Medicinrådet

Bilag til Medicinrådets vurdering af teprotumumab til behandling af aktiv moderat til svær Graves' orbitopati

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. teprotumumab
2. Forhandlingsnotat fra Amgros vedr. teprotumumab
3. Ansøgers endelige ansøgning vedr. teprotumumab

Indspilsnotat til Medicinrådets vurderingsrapport vedrørende teprotumumab (Tepezza)

Amgen takker for muligheden for at kommentere udkastet til vurderingsrapporten for teprotumumab ved moderat til svær Graves' orbitopati. Amgen anerkender, at vurderingen er forbundet med usikkerhed, særligt fordi der ikke foreligger et direkte randomiseret studie mellem teprotumumab og i.v. methylprednisolon (IVMP).

Efter Amgens vurdering har Medicinrådet gennemgående valgt konservative ændringer og antagelser, som i flere tilfælde ikke fremstår tilstrækkeligt begrundede eller understøttede af den tilgængelige dokumentation. Samlet har disse valg haft væsentlig betydning for ICER sammenlignet med den indsendte analyse. En central indvending vedrører Medicinrådets ændringer i nytteværdierne. Amgen mener, at dette bygger på antagelser, som ikke er klinisk plausible, og som derfor ikke udgør et egnet udgangspunkt for evalueringen. Amgen har gennem dialog med Medicinrådet ad flere omgange forgæves forsøgt at tydeliggøre og etablere dialog om, at udgangspunktet for evalueringen derfor ikke er klinisk relevant. Synspunkterne som også tidligere er delt med Medicinrådet beskrives nedenfor.

Fjernelsen af forskellen mellem aktiv og kronisk sygdom er ikke klinisk plausibel

Den enkeltstående modelændring med størst betydning for resultatet er beslutningen om at tildele identiske nytteværdier til aktive og kroniske helbredstilstande med samme grad af proptose og diplopi. Dette indebærer i praksis, at den inflammatoriske sygdomsaktivitet tillægges nul selvstændig betydning for patienternes livskvalitet. Medicinrådet begrunder ændringen med, at den relative opjustering i Amgens base case medfører, at enkelte kroniske nytteværdier overstiger baggrundsbefolkningens. Efter vores vurdering kan dette begrunde en revurdering af niveauet for nytteværdierne og/eller justeringsmetoden, men det giver ikke et fagligt grundlag for at fjerne forskellen mellem aktiv og kronisk sygdom.

Graves' orbitopati er en inflammatorisk autoimmun sygdom, hvor den aktive fase er karakteriseret ved smerter, hævelse, rødme, irritation og anden inflammatorisk sygdomsaktivitet. Disse manifestationer påvirker livskvaliteten ud over belastningen fra proptose og diplopi. Når sygdommen overgår til den kroniske fase, aftager den inflammatoriske komponent, selv om graden af proptose og diplopi kan være uændret. Det er derfor klinisk forventeligt, at livskvaliteten forbedres ved overgangen fra aktiv til kronisk sygdom. Denne vurdering understøttes af de danske kliniske eksperter, som Amgen har konsulteret, og af den tilgængelige publicerede litteratur. Den er også i overensstemmelse med det grundlæggende kliniske princip ved inflammatoriske sygdomme om, at sygdomsaktivitet og inflammation har en selvstændig negativ betydning for livskvaliteten.

Dette punkt har været genstand for gentagen og detaljeret skriftlig og mundtlig dialog med Medicinrådet. Amgen har blandt andet præciseret, at spørgsmålet om, hvorvidt den kroniske fase skal repræsenteres i modellen, må adskilles fra spørgsmålet om, hvordan forskellen i nytteværdierne skal estimeres. Medicinrådets svar og analyser har efter Amgens vurdering primært omhandlet størrelsen på eller implementeringen af nytteværdierne. Det dokumenteres ikke, at forskellen i livskvalitet mellem aktiv og kronisk sygdom er fraværende. Medicinrådets valgte antagelse står i direkte modstrid med den kliniske ekspertvurdering og det beskrevne sygdomsforløb. Hvis niveauet for enkelte kroniske nytteværdier vurderes at være for højt, må dette håndteres gennem en klinisk plausibel justering af værdierne – ikke ved at eliminere en central og klinisk begrundet del af

sygdomsforløbet. Amgens indvendinger på dette punkt er ikke blevet imødekommet, og er derfor grundlæggende uenige i den valgte tilgang.

Betydelig usikkerhed forbundet med nytteværdierne

Vurderingsrapportens nytteværdiestimater bygger på antagelsen om, at den gennemsnitlige EQ-5D-5L ved uge 24 i OPTIC-J kan repræsentere nytteværdien i den bedste helbredstilstand, og at de øvrige helbredstilstande kan estimeres ved hjælp af relative forskelle observeret i GO-QoL. Denne tilgang er forbundet med betydelig usikkerhed.

For det første er det dokumenteret, at generiske livskvalitetsmål som EQ-5D har begrænset sensitivitet over for centrale aspekter ved Graves' orbitopati, herunder udseenderelateret belastning, social tilbagetrækning og psykosociale konsekvenser.

For det andet findes der ikke patientniveaudata, som gør det muligt at koble EQ-5D-målingerne i OPTIC-J til de seks proptose- og diplopibaserede helbredstilstande, der indgår i modellen. Dette blev tidligere bekræftet over for Medicinrådet.

Endvidere har Medicinrådet fastsat nytteværdien for helbredstilstanden small proptosis, no diplopia (SPND) til 0,88, hvilket svarer til populationsnormen i den relevante aldersgruppe. Patienterne i denne helbredstilstand har imidlertid moderat til svær aktiv Graves' orbitopati. Selv i SPND-helbredstilstanden er det derfor ikke sandsynligt, at deres livskvalitet er på niveau med den generelle befolknings. Anvendelsen af 0,88 som nytteværdi for SPND fremstår derfor som klinisk lidet plausibel og kan medføre, at nytteværdierne i de øvrige helbredstilstande overvurderes.

Antagelsen om identisk risiko for sygdomsopblussen er utilstrækkeligt begrundet

Medicinrådet har valgt at antage identisk sygdomsopblussen (flare rate) for teprotumumab og IVMP med henvisning til forskelle i definitionerne mellem studierne.

Amgen er enige i, at der er usikkerhed forbundet med størrelsen af forskellen mellem behandlingerne. Usikkerhed er imidlertid ikke det samme som dokumentation for, at forskellen ikke eksisterer. Rapporten beskriver ikke, hvorfor variation i definitionerne nødvendigvis gør en identisk flare rate til den mest plausible antagelse.

IVMP er den mest anvendte førstelinjebehandling i dansk klinisk praksis

Medicinrådet skriver i vurderingsrapporten, at der er usikkerhed forbundet med valget af IVMP som komparator, og anslår, at 40 % af patienterne behandles med IVMP alene og 40 % med IVMP i kombination med mycophenolat. Den kliniske ekspert, som blev konsulteret i forbindelse med ansøgningen, anslog, at størstedelen (95–98 %) af patienterne behandles med IVMP alene i første linje, mens kun 2–5 % modtager IVMP i kombination med mycophenolat. Amgen mener derfor, at usikkerhed omkring valget af komparator ikke bør tillægges vægt.

CAS bør ikke være afgørende for vurderingen af den relative effekt

Amgen anerkender, at CAS er et centralt mål for inflammatorisk sygdomsaktivitet i den aktive fase af TED. Samtidig måler CAS inflammatorisk aktivitet, mens proptose og diplopi vedvarer, efter sygdommen er blevet kronisk, og er centrale for både funktion og livskvalitet.

Fraværet af en justeret sammenligning indebærer, at den relative effekt på CAS er usikker. Dette bør imidlertid ikke svække sammenligningen af effekten på proptose eller de understøttende resultater for diplopi.

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13.10.2026

DBS/LSC

Forhandlingsnotat

Dato for vurdering i Medicinrådet	28.10.2026
Leverandør	Amgen
Lægemiddel	Tepezza (teprotumumab)
Ansøgt indikation	Behandling af voksne med moderat til svær Graves' orbitopati (GO)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Tepezza:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tepezza	500 mg (1 stk.)	44.868,60	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale på Tepezza. Aftalen gælder fra den 01.11.2026 til den 31.03.2028 med mulighed for at forlænge i 1x12 måneder. Leverandøren har mulighed for at sætte prisen ned i løbet af aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Hos patienter med aktiv moderat til svær GO er nuværende behandling i førstevalglinje methylprednisolon i.v.. Formålet med behandlingen er at reducere den inflammatoriske aktivitet og begrænse sygdomsprogression i den aktive fase. Ved aktiv svær GO anbefales samtidig behandling med mycophenolat.

