Single	≥18	≥3/7	44.3	56.0	40.0	<6.0	22.2	44.0
He et al, 2017 (China)	RCT	18	Single	18-70	≥1/7	41.2	55.6	22.2	6.0	17.2	66.7
Kahaly et al, 2005 (Germany)	RCT	35	Single	≥18	≥3/7	48.0	71.0	60.0	4.0	23.8	75.0
Mu et al, 2020 (China)	RCT	46	Single	≥18	NR	35.2	60.9	34.8	12.6	17.1	34.8
Zhu et al, 2014 (China)	RCT	39	Single	≥18	≥3/7	45.3	61.5	25.6	13.6	22.1	71.8
Beleslin et al, 2020 (Serbia)	Retrospective	74	Single	NR	≥3/7	51.0	69.0	76.0	6.0	23.1	80.0
Li et al, 2021 (China)	Non-RCT	20	Single	18-60	≥3/7	45.5	55.0	40.0	8.0	18.9	65.0
Xing et al, 2015 (China)	Interventio-nal	54	Single	≥18	≥3/7	49.4	35.2	50.0	7.0	22.1	NR
Xu et al, 2020 (China)	Prospective pilot	15	Single	≥18	≥3/7	43.2	80.0	26.7	NR	19.4	100

Characteristics of studies included in the ITC											
Source	Study Design	Sample Size	Single vs Multicentre	Age Range	CAS	Age (y)	Female %	Smokers %	Duration of TED (mo)	Baseline Proptosis (mm)	Diplopia at Baseline %
Yang et al, 2014 (Netherlands)	Retrospec-tive	32	Single	18-75	≥3/7	52.0	78.0	50.0	NR	23.0	NR
				Teprotumumab							
Smith et al, 2017	RCT	42	Multicentre	18-75	≥4/7	51.6	65.1	25.6	4.7	23.4	50.0
Douglas et al, 2020	RCT	41	Multicentre	18-80	≥4/7	51.6	70.7	22.0	6.2	22.6	68.3
				Placebo							
Smith et al, 2017	RCT	45	Multicentre	18-75	≥4/7	54.2	81.8	40.9	5.2	23.1	40.0
Douglas et al, 2020	RCT	42	Multicentre	18-80	≥4/7	48.9	73.8	19.0	6.4	23.2	66.6

***Abbreviation**: CAS: clinical activity score, mo: months, NR: not reported, RCT: randomised controlled trial, TED: thyroid eye disease, y: year.Notes: Cfb indicates a change from baseline; Cfb_{raw}, raw change from baseline.*

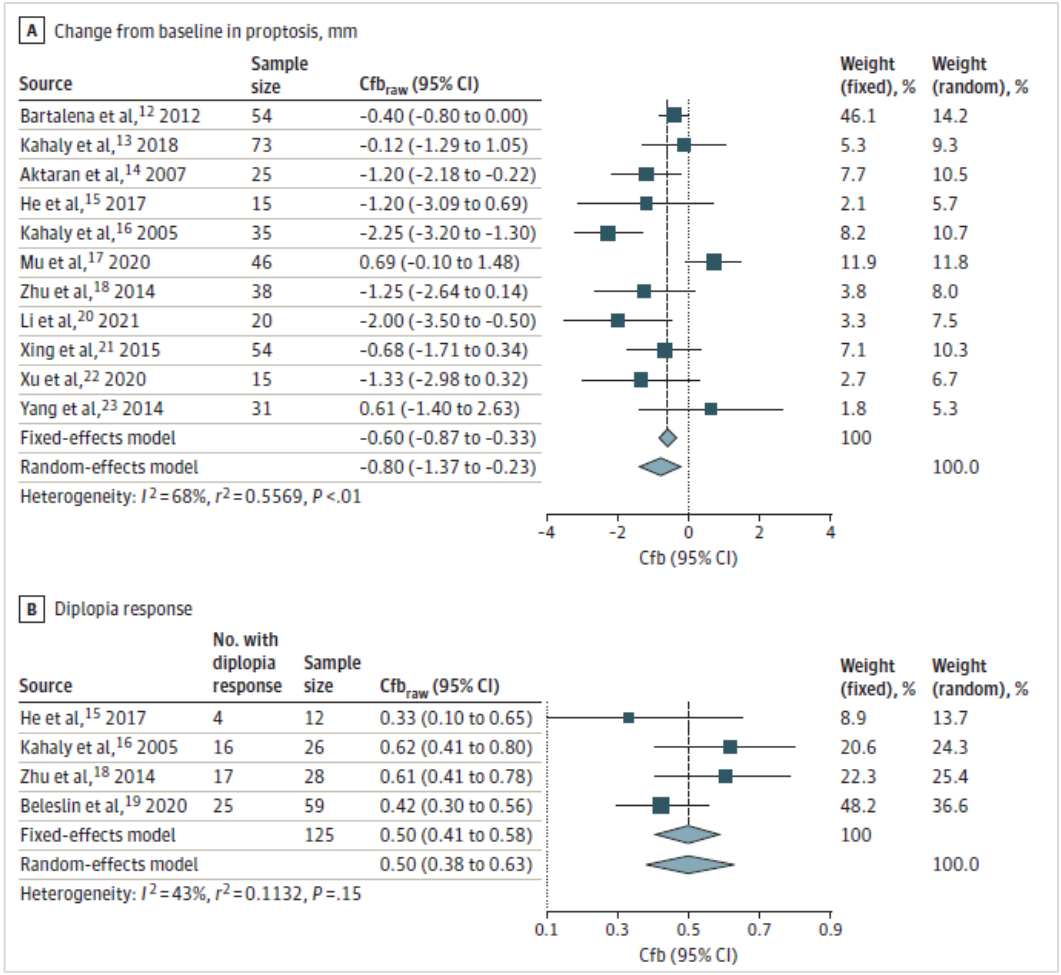

Figure 5-4: Metaanalyses to Obtain Pooled Estimates for Intravenous Methylprednisolone (IVMP) for Change From Baseline in Proptosis (A) and Diplopia Response (B) [4]