Tabel 2 viser en behandlingsforløb på 24 uger med behandling med Tepezza. Tepezza gives som intravenøs infusion i et fast behandlingsforløb over 24 uger, bestående af i alt 8 infusioner givet hver 3. uge. Første dosis er 10 mg/kg, efterfulgt af en dosis på 20 mg/kg ved de efterfølgende infusioner.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (AIP, DKK)	Lægemiddeludgift pr. behandling (24 uger) (AIP, DKK)
Tepezza	500 mg (1 stk.)	Første dosis 10 mg/kg, efterfulgt af 20 mg/kg hver 3. uge, i.v.	[redacted]	[redacted]

*Gennemsnitsvægt: 74,67 kg jf. Medicinrådets vurdering af teprotumumab til behandling af aktiv moderat til svær Graves' orbitopati

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Under vurdering	Link til status
England	Under vurdering	Link til status

Opsummering

Amgros har mulighed for at indgå en aftale på Tepezza, baseret på leverandørens betinget pristilbud.

Submission for the Assessment of Teprotumumab (Tepezza) for adult patients with active moderate to severe Thyroid Eye Disease

Contact Information

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Abbreviations

Abbreviation	Description of abbreviation	Abbreviation	Description of abbreviation
1L	First-line	**ITT**	Intention to treat
2L	Second-line	**IUD**	Intrauterine device
AAO	American academy of ophthalmology	IV	Intravenous
AE	Adverse event	**IVGC**	Intravenous glucocorticoid pulse therapy
AHRQ	Agency for healthcare research and quality	**IVMP**	Intravenous methylprednisolone
AIC	Akaike information criterion	**JNHB**	Joint nordic HTA bodies
ALT	Alanine aminotransferase	**LD**	Low dose
ANOVA	Analysis of variance	**LOCF**	Last observation carried forwards
AOS	American ophthalmological society	**LP**	Large proptosis

AST	Aspartate aminotransferase	**LS Mean**	Least squares mean
ATA	American thyroid association	**LY**	Life year
ATC	Anatomical therapeutic chemical	**MAIC**	Matching-adjusted indirect comparison
ATMP	Advanced therapy medicinal products	**MCID**	Minimal clinically important difference
ATP	Adult treatment panel	**MD**	Medium dose
BIC	Bayesian information criterion	**MedDRA**	Medical dictionary for regulatory activities
BMD	Bone mineral density	**MEDLINE**	Medical literature analysis and retrieval system online
BP	Blood pressure	**MMF**	Mycophenolate mofetil
CADTH	Canadian agency for drugs and technologies in health	**MMRM**	Mixed model repeated measures
CAS	Clinical activity score	**MR**	Monthly regimen
CD	Constant diplopia	**MRAW**	Untransformed raw means
CDSR	Cochrane database of systematic reviews	**MRI**	Magnetic resonance imaging
CEA	Cost-effectiveness analysis	**MS**	Microsoft
CEAC	Cost-effectiveness acceptability curve	**MTX**	Methotrexate
CEM	Cost-effectiveness model	**N, n**	Number
CENTRAL	Cochrane central register of controlled trial	**N/A**	Not applicable
ChiCTR	Chinese clinical trial registry	**NaCl**	Sodium chloride
CI	Confidence interval	**NCT**	National clinical trial
CLIA	Chemiluminescent immunoassay	**ND**	No diplopia
COPD	Chronic obstructive pulmonary disease	**NHS**	National health service
CON	Compressive optic neuropathy	**NICE DSU**	Nice decision support unit
CONITEC	National committee for health technology incorporation	**NICE**	National institute for health and care excellence
CRD	Centre for reviews and dissemination	**NOKC**	Norwegian knowledge centre for health services
CSR	Clinical study report	**NoMA**	Norwegian medical products agency
CT	Computed tomography	**NOSPECS**	No physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle signs, corneal involvement, and sight loss score

CTCAE	Common terminology criteria for adverse event	**NR**	Not reported
DARE	Database of abstract of reviews of effects	**OGC**	Oral methylprednisolone
DKK	Danish krone	**OGTT**	Oral glucose tolerance test
DMARDs	Disease-modifying antirheumatic drugs	**OR**	Odds ratio
DMC	Danish medicines council	**OS**	Overall survival
DON	Dysthyroid optic neuropathy	**OWSA**	One-way sensitivity analyses
DR	Daily regimen	**p/P**	Probability
DRG	Diagnosis related group	**P value**	Probability value
DXA	Dual-energy X-ray absorptiometry	**PBAC**	Pharmaceutical benefits advisory committee
EC	European commission	**PF**	Prognostic factor
ECG	Electrocardiogram	**PFS**	Progression free survival
EconLit	Economic literature	**PICO**	Population, intervention, comparison, outcome
eCRF	Electronic case report form	**PICOS**	Populations, interventions/comparators, outcomes, and study design
EED	Economic evaluation database	**PPP**	Pharmacy purchase price
eGFR	Estimated glomerular filtration rate	**PRISMA**	Preferred reporting items for systematic reviews and meta-analyses
EMA	European medicines agency	**PRO**	Patient-reported outcome
EMBASE	Excerpta medica database	**PROC MIXED**	Procedure for mixed models
ENDO	Annual meeting of the endocrine society	**PSA**	Probabilistic sensitivity analysis
EPAR	European public assessment report	**P-value**	Probability value
EQ-5D	EuroQoL 5-dimension	**Q3W**	Every three weeks
EQ-5D-5L	EuroQoL 5-dimension 5-level	**Q6**	Transition probability
ESOPRS	European society of ophthalmic plastic and reconstructive surgery	**QALY**	Quality-adjusted life year
ESS	Effective sample size	**QoL**	Quality of life
ETA	European thyroid association	**r**	Rate
EU	European union	**Rantes**	Regulated upon activation, normal T cell expressed and secreted
EudraCT	European union drug regulating authorities clinical trials database	**RCT**	Randomized clinical trial
EUGOGO	European group on graves' orbitopathy	**RDI**	Relative dose intensity

EUnetHTA	European network for health technology assessment	**RE**	Random effects
FDA	Food and drug administration	**RIT**	Radioiodine therapy
FinCCHTA	Finnish coordinating center for health technology assessment	**RoB 2**	Risk of bias 2
FT3	Free triiodothyronine	r_s	Spearman's rank correlation
FT4	Free thyroxine	**RWE**	Real-world evidence
F-test	Fisher's test (analysis of covariance)	**SAE**	Serious adverse event
G-BA	Germany's joint federal committee (gemeinsamer bundesausschuss)	**SAS**	Statistical analysis system
GC	Glucocorticoid	**SD**	Standard deviation
GCP	Good clinical practice	**SE**	Standard error
GD	Graves' disease	**SF-36**	36-item short form health survey
GEE	Generalized estimating equations	**SHR-1314**	Vunakizumab
GFR	Glomerular filtration rate	**SLR**	Systematic literature review
GI	Gastrointestinal	**SMC**	Scottish medicines consortium
GO	Graves' orbitopathy	**SmPC**	Summary of product characteristics
GO-QOL	Graves' ophthalmopathy - quality of life	**SP**	Small proptosis
HAS	Haute Autorité de Santé	**sTNFR1**	Soluble tumor necrosis factor receptor 1
HbA1c	Hemoglobin a1c	**sTNFR2**	Soluble tumor necrosis factor receptor 2
HCRU	Healthcare resource utilization	**SUSAR**	Suspected unexpected serious adverse reaction
HD	High dose	**TAO**	Thyroid-associated orbitopathy
HIV	Human immunodeficiency virus	**TAO-QOL**	Thyroid associated orbitopathy - quality of life
HRQoL	Health-related quality of life	**TEAE**	Treatment emergent adverse event
HSUV	Health state utility values	**TED**	Thyroid eye disease
HTA	Health technology assessment	**TED-QOL**	Thyroid eye disease - quality of life
HUI-3	Health utility index-3	**TEM**	Treatment effect modifier
HZN-001	Teprotumumab	**Th1**	T helper type 1

I^2	Higgins heterogeneity index	**TLV**	Swedish dental and pharmaceutical benefits agency
ICAM-1	Intercellular adhesion molecule 1	**TNF**	Tumor necrosis factor
ICER	Institute for clinical and economic review	**TRAB**	Thyrotropin receptor antibody
ICER	Incremental cost-effectiveness ratio	**TSAb**	Thyrotropin receptor antibodies
ICH	International conference of harmonization	**TSD 18**	Technical support document 18
ICUR	Incremental cost-utility ratio	**TSH**	Thyroid stimulating hormone
ID	Intermittent/Inconstant diplopia	**TSHR**	Thyroid-stimulating hormone receptor
IDEEL	Impact of dry eye in everyday life	**TSHR-Ab**	Thyroid-stimulating hormone receptor autoantibodies
IFG	Impaired fasting glucose	**TSI**	Thyroid-stimulating immunoglobulin
IFN-gamma	Interferon-gamma	**TTO**	Time trade-off
IGF-1	Insulin-like growth factor 1	**UK**	United kingdom
IGF-1R	Insulin-like growth factor 1 receptor	**ULN**	Upper limit of normal
IGT	Impaired glucose tolerance	**US**	United states
IL-β	Interleukin β	**VAS**	Visual analogue scale
INAHTA	International network of agencies for health technology assessment	**VB421**	Lonigutamab
INESSS	Institut national d'excellence en santé et en services sociaux	**VRDN-001**	Veligrotug
IPD	Individual patient data	**WR**	Weekly regimen
IQR	Interquartile range	**τ^2**	Heterogenetic variance
IQWiG	Institute for quality and efficiency in health care (Institut für qualität und wirtschaftlichkeit im gesundheitswesen)	**χ^2 test**	Chi-square test
ITC	Indirect treatment comparison		