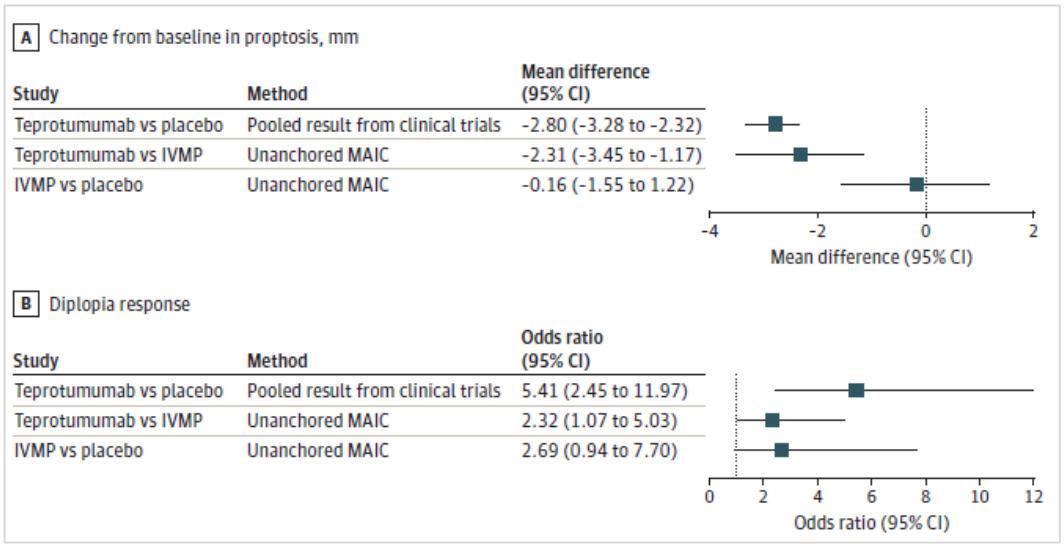

Figure 5-5: Unanchored Matching-Adjusted Indirect Comparisons (MAICs) and Pooled Results From Clinical Trials for Change From Baseline in Proptosis (A) and Diplopia Response (B) [4]

Table 5-20: Critical Appraisal of the published ITC study [12] according to ISPOR Guideline 2011 [13], PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses [14]

Section	Douglas et al. [12]
Introduction	
Are the rationale for the study and the study objectives stated clearly?	Yes
Methods	
Does the methods section include the following: description of eligibility criteria, information sources search strategy, study selection process, and data extraction (validity/quality assessment of individual studies)? Are the outcome measures described? Is there a description of methods for the analysis/ synthesis of evidence? Do the methods described include the following: description of analyses methods/models, handling of potential bias/inconsistency, analysis framework? Are sensitivity analyses presented?	Yes, except: ■ No quality assessment of individual studies. ■ No information about handling the risk of bias. ■ Limited evaluation of sensitivity to outliers.
Results	
Do the results include a summary of the studies included in the network of evidence: individual study data, network of studies? Does the study describe an assessment of model fit? Are competing models being compared? Are the results of the evidence synthesis (ITC/MTC) presented clearly? Are the findings of sensitivity/scenario analysis described?	Yes, except: ■ Assessment of the model fit was not done. ■ Lack of comparison of competing models.
Discussion	
Does the discussion include the following: description/summary of main findings, internal validity of analysis, and external validity? Implications of results for the target audience	Yes, except: ■ Missing systematic assessment of the internal and external validity, including generalisability to different patient populations and healthcare settings
Funding	
Are the sources of funding for the systematic review and other support (e.g., supply of data); and the role of funders for the systematic review reported?	Yes, but more detail about the specific role of funders in study design, data analysis decisions, and manuscript preparation would increase transparency.

Abbreviation: ITC: *indirect treatment comparison, MTC: mixed treatment comparison*

Indirect treatment comparison (placeholder for unpublished data)

Table 5-21: Critical Appraisal of the unpubplished ITC study according to ISPOR Guideline 2011 [13], PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses [14]

This part includes confidential information!

5.10 Ongoing studies

Table 5-22: List of ongoing studies with teprotumumab [15]

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date	Additional information
A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients With TED to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab	NCT05002998	HZNP-TEP-402 2020-005999-36 (EudraCT Number)	Phase 4	Active, not recruiting	2026-04-15	■ Evaluation of serum samples from participants with baseline CAS ≥3 for disease biomarkers. ■ Conducted to fulfil FDA post-marketing requirement for a descriptive trial.
A Phase 3, Randomized, Double-masked, Placebo-controlled, Parallel-group, Multicenter Trial to Evaluate the Efficacy, Safety and Tolerability of Subcutaneous Teprotumumab in Participants With Moderate-to-Severe Active TED	NCT06248619	HZNP-TEP-305	Phase 3	Recruiting	2026-05-01	-
The Effect of Teprotumumab on TED and Thyroid Dysfunction	NCT06275373	20-10974	Observational	Recruiting	2027-12-12	■ Evaluating of clinical outcome of patients with active thyroid disease with visually significant signs and symptoms of proptosis, pain, diplopia, lid/orbital oedema, or lid/orbital erythema. ■ Primary outcomes: CAS score improvement and TSI level.
Phase 3b, Multicenter, Open-label, Single-Arm Expanded Access Protocol of TEPROTUMUMAB (HZN-001)	NCT04040894	HZNP-TEP-401	Expanded Access	Approved for marketing	-	■ Intended to provide access to teprotumumab for the treatment of up to 60 patients in the US with active moderate-to-severe TED where there is no comparable or satisfactory alternative therapy for treatment.

Abbreviations: *CAS: Clinical Activity Score, FDA: Food and Drug Administration, TED: Thyroid eye disease, TSI: thyroid stimulating immunoglobulin*

6 Budget impact analysis

Table 6-1: Estimated population with thyroid eye disease and potential candidates for teprotumumab in Austria