1. Information on the Drug

Drug information	
Trade name	TEPEZZA
Generic name	Teprotumumab
Indication as formulated by the European Medicines Agency (EMA)	Adults for the treatment of moderate to severe thyroid eye disease (TED)
Marketing Authorisation Holder in Denmark	Amgen
ATC code	L04AG13
Combination therapy and/or concurrent treatment	No
Expected date of EU approval (marketing authorisation)	19th June 2025
Has the drug received a conditional marketing authorisation?	No
Has the drug undergone 'accelerated assessment' at EMA?	No
Has the drug received orphan drug designation?	No
Other indications approved by EMA	No
Other indications assessed by the Danish Medicines Council	No
Joint Nordic Assessment (JNHB): **Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?**	No - There is uncertainty regarding the comparability of clinical practice across the Nordic countries.
Joint Nordic Assessment (JNHB): **Is the drug suitable for a joint Nordic assessment?**	No - There is uncertainty regarding the comparability of clinical practice across the Nordic countries.
Has a Joint European Assessment (JCA) been conducted under EU HTA Regulation?	No

Dispensing	BEGR
Packaging – types, pack sizes/number of units, and strengths	Powder for concentrate for solution for infusion. Each vial contains 500 mg teprotumumab.

2. Summary Table

Overview	
Indication relevant to the assessment	Tepezza is indicated in adults for the treatment of moderate to severe Thyroid Eye Disease (TED) This application solely considers an indication for patients with active moderate to severe TED.
Dosage regimen and route of administration	Intravenous (IV) infusion 10 mg of teprotumumab per kg of body weight for the first infusion, and 20 mg per kg for seven subsequent infusions (once every three weeks for a total of eight IV infusions).
Choice of comparator	Intravenous methylprednisolone (IVMP).
Prognosis with current standard treatment (comparator(s))	Without effective treatment, TED typically progresses over a period of 6 to 24 months through an active inflammatory phase, followed by a chronic phase. Standard treatment, most often systemic glucocorticoids such as IVMP, offers partial and often temporary relief. Many patients either relapse or experience incomplete resolution of symptoms. Long-term outcomes frequently include permanent tissue changes resulting in proptosis, diplopia, or lid retraction (1, 2). Moderate to severe TED does not substantially alter patient mortality relative to the general population and is rarely recognized as life-threatening (3). However, TED significantly impairs health-related quality of life (HRQoL) due to functional and psychosocial burdens. Persistent double vision, disfigurement, eye pain, and visual disturbances are common, and patients score worse than population norms on the Graves' Ophthalmopathy Quality of Life (GO-QoL) assessments (4, 5). Studies have shown that TED can impact quality of life to a similar or greater extent than other chronic diseases, including diabetes and rheumatoid arthritis (6).
Type of documentation for the clinical evaluation	To compare the clinical efficacy of teprotumumab with IVMP, a matching-adjusted indirect comparison (MAIC) was conducted. This analysis utilized pooled data from the Phase 2 and OPTIC Phase 3 trials of teprotumumab (7, 8). For IVMP, pooled data from published studies reporting outcomes in

	patients with active moderate to severe TED were utilized as well.
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared with comparator(s))	Change in baseline proptosis (-2.41 mm [-3.22; -1.60]) Diplopia response rate (OR: 2.09 [0.93;4.68])
Serious adverse events for the intervention and comparator	<u>Teprotumumab:</u> Hearing impairment - Hearing loss (hypoacusis 5.3% and tinnitus 3.3%) - Deafness (1.3%) - Sensorineural hypoacusis (1.3%) - Unilateral deafness (0.7%) Hyperglycemia (5.3%) Elevated blood glucose (3.3%) Diabetes mellitus (2,6%) Inflammatory bowel disease (0.7%) Alopecia (13.3%) – all cases were mild <u>IVMP:</u> - Major depression (<5%) - Severe liver enzyme elevation (<5%) - Cardiovascular events (<5%)
Type of health economic analysis	Cost-utility analysis
Health economic model	Markov model
Outcomes and data sources used to extrapolate patient transitions	Proptosis Diplopia
Instrument and data sources for health-related quality of life	Clinical documentation: GO-QoL, Difference in least squares means (LS mean) compared to placebo: (8.43;22.53), <0.001 Health economic model: Time trade-off (TTO) used, 1.0 Quality-adjusted life year (QALY) gained compared to IVMP
Life-years gained (discounted, half-cycle corrected, and adjusted for background mortality)	0,0 Life-years

QALYs gained (discounted, half-cycle corrected, and adjusted for background mortality)	[redacted]
ICER (DKK/QALY) (discounted, half-cycle corrected, and adjusted for background mortality)	[redacted]
Applicant's assessment of uncertainty	Uncertainty related to health state utility values and patient weight has the largest impact on the ICER estimate.

3. Patient Population, Intervention, Choice of Comparator(s) and Outcome(s)

3.1 Patient Population

3.1.1 The Disease

Pathophysiology

Thyroid eye disease (TED), also known as Graves' ophthalmopathy or orbitopathy (GO), is a serious, progressive autoimmune disorder that can cause painful, disfiguring, and vision-threatening ocular complications (9-11).

TED most commonly occurs in the context of Graves' hyperthyroidism and is driven by autoantibody-mediated activation of the thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) complex on orbital fibroblasts. Overexpression of TSHR in retrobulbar orbital tissue - particularly in orbital fibroblasts - plays a central role in disease pathogenesis. Autoantibody activation triggers an inflammatory cascade with release of proinflammatory cytokines, including Th1-type cytokines and leukoregulin, leading to extraocular muscle edema, restricted eye movement, and diplopia. Expansion of orbital fat and inflammatory tissue increases orbital volume, causing venous congestion and proptosis (exophthalmos) (12-14). In severe cases, optic nerve compression may occur, resulting in optic neuropathy and permanent vision loss.

Clinical presentation and symptoms of the disease

Initially, TED exhibits inflammatory changes due to the activation of a pathogenic cascade in the orbit, marking the active phase. This phase typically lasts 18 to 24 months, after which the disease enters a more stable, chronic, and fibrotic phase as inflammation begins to subside (9, 10, 14, 15). Early intervention is crucial for improving patient outcomes and preventing potentially permanent damage. If there is a delay in treatment,

patients may develop serious complications such as dysthyroid optic neuropathy, which can lead to permanent and irreversible vision loss (16, 17).

During the chronic phase of the disease, although inflammation and tissue remodelling may improve, complete recovery remains rare for patients with moderate to severe TED, with eye dryness, decreased vision, proptosis and diplopia, excessive tearing, and facial disfigurement still being prevalent in patients with chronic TED (10, 14, 18). Moreover, even after entering a stable disease phase lasting several months or years, up to 15.7% of patients may still experience flares, characterized by a recurrence of inflammatory signs and symptoms after a period of remission, with worsening proptosis being the most common clinical presentation(13, 18-20).

TED presents a broad spectrum of ocular manifestations, ranging from mild irritation to vision-threatening complications. Common symptoms include dry eyes and upper eyelid retraction, leading to foreign body sensation, tearing, and increased risk of keratopathy, corneal scarring, or ulceration. Proptosis and lagophthalmos further exacerbate ocular surface exposure. Extraocular muscle involvement may cause restricted eye movements, diplopia, or strabismus. Patients may also experience orbital pain, excessive tearing, inflammatory signs (eyelid oedema, erythema, conjunctival injection, chemosis), and, in severe cases, vision loss due to compressive optic neuropathy or impaired color vision (9, 11).

Some features—such as eyelid retraction, proptosis, and strabismus—can result in facial disfigurement and functional difficulties, including impaired forward gaze and incomplete eyelid closure during sleep (10, 11). While presentation varies by severity, most patients with moderate to severe TED experience symptoms that substantially impair daily life (9, 14, 21-23).

A study involving 307 patients with active moderate to severe TED found the most commonly reported symptoms were ocular dryness/grittiness and soft tissue edema (each at 92%), followed by conjunctival redness (90%), eyelid redness (79%), proptosis (78%), excessive tearing (72%), conjunctival swelling (64%), decreased vision (63%), pain with eye movement (58%), and photophobia (56%). Diplopia and strabismus were observed in 42% and 39% of the patients, respectively (24).

TED has several risk factors, with the most significant non-modifiable ones being female sex and middle age, and the key modifiable risk factors including untreated thyroid dysfunction, thyrotropin receptor antibodies (TSAb) levels, treatment with radioactive iodine, and most notably, smoking (9, 10, 16).