Population	Year 1 (n)	Year 2 (n)	Year 3 (n)	Reference/assumption
A: Estimated **patient population** with **TED**, n (8.97/10,000 persons in Europe)	8251		[16, 17]	
B: **Incidence of TED** 0.54-0.90 (mean: 0.72) per 100,000 for **males** per year	33	33	33	EUGOGO 2021 [18]
C: **Incidence of TED** 2.67-3.30 (mean: 2.99) per 100,000 for **females** per year	140	140	140	EUGOGO 2021 [18]
D: TED patients with **hyperthyroidism** (86.2%), n (*A*0.862/3*)	2371	2371	2371	[19]
E: TED patients with **hyperthyroidism** who ONLY need **thyroid treatment** (90%), n (D*0.90)	2134	2134	2134	[2]
F: TED patients with **hypothyroidism** (10.36%), n (A*0.1036/3)	285	285	285	[19]
G: TED patients with **hypothyroidism** who ONLY need **thyroid treatment** (90%), n (F*0.90)	256	256	256	[2]
H: TED patients who need **thyroidectomy** (30%), n (A*0.30/3)	826	826	826	[2]
I: Moderate-to-severe TED who need SoC treatments (**first-line monotherapy corticoid**), n (0.161/10,000 persons/year)	148	148	148	[3]
J Moderate-to-severe TED who need SoC treatments (**first-line corticoid combination therapy**), n (*I*0.07*)	10	10	10	[2]
K: Moderate-to-severe TED who need SoC treatments (**second-line corticoid**), n (*I*0.15*)	22	22	22	[2]
L: Patients who need additional treatment regimens – **potential candidates for teprotumumab (20-40%; mean 30%),** n (*I*0.30*)	45	45	45	[4] Assumption is based on clinical information: all patients are adults, as cases in individuals under 18 years are sporadic.
M: Patients with **infusion reaction** (4%), n (*L*0.04*)	2	2	2	[6]
N: Patients with relapse and **retreatment with teprotumumab** (26-29%, mean 27.5%), n (*L*0.275*)	13	13	13	[20][32][6]
O: Patients receiving **second-line rituximab** (off-label; as long as dysthyroid optic neuropathy is excluded), n (*L**0.05)	2	2	2	[2]
P: Patients receiving **surgeries, orbital decompression**, n (*L**0.09)	4	4	4	[2]

Abbreviations: n: number of patients, SoC: standard of care, TED: thyroid eye disease

10 Drug development

Tabelle 10-1: Clinical Trials using teprotumumab (as of 02/2025) (for the treatment of thyroid eye disease highlighted in orange)

ClinicalTrials.gov ID / EudraCT number	Primary investigator	Condition	Phase	Participants	Study Start (Actual)	Primary Completion (Estimated)	Collaborators	Type of sponsor	Link to clinicaltrials.gov
A Phase II Trial of R1507, a Recombinant Human Monoclonal Antibody to the Insulin-Like Growth Factor-1 Receptor for the treatment of patients with recurrent or refractory Ewing's sarcoma, osteosarcoma, synovial sarcoma, rhabdomyosarcoma and other sarcomas									
2007-003940-30	Roche	Ewing's sarcoma	2	335	21.12.2007	19.02.2014	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-003940-30/GB#B
An open label study to determine the effect of R1507 (RO4858696) plus Tarceva (erlotinib) on progression-free survival in patients with stage IIIB/IV non-small cell lung cancer with progressive disease after clinical benefit to second or third line erlotinib monotherapy.									
2008-001762-85	Roche	lung cancer	2	43	11.09.2008	26.04.2013	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-001762-85/FR#B
A Randomized, placebo controlled study to determine the effect of two dose schedules of R1507 or placebo, both in combination with erlotinib (Tarceva®), on progression-free survival in patients with advanced non-small cell lung cancer with disease progression after first or second line chemotherapy									
2008-001736-12	Roche	Non-small cell lung cancer stage	2	150	08.10.2008	25.07.2011	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-001736-12/GB#P
An exploratory study to evaluate the biological activity of R1507, a human monoclonal antibody, antagonist of the insulin-like growth factor receptor (IGF-1R) in women with operable breast cancer									
2008-004128-22	Roche	breast cancer	1	70	17.10.2008	15.02.2010	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-004128-22/GB#B
A multiple ascending dose study to evaluate the safety, tolerability and effect on tumor response of the mTOR inhibitor (RAD001) in combination with the IGF-1R antagonist (R1507) in patients with advanced solid tumors									
2008-005806-38	Roche	various types of cancer	2	134	06.08.2009	06.06.2013	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-005806-38/FR#P
Teprotumumab (RV 001) Treatment in Patients With Active Thyroid Eye Disease									

NCT01868997	River Vision Development Corporation	thyroid eye disease	2	88	July.2013	22.02.2017	n.a.	Industry	https://clinicaltrials.gov/study/NCT01868997
A randomized, double-masked, placebo-controlled, efficacy and safety study of RV 001, an insulin-like growth factor-1 receptor (IGF-1R) antagonist antibody (fully human), administered every 3 weeks (q3W) by intravenous (iv) infusion in patients suffering from active thyroid eye disease (TED)									
2014-000113-31	River Vision Development Corporation	thyroid eye disease	2	84	14.07.2014	22.02.2017	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000113-31/DE
A Phase 1, Open-Label Study of Teprotumumab in Patients With Diabetic Macular Edema (DME)									
NCT02103283	River Vision Development Corporation	Diabetic Macular Edema	1	5	Oct.2014	Aug.16	n.a.	Industry	https://clinicaltrials.gov/study/NCT02103283
Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC)									
NCT03298867	Horizon Therapeutics	thyroid eye disease	3	83	04.10.2017	30.11.2020	n.a.	Industry	https://clinicaltrials.gov/study/NCT03298867
Treatment of Graves' Orbitopathy to Reduce Proptosis With Teprotumumab Infusions in an Open-Label Clinical Extension Study (OPTIC-X)									
NCT03461211	Horizon Therapeutics	thyroid eye disease	3	51	16.04.2018	17.02.2021	n.a.	Industry	https://clinicaltrials.gov/study/NCT03461211
A Study of TEPROTUMUMAB Subcutaneous Administration in Healthy Adults									
NCT06563856	Amgen	None	1	37	22.09.2020	27.05.2021	n.a.	Industry	https://clinicaltrials.gov/study/NCT06563856
The Effect of Teprotumumab on Thyroid Eye Disease and Thyroid Dysfunction (Teprotumumab)									
NCT06275373	Walter Reed National Military Medical Center	thyroid eye disease and thyroid dysfunction	observational	100	12.05.2021	12.12.2027	n.a.	Public (military)	https://clinicaltrials.gov/study/NCT06275373
A Study Evaluating TEPROTUMUMAB® Treatment in Patients With Chronic (Inactive) Thyroid Eye Disease									
NCT04583735	Horizon Therapeutics	thyroid eye disease	4	62	02.09.2021	12.10.2023	n.a.	Industry	https://clinicaltrials.gov/study/NCT04583735
TEPROTUMUMAB® (Teprotumumab-trbw) Post-Marketing Requirement Study									
NCT05002998	Horizon Therapeutics	thyroid eye disease	4	313	16.09.2021	15.04.2026	Horizon Therapeutics	Industry	https://clinicaltrials.gov/study/NCT05002998
A Study With TEPROTUMUMAB in Patients With Diffuse Cutaneous Systemic Sclerosis (dcSSc)									

NCT04478994	Amgen	diffuse cutaneous systemic sclerosis	1	3	17.11.2021	08.12.2022	n.a.	Industry	https://clinicaltrials.gov/study/NCT04478994
A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab									
2020-005999-36	Horizon Therapeutics	thyroid eye disease	3	300	24.11.2021	n.a.	n.a.	Industry	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-005999-36/IT
A Study of TEPROTUMUMAB® Treatment in Participants With Thyroid Eye Disease									
NCT06389578	Horizon Therapeutics	thyroid eye disease	1	16	14.07.2022	12.09.2023	n.a.	Industry	https://clinicaltrials.gov/study/NCT06389578
A Trial to Investigate Teprotumumab (High-concentration Formulation) Subcutaneous Administration in Healthy Adult Non-Japanese and Japanese Participants									
NCT06674941	Amgen	none	1	44	24.03.2023	14.11.2023	n.a.	Industry	https://clinicaltrials.gov/study/NCT06674941
A Study to Evaluate the Efficacy and Safety of LASN01 in Patients With Thyroid Eye Disease									
NCT06226545	Lassen Therapeutics Inc.	thyroid eye disease	2	41	05.03.2024	Jän.26	n.a.	Industry	https://clinicaltrials.gov/study/NCT06226545
A Trial to Investigate Teprotumumab Subcutaneous Administration Compared With Placebo in Male and Female Adult Participants With Moderate-to-severe Active Thyroid Eye Disease									
NCT06248619	Amgen	thyroid eye disease	3	80	05.07.2024	01.05.2026	n.a.	Industry	https://clinicaltrials.gov/study/NCT06248619
A trial to investigate teprotumumab mg/ml subcutaneous administration compared with placebo in male and female adult participants with moderate-tosevere active thyroid eye disease									
2024-515702-63-00	Horizon Therapeutics USA Inc.	thyroid eye disease	n.a.	n.a.	01.12.2024	31.03.2026	n.a.	Industry	https://euclinicaltrials.eu/ctis-public/view/2024-515702-63-00?lang=en
Expanded Access Protocol of Teprotumumab (HZN-001) for Patients With Active Thyroid Eye Disease (EAP)									
NCT04040894	Amgen	thyroid eye disease	n.a.	n.a.	n.a.	n.a.	n.a.	Industry	https://clinicaltrials.gov/study/NCT04040894

Tabelle 10-2: Studies that ultimately led to the development of TEPROTUMUMAB®

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Teprotumumab, an IGF-1R Blocking Monoclonal Antibody Inhibits TSH and IGF-1 Action in Fibrocytes					
Chen, H	2014	Teprotumumab reduces IGF-1R and TSHR expression in fibrocytes, blocking IGF-1 and TSH signaling and cytokine production, suggesting a potential therapeutic mechanism in TAO.	Departments of Ophthalmology and Visual Sciences University of Michigan Medical School	Academia	https://academic.oup.com/jcem/article-abstract/99/9/E1635/2537403?redirectedFrom=fulltext&login=false
			Department of Ophthalmology of Union Hospital, Medical College, Huazhong University of Science and Technology		
Mester, T Raychaudhuri, N Kauh, C Y Gupta, Sm			Departments of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	
Smith, T J			Departments of Ophthalmology and Visual Sciences, University of Michigan Medical School		
			Departments of Internal Medicine, University of Michigan Medical School		
Douglas, R S			Departments of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	
			Ann Arbor Veterans Administration Medical Center	Public (Military healthcare facility)	
TSH-Mediated TNFα Production in Human Fibrocytes Is Inhibited by Teprotumumab, an IGF-1R Antagonist					
Chen, H	2015	Treatment with TSH/M22 triggered inflammation (TNFα production) in eye cells. TMB was able to reduce this inflammation by blocking a specific pathway, suggesting it could be a promising treatment for Graves' eye disease.	Departments of Ophthalmology and Visual Sciences University of Michigan Medical School	Academia	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0130322
			Department of Ophthalmology of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology		
Shan, S J C Mester, T Wei, Y			Department of Ophthalmology and Visual Sciences, University of Michigan Medical School		
Douglas, R S			Department of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	
			Ann Arbor Veterans Administration Medical Center	Public (Military healthcare facility)	
Pentraxin-3 Is a TSH-Inducible Protein in Human Fibrocytes and Orbital Fibroblasts					
Wang, H	2015		Department of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	https://academic.oup.com/endo/article/156/11/4336/2423201?login=false
			Department of Ophthalmology, Shanghai Changzheng Hospital	Hospital	
Atkins, S J Fernando, R			Department of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Wei, R		Certain immune cells from bone marrow (called fibrocytes) can travel to the eye tissue in Graves' disease. When these cells are activated by thyroid-stimulating hormone, they produce an inflammatory protein called PTX-3, which might help explain how thyroid problems can lead to eye damage in this disease.	Department of Ophthalmology, Shanghai Changzheng Hospital	Hospital	
Smith, T J			Department of Ophthalmology and Visual Sciences, University of Michigan Medical School	Academia	
			Division of Metabolism, Endocrinology, and Diabetes, University of Michigan Medical School		
Novel Therapies for Thyroid Autoimmune Diseases					
Fallahi, P	2016	In autoimmune thyroid conditions (including Graves' disease and related eye problems), certain immune signals called CXCR3 and its chemokines drive inflammation, and researchers have found that patients have high levels of these signals during active disease. Various treatments, including new drugs, work by blocking these inflammatory signals, though more research is needed to confirm their effectiveness.	Department of Clinical and Experimental Medicine, University of Pisa	Academia	https://www.tandfonline.com/doi/full/10.1586/17512433.2016.1157468
Ferrari, S M					
Elia, G					
Nasini, F			Department of Surgical, Medical, Molecular Pathology and of Emergency, University of Pisa		
Colaci, M			Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena & Reggio Emilia		
Giuggioli, D			Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena & Reggio Emilia		
Vita, R			Department of Clinical and Experimental Medicine, Section of Endocrinology, University of Messina		
Benvenga, S			Department of Clinical and Experimental Medicine, Section of Endocrinology, University of Messina		
Ferri, C			Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena & Reggio Emilia		
Antonelli, A			Department of Clinical and Experimental Medicine, University of Pisa		
Teprotumumab for Thyroid-Associated Ophthalmopathy					
Smith, T J	2017	In patients with active ophthalmopathy, teprotumumab was more effective than placebo in reducing proptosis and the Clinical activity score. Study sponsored by River Vision Development)	University of Michigan Medical School (Dept. of Ophthalmology	Academia	https://www.nejm.org/doi/10.1056/NEJMoa1614949
			Visual Sciences, Kellogg Eye Center; Division of Metabolism, Endocrinology, and Diabetes, Dept. of Internal Medicine)		
Kahaly, G J			Johannes Gutenberg University Medical Center	Academia	
Ezra, D G			Moorfields Eye Hospital	Hospital	
Fleming, J C			University of Tennessee Health Science Center,	Academia	
Dailey, R A			Oregon Health and Science University (Oculofacial Plastic Surgery Division)	Academia	
Tang, R A			Eye Wellness Center, Neuro-Ophthalmology of Texas	Hospital	
Harris, G J			Medical College of Wisconsin	Academia	
Antonelli, A			University of Pisa, Dept. of Clinical and Experimental Medicine	Academia	
Salvi, M			University of Milan, Fondazione IRCCS Ca' Granda (Endocrinology and Diabetology Unit)	Academia	
Goldberg, R A			Jules Stein Eye Institute, University of California	Academia	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Gigantelli, J W			University of Nebraska Medical Center	Hospital	
Couch, S M			Barnes-Jewish Hospital, Washington University	Hospital	
Shriver, E M			University of Iowa Hospitals and Clinics	Academia	
Hayek, B R			Emory University	Academia	
Hink, E M			University of Colorado	Academia	
Woodward, R M			River Vision Development	Industry	
Gabriel, K					
Magni, G					
Douglas, R S			University of Michigan Medical School (Dept. of Ophthalmology and Visual Sciences, Kellogg Eye Center)	Academia	
IGF1 receptor and thyroid-associated ophthalmopathy					
Mohyi, M	2018	In Graves' eye disease (TAO), the tissues around the eyes become inflamed and swollen, which can be disfiguring and potentially cause vision loss. A new drug called teprotumumab shows promise in treating this condition by blocking a specific protein (IGF1R) that contributes to the inflammation, and this approach might help with other autoimmune diseases too.	Department of Ophthalmology and Visual Sciences University of Michigan	Academia	https://jme.bioscientifica.com/view/journals/jme/61/1/JME-17-0276.xml
Smith, T J			Department of Ophthalmology and Visual Sciences, University of Michigan		
			Division of Metabolism Endocrine, and Diabetes, Department of Internal Medicine, University of Michigan		
CD34- Orbital Fibroblasts From Patients With Thyroid-Associated Ophthalmopathy Modulate TNF-alpha Expression in CD34+ Fibroblasts and Fibrocytes.					
Lu, Y	2018	In Graves' eye disease, a specific type of eye cell (CD34- orbital fibroblasts) appears to release an unknown substance that prevents inflammation by blocking TNF-α production in other nearby cells. This finding helps explain why some cells in the eye don't produce inflammatory signals when exposed to thyroid-stimulating hormone.	Departments of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan Medical School	Academia	https://iovs.arvojournals.org/article.aspx?articleid=2683047
Atkins, S J					
Fernando, R					
Trierweiler, A					
Mester, T					
Grisolia, A B D					
Mou, P					
Novaes, P					
Smith T J			Departments of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan Medical School	Academia	
			Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan Medical School		
Insulin-like Growth Factor-I Receptor and Thyroid-Associated Ophthalmopathy					
Smith, T J	2019		Department of Ophthalmology and Visual Sciences University of Michigan Medical School	Academia	https://academic.oup.com/edrv/article/40/1/236/5094009?login=false
			Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan Medical School		