The influence on patients' functioning and health-related quality of life

Thyroid eye disease (TED) profoundly impairs physical, psychological, and social functioning, leading to markedly reduced quality of life (QOL). Pain, vision impairment, disfigurement, and loss of autonomy limit daily activities (e.g., reading, driving), reduce work capacity, drive social withdrawal and diminished self-esteem. The greatest QOL burden is driven by pain, proptosis, diplopia and disfigurement. In a US medical record review of 714 patients with moderate-to-severe TED, physicians rated QOL on a 7-point

Likert scale (1 = not at all impaired, 7 = extremely impaired), considering mental health, vision changes, and ocular signs/symptoms. The mean score was 4.1 (SD 1.5), with high impact (≥4) reported in 62% of moderate and 89% of severe cases; higher scores were linked to pain, visual disturbances (including diplopia), and orbito-facial changes (25). Nearly half of patients (45%) experience mental health conditions such as anxiety and depression (26). TED impacts patients' everyday life and causes major work disability due to impaired vision, and time-consuming treatment practices, leading to significant productivity loss costs, especially in middle-aged patients (27). This is consistent with statements from a Danish clinical expert, who noted that the patients experience substantially impaired QOL due to their highly burdensome symptoms.

3.1.2 Selected patient population

TED is a complex condition that can be classified into different categories based on disease severity and activity status (active or inactive/chronic). In terms of severity, TED patients are categorized as having mild, moderate to severe, or very severe (sight-threatening) disease, depending on the presence and extent of specific symptoms and signs. For this application, the relevant patient population comprises those diagnosed with moderate to severe active TED disease. In accordance with clinical classification systems, this population is characterized by active orbital inflammation, typically defined by a clinical activity score (CAS) of 3 or higher. In addition, patients must exhibit a clinically relevant disease burden, as evidenced by the presence of at least two objective features commonly associated with moderate to severe TED. These include lid retraction of 2 mm or more, moderate to severe soft-tissue involvement such as periorbital oedema or inflammation, proptosis of 3 mm or more above normal values adjusted for age and sex, and/or intermittent or constant diplopia (1).

Patients who present only mild symptoms, defined as limited clinical findings without functional impairment, or who have chronic disease, are not considered part of the eligible population. This definition serves to delineate a population with a clinically meaningful need for treatment (1). TED most commonly affects individuals between the ages of 40 and 65 years, and several studies have shown that the prevalence is at least three times higher among females (10, 28). According to a Danish clinical expert, patients of all ages are observed, however, the largest proportion of patients fall within the specified age range.

Incidence and prevalence

Estimating the incidence of moderate to severe TED in Denmark is challenging due to limited epidemiological evidence. A Danish study reported an incidence of 16.1 cases per million annually (26.7 among women and 5.4 among men), with stable trends between 1992 and 2009 (29). Applying this incidence to the Danish population as of May 2026 (6,031,008247 inhabitants) would give approximately 97 new cases per year (30). Further support comes from national and European data: a Danish study found an incidence of 1 case per million for GD, and European studies report that about 5% of GD patients develop moderate to severe TED, corresponding to roughly 96 new cases annually (31, 32). However, according to a Danish clinical expert a decline in TED incidences have been observed, suggesting an adjustment to 85 new cases per year.

While incidence can be approximated, the prevalence of moderate to severe TED is far more difficult to determine. Available data often reflects the total TED population, including patients in the chronic phase. Consequently, prevalence estimates will not represent the number of patients eligible for teprotumumab in this application. In the absence of phase-specific data, the prevalence estimates for moderate-to-severe TED, encompassing both active and chronic cases, will be used to inform the analysis. The most valid estimate available, based on a European study created in the United Kingdom (UK), suggests a prevalence of 30 cases per 100,000 people (33). Applying this to the Danish population in 2026, approximately 1,800 individuals have moderate to severe TED.

The estimation of the number of patients who will be eligible for treatment with teprotumumab over a five-year period is shown in Table 1. However, gradual implementation is expected, as clinical adoption requires familiarity with the product's use and alignment with existing care pathways and unit-level practices. Teprotumumab will not be considered an appropriate treatment option for all patients. Specifically, patients presenting with active orbital inflammation but without clinically significant proptosis or diplopia are not expected to be eligible candidates for treatment with teprotumumab. Treatment with teprotumumab will be subject to a thorough clinical assessment. The expected number of patients and patient uptake in year 1-5 (Table 1) is proposed by the Danish clinical expert and used in the budget impact analysis in Section 13.

Table 1. Expected number of patients and patient uptake of teprotumumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of patients	70	70	70	70	70
Patient uptake	*10 (14%)*	*20 (29%)*	*40 (57%)*	*60 (86%)*	70 (100%)

Source: Danish clinical expert
*The number of patients in Denmark eligible for the new treatment in accordance with the EMA indication, minus the number of patients who are not considered suitable for treatment (e.g., due to age or comorbidity), and minus those who are expected to decline treatment.
**Patient uptake is defined relative to the expected number of eligible patients.

3.1.2.1 Current treatment options

Currently, the Danish treatment guidelines available follow the European group on GO (EUGOGO) recommendations (1, 34); however, according to the Danish clinical expert, an update is pending in 2026 awaiting introduction of new treatment(s).

No treatments in Denmark are currently regulatory approved for TED. Treatment for patients with TED aims for disease inactivation, reduction of soft tissue involvement and proptosis, and the improvement of diplopia and eye motility (35). Additional aims include improving visual ability, providing relief from eye symptoms, and enhancing patients' QoL, as studies suggest that TED can negatively impact vision, work productivity, psychological and physical burden of pain and disfigurement (13, 36, 37).

Management of active moderate to severe TED primarily relies on high-dose intravenous methylprednisolone (IVMP) (1, 38). IVMP has anti-inflammatory effects and may lead to symptomatic relief, including superficial soft tissue swelling, visual acuity, and ocular motility associated with inflammation (39, 40). Although IVMP can reduce inflammatory activity, it has limited effect on proptosis and diplopia in patients with active moderate to severe TED, which are among the most burdensome symptoms. This reflects the key limitations of current treatment options. As a result of IVMP not addressing proptosis and diplopia, several patients require subsequent treatment and/or surgeries once the disease enters its chronic phase (1, 41). Furthermore, IVMP is associated with high rates of adverse reactions, playing a major role in patients (42, 43) . Alternative treatments, such as off-label use of biologics including rituximab and tocilizumab, have been used in Denmark in cases of IVMP resistance or limited treatment response (44, 45). The number of patients receiving rituximab and tocilizumab is limited; however, the exact number remains unknown. While tocilizumab has been found to improve inflammation in a randomized, placebo-controlled trial conducted in glucocorticoid resistant patients, the data showed minimal effect on proptosis and diplopia, especially in the off-treatment period (46).

Retrobulbar radiation which has a synergistic effect with steroids and may be more effective for muscle thickening can be considered as a supplementary “one off” treatment for selected patients with active moderate to severe TED, as supported by evidence and confirmed by the consulted Danish clinical expert (47). Retrobulbar radiation is not used based on defined criteria, but rather on the physician’s judgement and the patient’s own preference. Thus, the exact number of patients receiving therapy is unclear. According to a Danish clinical expert, this treatment can be particularly burdensome for patients, as it is only available at oncology departments at university hospitals in Denmark and requires attendance on ten consecutive weekdays where treatments are delivered over 2-3 minutes each. Patients must therefore visit the hospital daily (Monday to Friday) for two weeks to receive treatment. Nevertheless, retrobulbar radiation therapy has shown a certain degree of efficacy in some patients - typically after 2-3 months. However, the current treatment options do not target the root cause of the disease, provide only symptom relief with only minor changes in proptosis and diplopia, and can be associated with numerous adverse events (AEs) such as cataract, erythema, and significant tearing and oedema (48, 49).

Neither steroids nor radiotherapy have a strong effect on diplopia, and both may lead to fibrosis.

Collectively, current treatment options fail to target the underlying pathogenic mechanism of TED. Because of suboptimal medical control, a considerable proportion of patients progress to the chronic phase of TED with residual deformities and functional impairments. In the chronic phase, patients may become eligible for rehabilitative surgical interventions. Typically, this occurs approximately 18 to 24 months after disease onset. This was validated by a Danish clinical expert. Surgical procedures are tailored to address persistent functional and aesthetic sequelae that are not adequately managed by medical therapy alone (50, 51). Orbital decompression surgery, strabismus surgery, and eyelid surgery may be indicated in cases of vision-threatening compressive optic

neuropathy refractory to medical treatment, severe exposure keratopathy unresponsive to local supportive measures, disfiguring proptosis, or chronic orbital pain and congestion. The aim of orbital decompression surgery is to reduce proptosis and relieve optic nerve compression by removing bone and/or fat from the orbit to create more space. Strabismus surgery is performed to realign the eyes and reduce double vision by adjusting the position of extraocular muscles. Lastly, eyelid surgery is intended to correct eyelid retraction or exposure by restoring eyelid position and function, thereby protecting the eye and improving comfort. Generally, the aim is to improve patients' QOL. Importantly, rehabilitative surgery addresses the consequences of TED but does not modify the underlying disease.

The current treatment paradigm, centered around transient medical management followed by extensive surgical rehabilitation, places a substantial physical, psychological, and logistical burden on patients. This highlights an urgent unmet need for effective, approved therapies that can achieve early and sustained control of both inflammatory activity and functional impairments, thereby reducing the need for complex surgical interventions and improving long-term QOL.