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Janssen, J A M J L		A new drug called teprotumumab that blocks a specific receptor (IGF-IR) has shown dramatic improvements in treating Graves' eye disease, potentially changing how we treat this condition. The drug is based on the discovery that certain immune cells called fibrocytes carry both thyroid and growth factor receptors that work together to cause inflammation in the eye.	Department of Internal Medicine, Erasmus Medical Center, Rotterdam	Academia	
Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active thyroid eye disease: a focus on proptosis					
Douglas, R S	2019	A therapeutic agent called teprotumumab significantly reduced eye bulging (proptosis) in patients with thyroid eye disease, working as well as surgery but without surgical risks. The drug was effective across different patient groups (including smokers and non-smokers), showing benefits as early as 6 weeks into treatment, with 71.4% of patients seeing meaningful improvement compared to only 20% in the placebo group.	Cedars Sinai Medical Center Los Angeles	Hospital	https://www.nature.com/articles/s41433-018-0321-y
			Zhongshen Ophthalmic Center, Guangzhou		
Novel therapies for thyroid autoimmune diseases: An update					
Ferrari, S M	2019	Autoimmune thyroid disorders (including AT, GD, and GO) are driven by Th1 immune responses and associated chemokines, with various therapeutic approaches being investigated - from traditional treatments like methimazole to newer targeted therapies such as teprotumumab and TSH-R peptide immunization.	Department of Clinical and Experimental Medicine, University of Pisa	Academia	https://www.sciencedirect.com/science/article/abs/pii/S1521690X19301174?via%3Dihub
Fallahi, P			Department of Translational Research of New Technologies in Medicine and Surgery, University of Pisa	Academia	
Elia, G			Department of Clinical and Experimental Medicine, University of Pisa	Academia	
Ragusa, F					
Camatra, S					
Paparo, S R					
Giusti, C					
Gonnella, D					
Ruffilli, I					
Shoenfeld, Y			Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel	Hospital	
			Sackler Faculty of Medicine, Tel-Aviv University	Academia	
			First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)	Academia	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Antonelli, A			Department of Clinical and Experimental Medicine, University of Pisa		
New insights into the pathogenesis and nonsurgical management of Graves orbitopathy					
Taylor, P N	2020	The main treatment for thyroid eye disease is steroid medication, but patients often need special surgery since steroids alone don't fully work for more than 60% of people. New treatments like teprotumumab, rituximab, and tocilizumab show promise in reducing eye swelling and inflammation.	Cardiff University School of Medicine	Academia	https://www.nature.com/articles/s41574-019-0305-4
Zhang, L					
Lee, R W J			Moorfields Eye Hospital NHS Foundation Trust	Hospital	
			University of Bristol	Academia	
Muller, I			Cardiff University School of Medicine	Academia	
Ezra, D G			Moorfields Eye Hospital NHS Foundation Trust	Hospital	
Dyan, C M			Cardiff University School of Medicine	Academia	
Kahaly, G J			Johannes Gutenberg University Medical Center		
Ludgate, M			Cardiff University School of Medicine		
Teprotumumab for the Treatment of Active Thyroid Eye Disease					
Douglas, R S	2020	In the clinical trial (OPRIC) the drug teprotumumab for thyroid eye disease, 83% of patients who received the medicine showed significant improvement in their bulging eyes and other symptoms, compared to only 10% of patients who got a placebo. The medicine was generally safe with few serious side effects. (Study funded by Horizon Therapeutics)	Cedars-Sinai Medical Center	Hospital	https://www.nejm.org/doi/10.1056/NEJMoa1910434
Kahaly, G J			Johannes Gutenberg University Medical Center	Academia	
Patel, A			Cedars-Sinai Medical Center	Hospital	
Sile, S			Horizon Therapeutics	Industry	
Thompson, E H Z					
Perdok, R					
Fleming, J C			University of Tennessee Health Science Center	Academia	
Fowler, B T					
Marcocci, C			University of Pisa		
Marinò, M					
Antonelli, A					
Dailey, R			Oregon Health and Sciences University		
Harris, G J			Medical College of Wisconsin Eye Institute		
Eckstein, A			University Hospital Essen		
Schiffman, J			Eye Wellness Center-Neuro-Eye Clinical Trials	Hospital	
Tang, R					
Nelson, C			Kellogg Eye Center-Michigan Medicine	Hospital	
Salvi, M			Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Hospital	
Wester, S			Bascom Palmer Eye Institute	Hospital	
Sherman, J W			Horizon Therapeutics	Industry	
Vescio, T					
Holt, R J					
Smith, T J			Kellogg Eye Center-Michigan Medicine	Hospital	
			University of Michigan Medical School	Academia	
Graves' disease: Clinical manifestations, immune pathogenesis (cytokines and chemokines) and therapy					
Antonelli, A	2020		University of Pisa	Academia	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Fallahi, P		Graves' disease, characterized by thyrotoxicosis and extrathyroidal manifestations, is primarily driven by thyroid stimulating antibodies and Th1 immune responses, with current treatments being suboptimal as they either have low remission rates or cause hypothyroidism, though newer targeted therapies like teprotumumab and TSH-R peptide immunization show promise.			https://www.sciencedirect.com/science/article/abs/pii/S1521690X20300154?via%3Dihub
Elia, G					
Ragusa, F					
Paparo, S R					
Ruffilli, I					
Patrizio, A					
Gonnella, D					
Giusti, C					
Virili, C			Sapienza University of Rome		
Centanni, M					
Shoenfeld, Y			Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center	Hospital	
Ferrari, S M			University of Pisa	Academia	