3.2 Intervention

Table 2: Overview of teprotumumab (intervention)

Therapeutic indication relevant to the assessment	Tepezza is indicated for the treatment of moderate to severe TED in adults. This application focuses on patients with active disease.
Generic name	Teprotumumab
ATC code	L04AG13
Mechanism of action	Teprotumumab binds to IGF-1R and blocks its activation and signaling.
Route of administration	Intravenous (IV) infusion
Packaging type, pack sizes, shelf life, and strengths	One vial of 500 mg powder for concentrate for solution for infusion. Shelf life is three years.
Package size(s)	Single-dose vial with 500 mg teprotumumab.
If vials: Can these be shared?	Yes
Pre-medication: Is premedication required? If yes, specify which	No

Co-administration: Is the drug to be administered with other drugs? If yes, specify which	No
Need for diagnostics, monitoring, or other tests (e.g., companion diagnostics)	No difference between intervention and comparator

Table 3. The intervention in the clinical study and in the health economic model

	Clinical study	Health economic model
Dosage and frequency **[if weight-based, specify body weight in parenthesis and any criteria for switching to a flat dose]**	Initial dose: 10 mg/kg for 1st IV infusion. Following dose: 20 mg/kg 1 every 3 weeks for 7 additional IV infusions.	IV infusion of 10 mg/kg for the initial dose followed by an IV infusion of 20 mg/kg Q3W for 7 additional infusions. (assumed body weight: 74.67 kg, based on mean baseline weight in the clinical trial).
Average dose	18.75 mg/kg 1.463 mg per infusion (mean body weight: 78.07 kg)	18.75 mg/kg 1.400 mg per infusion (mean body weight: 74.67 kg)
Criteria for treatment discontinuation	Adverse events Patient withdrawal Investigator decision There were no effect-based stopping criteria, and treatment was planned as a fixed course of 8 infusions.	Treatment discontinuation for teprotumumab er sourced from pooled Phase II + OPTIC
Treatment duration	24 weeks (5,5 months)	22,5 weeks (5.20 months)
Dose adjustment: Specify whether/how dose adjustments are applied	NA	NA
Treatment interruption: Specify whether/how treatment interruptions (pause) are applied*	NA	NA

Dose distribution Phase 2 teprotumumab

The study drug (teprotumumab or placebo) was administered q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. All subjects were started at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and remained there for the rest of the study (7).

Dose distribution OPTIC Phase 3 teprotumumab

Extent of exposure to study drug in the Double-Masked Treatment Period is summarized by treatment group in Table 4. The majority of the subjects in both the placebo and teprotumumab groups received all 8 infusions of study drug (95.2% and 92.7%, respectively).

Table 4: Duration of Exposure in Double-Masked Treatment Period (Safety Population)

Duration of exposure	Placebo (N=42)	Teprotumumab (N=41)
Number of doses administered		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min,max	[redacted]	[redacted]
Number of doses administered, n (%)		
1 dose	[redacted]	[redacted]
2 doses	[redacted]	[redacted]
3 doses	[redacted]	[redacted]
4 doses	[redacted]	[redacted]
5 doses	[redacted]	[redacted]
6 doses	[redacted]	[redacted]
7 doses	[redacted]	[redacted]
8 doses	[redacted]	[redacted]
Number of days on drug		
Mean (SD)	[redacted]	[redacted]

Median	[redacted]	[redacted]
Min,max	[redacted]	[redacted]
Number of days on study (double-masked treatment period)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min,max	[redacted]	[redacted]
Subjects with any doses not completely administered, n (%)	[redacted]	[redacted]
Subjects with any infusion interruptions, n (%)	[redacted]	[redacted]

SD = standard deviation

Source: Clinical study report, OPTIC phase 3 (27)

3.2.1 The Intervention in the Context of Danish clinical practice

In Danish clinical practice, teprotumumab is expected to be used in patients with active moderate to severe TED. In that respect, teprotumumab will be reflected as a first line (1L) treatment and will replace the use of steroids, particularly IVMP. This was validated by the Danish clinical expert consulted. No new diagnostic tests or methods are required.

3.2.2 Advanced Therapy Medical Products

Not applicable (N/A)

3.3 Choice of Comparator

IVMP has been chosen as the comparator for this application concerning patients with active moderate to severe TED. This choice is based on statements from a Danish clinical expert as well as clinical treatment guidelines in Denmark, both confirming that IVMP is the standard treatment for active moderate to severe TED in Denmark.

Dose distribution overview N/A. Data on IVMP is pooled from seven different studies. A fixed dose is used in the health economic analysis, aligned with Danish clinical practice.

Table 5. Overview of IVMP (comparator)

Overview	
Therapeutic indication relevant to the assessment	IVMP is not regulatory approved for TED (off-label use)
Generic name	Methylprednisolone
ATC code	H02AB04
Mechanism of action	Methylprednisolone is a synthetic glucocorticoid that exerts anti-inflammatory and immunosuppressive effects by binding to glucocorticoid receptors, leading to transcriptional regulation of anti-inflammatory proteins and inhibition of pro-inflammatory cytokine expression.
Route of administration	IV infusion.
Packaging type, pack sizes, shelf life, and strengths	Vials + ampules 40 mg: 10 sets 125 mg: 1 set 500 mg: 1 set 1 g: 1 set
Package size(s)	IV methylprednisolone is available in the following package sizes: 40 mg, 125 mg, 500 mg, and 1 g vials. For example, Solu-Medrol® is available as 500 mg and 1 g vials.
If vials: Can these be shared?	No
Pre-medication: Is premedication required? If yes, specify which	No
Co-administration: Is the drug to be administered with other drugs? If yes, specify which	No
Need for diagnostics, monitoring, or other tests (e.g., *companion diagnostics*)	No

Table 6. Comparator in the clinical study and in the health economic model

	Clinical study	Health economic model
Dosage and frequency **[if weight-based, specify body weight in parenthesis and any criteria for switching to a flat dose]**	500 mg for the first 6 infusion. Once a week. 250 mg for the next 6 infusion. Once a week.	500 mg for the first 6 infusion. Once a week. 250 mg for the next 6 infusion. Once a week.
Average dose	4.5 g	4.5 g
Criteria for treatment discontinuation	The criteria for discontinuation include either achievement of therapeutic goals or development of AEs requiring cessation.	Discontinuation rates were sourced from Kahaly et al. (2018) (52)
Treatment duration	12 weeks (2,75 months)	11,9 weeks (2.74 months)
Dose adjustment: Specify whether/how dose adjustments are applied	NA	NA
Treatment interruption (pause): Specify whether/how treatment interruptions are applied	NA	NA

3.4 Subsequent Treatment

No subsequent treatments were given in the clinical trials Phase 2 and OPTIC phase 3 (7, 8). However, in clinical practice, some patients may receive subsequent treatment. Therefore, the model considers a course of 2L treatment for a proportion of non-responders, following EUGOGO guidelines (1). Only the cost of subsequent treatment is included in the model, applied to 100% of patients in the four most severe health states (excludes 'Small proptosis, no diplopia', and 'Small proptosis, intermittent/inconstant diplopia'). Hence, all patients who are not in the 'Small proptosis, no diplopia' (SP, ND) or 'Small proptosis, intermittent/inconstant diplopia' (SP, ID) health states at the time they finish their 1L treatment will receive 2L treatment. The cost of subsequent treatment is applied as a one-off cost in the cycle after patients complete their 1L treatment (cycle 5 for teprotumumab and cycle 3 for IVMP). In addition, subsequent treatment costs are also applied for any patients that discontinue their initial 1L treatment course before completion, or to any patients that flare, applied as a one-off cost in the cycle at which they discontinue or flare; this applies for patients in any health state. A relative dose

intensity (RDI) of 100% is assumed for tocilizumab, rituximab, and mycophenolate mofentli (MMF), while 98.21% is used for IVMP, as expected for the 1L treatment described in section 11.1. No waste was assumed for rituximab, IVMP, and MMF, as the dose of these treatments all correspond to the packaged dosing. The method of rounding was used for calculating waste associated with tocilizumab treatment.

Table 7. Assumptions regarding subsequent treatment in the health economic analysis

	Teprotumumab %	IVMP %	Mean treatment duration (incl. source)	Dosage (dose, frequency and route of administration, incl. source)	Any assumptions regarding dose adjustments and treatment interruptions, incl. source)
Proportion of patients receiving a subsequent line of treatment	100% of patients in the four most severe health states		NA	NA	NA
Tocilizumab	0%	10%	NA	NA	NA
Rituximab	0%	10%	NA	NA	NA
IVMP	95%	55%	NA	NA	NA

3.5 Relevant Outcomes

3.5.1 Definition of Outcomes

To reflect the disease effect, both primary and secondary efficacy outcomes from the teprotumumab studies were considered. As the primary endpoints, a reduction in overall CAS ≥ 2 points and a reduction in proptosis ≥2 mm, were chosen. Secondary outcomes include reduction of proptosis, reduction of CAS, and subjective diplopia response rates. While surgery is considered a relevant treatment modality, no data on surgical outcomes was reported in the available clinical trials. Consequently, surgery is not included in the efficacy analysis presented below. All relevant efficacy outcome measures are presented in Table 8.

Table 8. Outcomes

Outcome	Follow-up time point*	Definition
Response/overall response rate - **Phase 2**** - **OPTIC Phase 3**	Week 24	A responder was defined as a subject with the following: A decrease in overall CAS ≥2 points and a reduction in proptosis ≥2 mm, and no deterioration of CAS in the Non-Study Eye (i.e., increase of CAS ≥2 points OR increase in proptosis ≥2 mm) at the 24-week evaluation.
Mean change from baseline in the GO-QOL overall score - **Phase 2** - **OPTIC Phase 3**	Week 24	A MMRM was fit to the individual change from baseline in QOL scores, incorporating the baseline health score, smoking status, treatment group, time, time by treatment, and time by baseline health score interaction.
Mean change from baseline in proptosis - **Phase 2** **OPTIC Phase 3**	Week 24	Analyses of the changes from baseline in proptosis values in the Study Eye were conducted using the same MMRM primary and sensitivity analyses as the QOL analyses, substituting the appropriate baseline assessments.
CAS **Phase 2**	Week 24	Analyses of the changes from baseline in CAS values in the Study Eye were conducted using the same MMRM primary and sensitivity analyses as the QOL analyses, substituting the appropriate baseline assessments.
Diplopia response rate **OPTIC Phase 3**	Week 24	Percentage of subjects with Baseline diplopia grade >0 in the study eye who had a reduction of ≥1 grade with no corresponding deterioration (≥1 grade worsening) in the fellow eye.

* Time point for data collection used in analysis (follow-up time for time-to-event measures).
The most severely affected eye was designated at Baseline by the investigator and referred to as the "Study Eye." While both eyes were assessed for efficacy, the Study Eye was used to assess the primary efficacy endpoint.
**Does not have a trial name, and is therefore referred to as phase 2.
Abbreviations: CAS, clinical activity score; GO-QOL, graves' ophthalmopathy quality of life questionnaire; MMRM, mixed model repeated measure; Q3W, every three weeks; QOL, quality of life; TED, thyroid eye disease.
Source: (7, 8)

3.5.2 Relevance and validity of Outcomes

Overall responder rate

The overall responder rate is a composite endpoint commonly used in clinical trials of TED. It can be defined in several manners; however, in the Phase 2 (no official trial name) and OPTIC Phase 3 trials, it is defined as the proportion of patients achieving both a ≥2 mm reduction in proptosis and a ≥1 grade improvement in diplopia (for those with baseline diplopia) or a reduction of 2 points or more in the CAS, with no corresponding deterioration in the fellow eye (7, 8). This composite measure reflects meaningful improvement in two of the often-reported clinical aspects of TED, proptosis and diplopia, while ensuring bilateral disease control. The endpoint has been recognized by regulatory authorities as clinically meaningful. While the individual components (proptosis and diplopia responder rates) have established clinical and measurement validity, the composite outcome has not undergone formal psychometric validation. However, it is supported by international consensus, and its consistent use across TED trials is a robust indicator of multidimensional clinical response.

Clinical Activity Score

The CAS is a seven-point scale used to assess the inflammatory activity of TED. It includes signs such as spontaneous retrobulbar pain, pain during eye movement, eyelid erythema, conjunctival redness, chemosis, eyelid swelling, and caruncle inflammation. Each present item contributes one point to the total score (0–7), with a higher score indicating greater inflammatory activity. A CAS ≥3 is commonly used as a threshold to define active disease in both clinical trials and routine clinical practice (1). CAS has been widely used in TED studies, including those supporting regulatory approval of teprotumumab, and is recommended by the EUGOGO guidelines (1). The scale has demonstrated face validity, clinical relevance, and sensitivity to change, and remains one of the most established tools for monitoring disease activity in TED and is considered appropriate for both clinical and regulatory use (17, 53).

Proptosis responder rate

The proptosis responder rate is a patient-related outcome, often defined as the proportion of patients achieving a ≥2 mm reduction in proptosis from baseline, typically measured using a Hertel exophthalmometer. This measure is objective, reproducible, and has been widely adopted in clinical trials investigating treatments for TED. A reduction of ≥2 mm is generally considered to exceed the measurement error associated with exophthalmometry and is regarded as a clinically meaningful improvement by both clinicians and regulatory bodies (1). The validity of this outcome has been acknowledged in assessments by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) (54). Its use in multiple randomized controlled trials (RCTs) supports its validity and international acceptance as a core efficacy endpoint in TED (52, 55, 56).

Diplopia responder rate

The diplopia responder rate is a patient-related outcome relevant to indicate improvement in double vision (57). It can be defined as the proportion of patients who demonstrate at least a one-grade improvement on the Gorman Subjective Diplopia Scale. This scale categorizes diplopia into four levels: 0 (no diplopia), 1 (intermittent), 2

(inconstant), and 3 (constant). Although the Gorman scale has not undergone formal psychometric validation, it has been consistently used in clinical trials for TED. An improvement of at least one grade is generally considered clinically meaningful (7). The Gorman scale captures patient-perceived improvement in visual function and is thus a relevant and pragmatic instrument for evaluating therapeutic effects on diplopia in TED.

4. Health Economic Analysis

4.1 Reference-case Assumptions

Table 9. Reference-case assumptions in the health economic analysis

	Assumption	Justification
Patient population	Adult patients ≥18 years with active moderate to severe TED.	According to the patient population relevant for the application.
Intervention	Teprotumumab IV infusion of 10 mg/kg for the initial dose followed by an IV infusion of 20 mg/kg Q3W for 7 additional infusions. RDI: 98.21% (pooled data from Phase 2 and OPTIC Phase 3 trials)	Dose as per SmPC (58)
Comparator(s)	IVMP IV infusion of 500 mg weekly for 6 weeks, followed by IV infusion of 250 mg weekly for 6 weeks, based on EUGOGO guidelines. RDI: 98.21% (assumed same as teprotumumab)	According to national treatment guidelines (1). The choice of comparator was validated by Danish clinical expert.
Clinical outcomes	Degree of proptosis and diplopia	Proptosis and diplopia are two of the key patient-relevant symptoms of moderate to severe TED that impact the daily life of patients and their QoL.
Type of analysis	Cost-utility analysis	To assess the cost per QALY of treating patients with active moderate to severe TED with

	Assumption	Justification
		teprotumumab compared to IVMP in 1L.
Type of model	Cohort-based Markov model	Most relevant for TED as it appropriately mapped the clinical pathway of care while presenting a simple and transparent structure
Mean age at model entry	51.58 years	Based on the pooled data.
Time horizon	48.42 years corresponding to lifetime (until patients reach 100 years).	A lifetime time horizon was included to capture all health benefits and costs in line with DMC guidelines. As per initiation of the model, the patients are at age 51.58 years, based on the pooled data; hence the time horizon is 48.42 years
Cycle length	6 weeks	A cycle length of 6 weeks was used in the model to align with the timepoint treatment efficacy data collected in the trials and to make use of the individual patient-level data available.
Half-cycle correction	Yes	Applied to ensure accurate timing of transitions, costs, and outcomes in a model with relatively long cycles.

4.2 Model Type and Model Structure

Table 10. Choice of health economic analysis, model, and model structure

Type of health economic analysis	Type of model	Model structure	Assumptions
Cost-utility analysis	Cohort-based Markov model	**6 active disease-health states**: - 1) SP, ND; 2) LP, ND; 3) SP, ID; 4) LP, ID; 5) SP, CD; 6) LP, CD	NA

Type of health economic analysis	Type of model	Model structure	Assumptions
		1 tunnel health state for surgery - **1 health state for post-surgery** - **1 absorbing health state for death**	

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

A cohort-based Markov model was developed to estimate the costs and QALYs of patients treated with teprotumumab or IVMP over a lifetime horizon. The Markov model was deemed most relevant for TED as it appropriately maps the clinical pathway of care while presenting a simple and transparent structure. The model accounts for disease progression, surgery, post-surgery, and long-term QoL.

The model comprised six health states for active disease, one tunnel health state for surgery, one health state for post-surgery disease, and one absorbing health state for death, see Figure 1.

The six health states for active disease were defined by levels of proptosis and diplopia to indicate the severity of the patients' conditions. Proptosis and diplopia are essential symptoms of moderate to severe TED that affect patients' daily lives and QoL (59). Additionally, proptosis and diplopia scores were considered appropriate endpoints for defining health states due to their direct measurement of patient symptoms, unlike CAS, which measures inflammation extent and may not correlate with patient symptoms and health-related quality of life (HRQoL) burden, particularly after the initial few years following diagnosis when inflammation decreases. This assumption was validated by the Danish clinical expert consulted for this application.