Tabelle 10-3: Financing/patent deals/ licensing/funding rounds of all companies involved in the development of TEPROTUMUMAB® (TEPROTUMUMAB® specific information in colour)

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/ Investors/ Acquiror	Source
Horizon Therapeutics					
Acquisition	Amgen Completes $27.8B Horizon Acquisition Following FTC Challenge	2023	Acquisition for $27.8B	Amgen	https://www.biospace.com/amgen-completes-27-8b-horizon-therapeutics-acquisition-following-ftc-challenge
Acquisition	Horizon Therapeutics has struck a $3 billion deal to buy AstraZeneca spinout Viela Bio. The takeover will give Horizon a clutch of clinical-phase autoimmune and inflammatory disease drug candidates, R&D capabilities and an approved monoclonal antibody.	2021	$ 3B	AstraZeneca	https://www.fiercebiotech.com/biotech/horizon-inks-3b-deal-to-buy-astrazeneca-spinut-viela-for-autoimmune-drugs
Acquisition	Horizon is putting up $65 million in cash to acquire a drug product manufacturing plant from OPKO Health's EirGen Pharma, the company said in a release. The 44,000-square-foot facility in Waterford, Ireland, comes equipped with a filling line and lyophilizer—or freeze dryer—that the company is eyeing for production of its commercial rare disease meds Teprotumumab, Krystexxa and Uplizna, plus its pipeline of biologics. The plant also boasts analytical laboratory capabilities, Horizon said.	2021	$ 65M	OPKO Health's EirGen Pharma	https://www.fiercepharma.com/manufacturing/horizon-lays-out-65m-for-house-manufacturing-plant-as-its-eye-med-teprotumumab-resets
Licensing	Halozyme has struck a licensing deal worth upward of $190 million with Horizon Therapeutics, granting the drugmaker access to Halozyme's Enhanze drug delivery platform. Horizon will tap Enhanze to develop a subcutaneous formulation of its thyroid eye disease med Teprotumumab (teprotumumab-trbw), the companies said in a release.	2020	Up to $190M	Access to Halozyme's Enhanze drug delivery platform	https://www.fiercepharma.com/drug-delivery/horizon-pays-halozyme-190m-to-develop-subq-thyroid-eye-disease-med

Acquisition	Horizon Pharma Plc to acquire River Vision Development Corp Horizon Pharma Plc - deal for upfront cash payment of $145 million	2017	$ 145M	Acquisition of River Vision Development Corp	https://www.reuters.com/article/business/horizon-pharma-plc-to-acquire-river-vision-development-corp-idUSASA09NMZ/
Acquisition	Ireland's Horizon Pharma ($HZNP) will pay a 21% premium for California-based Raptor Pharmaceutical as it looks to bolster its rare disease portfolio while also expanding its geographical footprint. But it will also gain a tough pipeline that has been hit by failures over the past year. The deal, which is worth $9 a share--or around $800 million--will see Horizon gain access to Procysbi (cysteamine bitartrate) for the orphan condition nephropathic (kidney) cystinosis, as well as Quinsair, which is licensed in Europe and Canada to help manage chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis.	2016	$ 800M	Acquisition of Raptor Pharmaceutical	https://www.fiercebiotech.com/biotech/horizon-pharma-800m-raptor-rare-disease-buy-but-pipeline-beset-by-failures
Acquisition	Horizon Pharma Buys Crealta Holdings for $510M	2015	$ 510M	Acquisition of Crealta Holdings	https://www.genengnews.com/topics/drug-discovery/horizon-pharma-buys-crealta-holdings-for-510m/
Acquisition	Horizon Pharma Acquires Hyperion Therapeutics and Its Revenue-Boosting Pipeline for $1.1B	2015	$ 1.1BN	Acquisition of Hyperion Therapeutics	https://www.biospace.com/horizon-pharma-acquires-hyperion-therapeutics-and-its-revenue-boosting-pipeline-for-1-1b
Acquisition	Horizon Pharma to Acquire Vidara Therapeutics International Ltd. and Become Horizon Pharma plc. Vidara Therapeutics International Ltd. (Vidara) today announced they have entered into a definitive agreement under which Horizon Pharma will acquire Vidara through a reverse merger for stock and cash valued at approximately $660 million	2014	$ 660M	Acquisition of Vidara Therapeutics International Ltd.	https://www.fiercepharma.com/pharma/horizon-pharma-to-acquire-vidara-therapeutics-international-ltd-and-become-horizon-pharma
Financing	JMP Securities LLC, Cowen and Company, LLC and Stifel Nicolaus Weisel	2012	$ 50.8M	Private placement joint-lead placement agents were from JMP Securities LLC, Cowen and Company, LLC and Stifel Nicolaus Weisel	https://www.fiercebiotech.com/biotech/horizon-pharma-announces-50-8-million-private-placement
Initial Public Offering	Horizon Pharma, Inc. (NASDAQ: HZNP) today announced the pricing of its initial public offering of 5,500,000 shares of common stock at a price to the public of $9.00 per share. Horizon's common stock is scheduled to begin trading on The NASDAQ Global Market on July 28, 2011 under the symbol "HZNP." Horizon has also granted the underwriters a 30-day option to purchase up to an additional 825,000 shares at the initial public offering price to cover overallotments, if any.	2011	n.a. (share 5.5 M shares á $9)	Stifel Nicolaus Weisel, Cowen and Company and JMP Securities LLC act as join bookrunners for the offering	https://www.biospace.com/horizon-pharma-inc-announces-pricing-of-its-initial-public-offering
Merger	Horizon Therapeutics and Nitec Pharma Complete Merger and Combine Businesses	2010	n.a.	Horizon Therapeutics and Nitec Pharma merger	https://www.prnewswire.com/news-releases/horizon-therapeutics-and-nitec-pharma-complete-merger-and-combine-businesses-89705152.html

Series A – C Financing	Horizon Therapeutics, Inc., a privately held biopharmaceutical company, today announced that it has **closed a $30 million Series C** financing to advance the development of its lead investigational product candidate HZT-501 and pipeline of other "GI-friendly" prescription non-steroidal anti-inflammatory drugs (NSAID). Essex Woodlands Health Ventures (EWHV) led the round with participation from existing investors Scale Venture Partners, Sutter Hill Ventures and Pequot Ventures. Horizon has previously raised **$21 million** in equity funding.	2007	$ 51M	Essex Woodlands Health Ventures (EWHV)/ Scale Venture Partners, Sutter Hill Ventures and Pequot Ventures	https://www.biospace.com/horizon-therapeutics-completes-30-million-equity-financing-to-advance-pipeline-of-gi-friendly-nsaids-for-mild-to-moderate-pain
River Vision Development Corporation					
Series A financing	River Vision Announces Completion of $17 million Series A Financing	2012	$ 17M	SR One, Lundbeckfond Ventures	https://www.fiercebiotech.com/biotech/river-vision-announces-completion-of-17-million-series-a-financing
Rights to TEPROTUMUMAB revenue	S.R. One and Lundbeckfond, as two of the former River Vision stockholders, both held rights to receive approximately 35.66% of any future TEPROTUMUMAB payments. As a result of the Company's agreements with S.R. One and Lundbeckfond in April 2020, the Company's remaining net obligations to make TEPROTUMUMAB payments for sales milestones and royalties to the former stockholders of River Vision was reduced by approximately 70.25%, after including payments to a third party.	n.a.	35.66% of any future TEPROTUMUMAB payments (each but reduced in 2020)	S.R. One, Lundbeckfond,	https://www.sec.gov/Archives/edgar/data/1492426/000156459021007818/R21.htm
Licensing deal	The Lundquist Institute licensed the treatment of thyroid eye disease to River Vision Development Corporation	n.a.	n.a.	The Lundquist Institute	https://lundquist.org/news/technologies-first-created-lundquist-institute-achieve-3rd-fda-approval-5-years
Licensing agreement	Under the Company's license agreement with Roche, the Company is required to pay Roche up to CHF103.0 million upon the attainment of various development, regulatory and sales milestones for TEPROTUMUMAB. During the years ended December 31, 2019 and 2017, CHF3.0 million and CHF2.0 million, respectively, was paid in relation to these milestones. The Company made a milestone payment of CHF5.0 million) during the first quarter of 2020. The agreement with Roche also includes tiered royalties on annual worldwide net sales between 9 and 12 percent	Up to CHF103 M	CHF103.0 M	Roche	https://www.sec.gov/Archives/edgar/data/1492426/000156459021007818/R21.htm
University of Michigan Medical School (Raymond S Douglas, Terry J Smith, Alon Kahana)					
Basic research	Immune Activation of Fibroblasts	2008	$71,770	NEI	https://reporter.nih.gov/search/UtBDEmD1YUGC4BP4Lwubfg/project-details/7935001
	The role of CD40+ fibrocytes in thyroid associated ophthalmopathy	2011-2015	$1,899,067	NEI	https://reporter.nih.gov/search/klRLMIHTDUicDFC6NV2B1g/projects
	Regulation of Retroocular Connective Tissue	2008-2020 (break in 2009-2010 & 2016)	$3,663,799	NEI	https://reporter.nih.gov/search/IrTGrU_8dEeOKJGkycxtNA/projects
	Functional Diversity of Orbital Fibroblasts	2009-2011	$1,226,098	NEI	https://reporter.nih.gov/search/oKC38798b0G5tT_Biowa8g/projects
	Immunoglobulin Activation of Fibroblasts	2009-2012	$1,504,236	NIDDK	https://reporter.nih.gov/search/Kkoe67cxFkSrwR0aTTJjqQ/projects