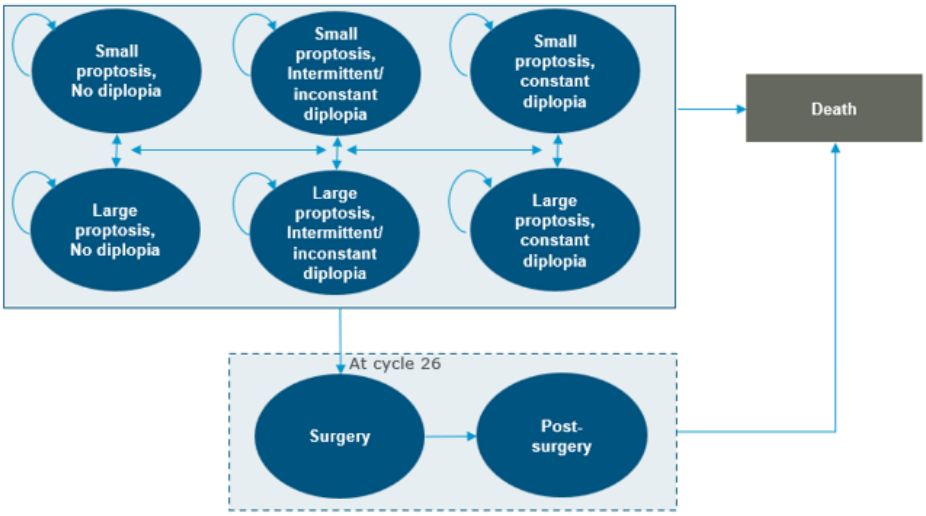


Figure 1: Model structure

Note: Surgery is applied from cycle 14 and not 26

The proptosis health state definitions used in the model are based on the numerical equivalent of significant proptosis referenced in the American Thyroid Association (ATA)/ European Thyroid Association (ETA) guidelines, with small proptosis defined as <3 mm above the upper limit of normal for a non-TED patient of the same race and sex, and large proptosis defined as ≥3 mm (35). Diplopia response is defined based on the diplopia response rate as described in section 3.5.2 utilizing the Gorman subjective diplopia score. Intermittent and inconstant diplopia were combined when defining the health states to reduce the number of health states used in the cost-effectiveness model (CEM). This approach helps address the uncertainty in generating transition probabilities from the relatively small sample size of the pooled teprotumumab Phase 2 and OPTIC Phase 3 data (27).

Table 11: Health states with descriptions

Health State	Description
Small proptosis, No diplopia (SP, NP)	Proptosis <3 mm above the upper limit of normal No double vision in any gaze position.
Large proptosis, No diplopia (LP, NP)	Proptosis ≥3 mm above the upper limit of normal No double vision in any gaze position.
Small proptosis, Intermittent/Inconstant diplopia (SP, NP)	Proptosis <3 mm above the upper limit of normal Double vision intermittently or only in certain gaze positions, not constantly in primary gaze.
Large proptosis, Intermittent/Inconstant diplopia (LP, NP)	Proptosis ≥3 mm above the upper limit of normal

	Double vision intermittently or only in certain gaze positions, not constantly in primary gaze.
Small proptosis, Constant diplopia (SP, NP)	Proptosis <3 mm above the upper limit of normal Persistent double vision in primary gaze and most or all gaze positions, causing continuous visual impairment.
Large proptosis, Constant diplopia (LP, NP)	Proptosis ≥3 mm above the upper limit of normal Persistent double vision in primary gaze and most or all gaze positions, causing continuous visual impairment.

Patient flow

Patients enter the model within one of the six mutually exclusive health states, with the distribution being sourced from the pooled Phase 2 and OPTIC Phase 3 data, as described in section 9. For the initial 24 weeks, to capture the active stage of TED, patients transition between health states: 'Small Proptosis, No Diplopia', 'Large Proptosis, No Diplopia', 'Small Proptosis, Intermittent/Inconstant Diplopia', 'Large Proptosis, Intermittent/Inconstant Diplopia', 'Small Proptosis, Constant Diplopia', and 'Large Proptosis, Constant Diplopia', with an absorbing state for death. During the initial period of treatment lasting 24 or 12 weeks for the teprotumumab and IVMP treatment arms respectively, patients can discontinue treatment.

Patients can either transition between health states or remain in their current state at any cycle. Following the active phase, patients enter the chronic phase, during which patients are eligible for surgery. Surgery is included in the model as a tunnel state, serving as a bridge between the six health states and post-surgery, where all patients transition to, after undergoing surgery. Here they stay for the remainder of the model time horizon.

Surgery included in the model

TED typically progresses through phases, initially the active phase with inflammation, followed by a static non-inflammatory phase reflecting the chronic phase (1). The model reflects a six-week cycle length to align with the timepoint treatment efficacy data collected in the trials. As this model reflects a lifetime horizon, to be able to represent the underlying disease change from active to chronic disease phase, surgery is included. Surgery is only given to patients when they are in the chronic and thus stable disease phase. Surgery is included in the model as a tunnel state that a proportion of patients transition to after 14 cycles, approximately corresponding to 1.5 years. As no evidence was available to inform time spent and number of surgeries for the surgery state, inputs were sourced from an interview with the Danish clinical expert consulted for this application.

The proportion of patients transitioning from the six disease stages to the surgery state was based on input from UK clinicians and validated by the Danish clinical expert (27). Some patients receive multiple surgeries over a lifetime, this is reflected by the model as the patients remain in the surgery state for 30 cycles, reflecting a period of approximately 3.5 years to complete all surgeries.

Patients with TED can receive different surgeries, of which three are considered of relevance: orbital decompression surgery, strabismus surgery, and eyelid surgery. This was validated by the Danish clinical expert. These surgeries are indicated in relevant guidelines as the most common types of surgeries as well (1). For the sake of simplicity, a standard average number of surgeries in total and an expected distribution of the three surgeries is utilized for all patients entering the surgery state (see section 11.2.5).

Disease flares in the model

Following initial treatment, it has been observed that a small percentage of patients' experience 'flare', i.e. a worsening of TED symptoms such as proptosis or diplopia after an initial response to treatment. Therefore, disease flares are included in the base case. For proptosis, flare is modelled as a transition from small to large proptosis. For diplopia, flare is modelled as a one-step worsening: 'No Diplopia' to 'Intermittent/Inconstant Diplopia', or 'Intermittent/Inconstant Diplopia' to 'Constant Diplopia'. Flare is implemented in the model through flare transition matrices which determine patient movement to more severe health states. Different rates of disease flare were observed for proptosis and diplopia in the Phase 2 and OPTIC Phase 3 trials based on the individual patient data (IPD); therefore, separate flare transition probability matrices were developed for each outcome.

Flare proportions were sourced from Phase 2 and OPTIC Phase 3 IPD for teprotumumab, and the published literature for IVMP (7, 8). The time point at which the flare proportions were obtained for each treatment were converted from weeks to model cycles to determine which cycles flare is applied in. For example, if treatment duration is 24 weeks and flare proportions are calculated 12 weeks after treatment completion, this would be applied from the cycle immediately after the first course of treatment is finished (cycle 5 in this example) for two 6-week cycles (ending at cycle 6, in this example, as the duration is inclusive of the start cycle).

The following steps outline the implementation of flare in the model:

1. The proportions of proptosis and diplopia flare observed from the data sources (as described above) were converted to a per-cycle constant probability of worsening for each outcome, assuming a linear increase in the overall proportion of flared patients between the start and end cycles.

2. The per-cycle flare probability for proptosis and diplopia was applied to the relevant transitions in separate proptosis and diplopia transition matrices. Proptosis transition matrices for each treatment demonstrate the per-cycle probability of transitioning from 'Small Proptosis' to 'Large Proptosis', defined as proptosis flare. Similarly, diplopia transition matrices for each treatment

demonstrate the per-cycle probability of transitioning from 'No Diplopia' to 'Intermittent/Inconstant Diplopia' or 'Intermittent/ Inconstant Diplopia' to 'Constant Diplopia', defined as diplopia flare. The same probability of transition is applied to both the 'No Diplopia' to 'Intermittent/ Inconstant Diplopia' transition and 'Intermittent/ Inconstant Diplopia' to 'Constant Diplopia' transition in the diplopia matrix.

3. The separate proptosis and diplopia flare transition matrices were then combined into one composite transition matrix, that accounts for different levels of outcome deterioration. This composite transition probability matrix was created by multiplying together each pair of transitions, assuming independence of endpoints, to show proportions of patients who experience flare across all six health states.

4. Probabilities were set to zero for all transitions where flare is not possible within the definitions, i.e. improving health state or remaining in the same health state.

It is assumed that flares can only occur after the completion of the initial treatment course as any flare before this point is captured in the transition probability matrices applied whilst patients are on treatment. For cycles where flares are enabled, the flare matrix is applied each cycle to transition patients to worse health states based on the observed flare proportions. Flare proportions, as well as the start and end cycles for each comparator, are user-editable in the model. The start cycle must occur after completion of the initial treatment course, and the end cycle must be equal to or higher than the starting cycle. The duration of flare is inclusive of the start cycle, so the same start and end cycles can be entered, which would reflect a flare duration of one cycle (6 weeks). After moving to a health state with worse diplopia or proptosis, patients who experienced flare receive the same long-term transitions as patients who do not flare.