	A zebrafish model for studying orbital development and disease	2008-2012	$1,079,481	NEI	https://reporter.nih.gov/search/XhDMGYUYHUm7pceGZrZ2ew/projects
LUNDQUIST INSTITUTE FOR BIOMEDICAL INNOVATION AT HARBOR-UCLA MEDICAL CENTER (Raymond S Douglas, Terry J Smith)					
Basic research	Immune Activation of Fibroblasts	2004-2008	$913,818	NEI	https://reporter.nih.gov/search/4kYpy0uHN0m38GXMGccO0A/projects
	Immunoglobulin Activation of Fibroblasts	2004-2008	$1,660,017	NIDDK	https://reporter.nih.gov/search/Zowz6lG2PUy94gDFq8PUWA/projects
	Regulation of Retroocular Connective Tissue	2000-2008	$2,719,043	NEI	https://reporter.nih.gov/search/iE3VdZCBZE6V8wMUwQlSIg/projects
	Regulation of Retroocular Connective Tissue: Interleukin IL-16 Levels in Pati	2004-2010	$107,084	NCRR	https://reporter.nih.gov/search/iE3VdZCBZE6V8wMUwQlSIg/projects
	Functional Diversity of Orbital Fibroblasts	1999-2008	$3,261,497	NEI	https://reporter.nih.gov/search/_9TsY827mker44XC8RcujA/projects

Abbreviations: NEI = National Eye Institute; NCRR = National Center for Research; Resources; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; FDA = Food and Drug Administration

Tabelle 10-4: Therapies under development for the treatment of TED

Indication	Active ingredient	NCT Number	Originator	Developer	Estimated EC decision
Vrdn-003: Vrdn-003 monotherapy for treatment of moderate to severe active Thyroid eye disease in adults and elderly					
Active thyroid eye disease	VRDN-003	NCT06625411	Viridian Therapeutics	Viridian Therapeutics	Jul 2027
Vrdn-003 monotherapy for treatment of moderate to severe chronic Thyroid eye disease in adults and elderly					
Chronic thyroid eye disease	VRDN-003	NCT06625398	Viridian Therapeutics	Viridian Therapeutics	Aug 2027
Batoclimab monotherapy for treatment of moderate to severe active Thyroid eye disease in adults and elderly who do not require immediate surgical intervention and are not planning corrective surgery/irradiation or medical therapy					
Active thyroid eye disease	Batoclimab	NCT05524571 NCT05517447 NCT05517421 NCT03938545 NCT03922321	Immunovant	Immunovant	Jul 2026
Satralizumab monotherapy for treatment of moderate to severe Thyroid eye disease in adults and elderly					
Thyroid eye disease	Satralizumab (brand name: Enspryng)	NCT06106828 NCT05987423	Hoffmann-La Roche	Hoffmann-La Roche	Sep 2026
Veligrotug monotherapy for treatment of moderate to severe, active Thyroid eye disease in adults and elderly					
Thyroid eye disease	Veligrotug	NCT05176639	Viridian Therapeutics	Viridian Therapeutics	Oct 2026
Linsitinib monotherapy for treatment of moderate to severe active Thyroid eye disease in adults and elderly					
Thyroid eye disease	Linsitinib	NCT06112340 NCT05276063	Sling Therapeutics	Sling Therapeutics	Dec 2028
Efgartigimod alfa / hyaluronidase-qvfc monotherapy for treatment of active, moderate to severe Thyroid eye disease in adults and elderly associated with autoimmune thyroid conditions (Graves' disease or Hashimoto's thyroiditis)					
Thyroid eye disease associated with autoimmune thyroid conditions (Graves' disease or Hashimoto's thyroiditis)	Efgartigimod Alfa / Hyaluronidase-qvfc	NCT06307626 NCT06307613	argenx	argenx	Dec 2026
Ag22515 monotherapy for treatment of moderate-to-severe Thyroid eye disease in adults and elderly					
Thyroid eye disease	Ag22515	NCT06557850	H. Lundbeck	H. Lundbeck	n.a.

Tabelle 10-5: Search terms used to identify the development history and public contributions of TEPEZZA®

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	Tepezza Teprotumumab		no	Earliest mention – 01/2025	Active substance, Medical specialty, Pharmacotherapeutic group, Therapeutic area, Class, Orphan designation, Categorization, Additional monitoring, Conditional approval, Accelerated assessment, PRIME: priority medicines, Marketing authorisation issued
https://www.fda.gov/			yes		
https://adisinsight.springer.com/			yes		Alternative names:
https://pubmed.ncbi.nlm.nih.gov/	1036734-93-6, hzn001, immunoglobulin g1, anti-(human insulin-like growth factor 1 receptor (cd221)), human monoclonal imc-11f8 .gamma.1 heavy chain (221-215')-disulfide with human monoclonal imc-11f8 .kappa. light, dimer (227-227'':230-230'')-bisdisulfide immunoglobulin g1, anti-(human insulin-like growth factor i receptor) (human monoclonal heavy chain), disulfide with human monoclonal light chain, dimer, r-1507, ro4858696, rv001 monoclonal, rv-001, y64gq0kc0a		yes	Earliest mention – FDA approval 21st Jan 2020	Development history Tepezza
https://clinicaltrials.gov/			Yes	Earliest mention – 01/2025	Clinical trials using teprotumumab
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://cordis.europa.eu/			Yes		
https://reporter.nih.gov/		Horizon Therapeutics, River Vision Development Corporation, Amgen, Roche, Genmab	Yes		Basic research for teprotumumab. Authors selected based on literature found on PubMed
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm			Yes		Patent information and associated references
https://trialsearch.who.int/			Yes		n.a.
https://competition-cases.ec.europa.eu/search			No		
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		
https://eic.ec.europa.eu/index_en			No		
https://www.eib.org/en/index			No		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			No		

https://www.sbir.gov/			Yes		Project funding for companies involved in the development of teprotumumab.
https://www.nsf.gov/			No		
https://www.ukri.org/			No		
https://foerderportal.bund.de/			No		
https://www.health-holland.com/			No		
https://www.bpifrance.com/			No		
https://www.inserm.fr/en/home/			No		n.a.
https://innovationsfonden.dk/da			No		
https://www.ucc.ie/en/apc/			No		
https://www.amractionfund.com/about			No		
https://reporter.nih.gov/			Yes		
https://www.gatesfoundation.org/			No		
https://www.google.com/			Yes		Patent deal information
https://www.forbes.com/			No		
https://www.reuters.com/			No		n.a.
https://www.science.org/			Yes		
https://www.cafepharma.com/			No		
https://www.livescience.com/			Yes		
https://www.biospace.com/			Yes		
https://www.bioworld.com/			Yes		
https://www.biopharmadive.com/			Yes		
https://pharmaphorum.com/			Yes		Collaborations, funding, financing, patent dispute, acquisitions
https://pharmatimes.com/			Yes		
https://pharmafile.com/			Yes		
https://www.fiercepharma.com/			Yes		
https://www.businesswire.com/			Yes		
https://www.businessinsider.com/			Yes		
https://www.statnews.com/			Yes		

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