Discontinuation in the model

The model accounts for treatment discontinuation to capture the number of patients that stop treatment each cycle. In each cycle, treatment-specific probability of discontinuation is applied to patients. Patients who discontinue treatment no longer have drug acquisition or treatment costs assigned to them. Once discontinued, patients remain on the cycle-specific transition probabilities of their initial treatment, meaning there are no efficacy implications from discontinuing treatment, only cost implications. This is because all-cause discontinuation was used, so discontinuation reasons are not limited to a lack of therapeutic benefit. Additionally, in clinical practice, these patients would go on to receive second-line (2L) therapy; however, no published data was available that could be used to inform 2L transition probabilities. Discontinued patients are still eligible for surgery in the cycle where surgery is applied.

5. Literature Review

5.1 Literature Used to Assess Clinical Effectiveness and Safety

A comprehensive global clinical systematic literature review (SLR) was conducted on June 9, 2023, to identify the efficacy and safety of teprotumumab and other treatments associated with TED, with an SLR update conducted on September 11, 2024 and December 17, 2025. Database searches via the Ovid search platform were conducted in the following electronic databases: EMBASE, MEDLINE, MEDLINE In-Process, and the Cochrane database of systematic reviews (CDSR) for full-text publications and conference abstracts. Additionally, the Database of Abstract of Reviews of Effects (DARE) and the Cochrane Central Register of Controlled Trial (CENTRAL) were searched. For detailed information on the SLR, Appendix H.

A total of 71 unique studies met the inclusion criteria and were included. Among these, seven studies reported data for teprotumumab. All were conducted by the same research group and represent a progression from single-arm trials to increasing phases of RCT.

Among these, teprotumumab was included in two RCTs, including the teprotumumab Phase 2 and OPTIC Phase 3. These two studies are both included in the present application.

54 studies were found for other relevant treatments; however, as this application only focuses on IVMP and reflects specific outcomes of interest, a further selection of studies was performed. Eight studies on IVMP, following the inclusion and exclusion criteria were included in the analysis. All included studies are presented in Table 12. A more detailed description of the inclusion and exclusion of studies can be found in Appendix H.

Table 12: Relevant literature included in the assessment of effectiveness and safety

Reference	Study name	NCT number	Study (Start and expected end date, data cut-off, and expected data cut-offs)	Used for comparison of
Smith TJ, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017 May 4;376(18):1748-1761.	No trial name, but denoted 'Phase 2' in this submission dossier	NCT01868997	Start: 01/07/2013 Completion (study): 22/02/2017	Teprotumumab vs. placebo in the treatment of subjects with active moderate to severe TED

Reference	Study name	NCT number	Study (Start and expected end date, data cut-off, and expected data cut-offs)	Used for comparison of
			Data cut-off: 01/03/2016	
Douglas RS, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020 Jan 23;382(4):341-352.	OPTIC Phase 3	NCT03298867	Start: 04/10/2017 Completion (study): 30/11/2020 Data cut-off: 13/02/2019	
Bartalena L, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012 Dec;97(12):4454-63.	N/A	N/A	N/A	Three different cumulative doses of IVMP (2.25 g vs. 4.98 g vs. 7.47 g) for patients with active moderate to severe TED
Aktaran S, et al. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. Int J Clin Pract. 2007 Jan;61(1):45-51.	N/A	N/A	N/A	IVMP vs. oral methylprednisolone in patients with active, moderately severe TED
He Y, et al. Comparison of two different regimens of intravenous methylprednisolone for patients with moderate to severe and active Graves' ophthalmopathy: a prospective, randomized controlled trial. Endocr J. 2017 Feb 27;64(2):141-149.	N/A	ChiCTR-IPR-15006848	Start: 01/03/2011 Completion (study): 30/06/2012 Data cut-off: N/A	IVMP (MR) vs. IVMP (WR) in patients with active moderate to severe TED

Reference	Study name	NCT number	Study (Start and expected end date, data cut-off, and expected data cut-offs)	Used for comparison of
Zhu W, et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with Graves' ophthalmopathy. J Clin Endocrinol Metab. 2014 Jun;99(6):1999–2007.	N/A	NCT01969019	Start: 01/10/2010 Completion (study): 21/10/2013 Data cut-off: N/A	IVMP (WR) vs. IVMP (daily regimen) in patients with active moderate to severe TED
Kahaly GJ, et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005 Sep;90(9):5234-40.	N/A	N/A	N/A	IVMP vs. oral methylprednisolone in patients with active, moderately severe TED
Kahaly GJ, et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018;6(4):287–98.	MINGO	EudraCT number: 2008-002123-93	Start: 30/07/2009 Completion (study): 10/15/2017 Data cut-off: 12/10/2015	IVMP vs. IVMP + MMF in patients with active moderate to severe TED
Shen L, et al. Methotrexate plus reduced or full-dose glucocorticoids for the treatment of active, moderate-to-severe Graves' orbitopathy. Eur Thyroid J. 2022;11(5):e220017.	N/A	ChiCTR1800015912	Start: 30/04/2018 Completion (study): 31/12/2018 Data cut-off: N/A	IVMP vs. IVMP + MTX vs. Reduced IVMP + MTX in patients with active moderate to severe TED
Mu PW, et al. Comparison of two regimens for patients with thyroid-associated ophthalmopathy receiving intravenous methyl prednisolone: A single center prospective	N/A	N/A	N/A	IVMP (WR) vs. IVMP (daily regimen) in patients with active moderate to severe TED

Reference	Study name	NCT number	Study (Start and expected end date, data cut-off, and expected data cut-offs)	Used for comparison of
randomized trial. Exp Ther Med. 2020;20(3):153.				

Abbreviations: ChiCTR, chinese clinical trial register; EudraCT, european union drug regulating authorities clinical trials database; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MR, monthly regimen; MTX, methotrexate; N/A, not applicable; NCT, national clinical trial; TED, thyroid eye disease; WR, weekly regimen.

5.2 Literature Used to Assess Health-Related Quality of Life

No head-to-head study was available for teprotumumab compared to IVMP for patients with active moderate to severe TED. Thus, a comprehensive global SLR for HRQoL/utilities was conducted on June 9, 2023, to identify the HRQoL, patient-reported outcomes (PROs), and utilities relevant for patients with TED, with an SLR update conducted on October 3, 2024 and December 17, 2025. Database searches via the Ovid search platform were conducted in the following electronic databases: EMBASE, MEDLINE, MEDLINE In-Process, and CDSR for full-text publications and conference abstracts. Additionally, DARE, CENTRAL, the HTA database, the National Health Service (NHS), Economic Evaluation Database (EED) and Economics Literature (EconLit) databases were searched. For detailed information on the HRQoL/utilities SLR, see Appendix I.

A total of 124 unique studies reporting humanistic burden or utility values were found through the SLR for HRQoL/utilities and the clinical SLR. Of these only two studies examined utilities, with only one of these studies reporting utilities across six health states using time trade-off (TTO) and visual analog scale (VAS), corresponding to the model structure utilized in this application, see Table 13. None of the identified studies reported EuroQoL 5-dimension (EQ-5D) evidence.

An ad-hoc grey literature search was conducted to identify studies including disutilities for IV administration and AEs. All studies identified and utilized for disutilities from this search are presented in Appendix F.

Table 13. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in section
Smith TJ, et al. Utility Assessment of Moderate to Severe Thyroid Eye Disease Health States. JAMA Ophthalmol. 2023 Feb 1;141(2):159-166. doi: 10.1001/jamaophthalmol.2022.3225. Erratum in: JAMA Ophthalmol. 2023 Feb 1;141(2):213. (59)	TTO. Health states: SP, ND LP, ND SP, ID LP, ID SP, CD LP, CD	Systematic literature search (SLR)	10.3

5.3 Literature Used as Input in the Health Economic Model

A comprehensive global economic/Healthcare resource utilization (HCRU) SLR was conducted on May 22, 2023, to identify evidence on the cost burden and HCRU associated with active moderate to severe TED, and any economic evaluations of relevant comparators in TED, with an SLR update conducted on October 3, 2024 and December 17, 2025. Database searches via the Ovid search platform were conducted in the following electronic databases: EMBASE, MEDLINE, and MEDLINE In-Process for full-text publications and conference abstracts. Additionally, the HTA database, the NHS, EED, and EconLit databases were searched. A total of 20 studies met the inclusion criteria and were included. Among these, only ten studies reported data on moderate to severe TED. None of the 20 identified studies were included due to local adaptations. For detailed information on the SLR and inclusion evaluation, see Appendix J. Additionally, model inputs/estimates were sourced from the Phase 2 and OPTIC Phase 3 trials identified in the clinical SLR described in Section 5. Most healthcare utilization is based on assumptions made by either UK clinical experts, or the consulted Danish clinical expert, while most costs are based on the diagnosis related group (DRG) tariff system.

Table 14. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in section
N/A			

6. Clinical Studies

6.1 Teprotumumab Compared with IVMP in patients with active moderate to severe TED

For the comparison of teprotumumab and IVMP, several studies were utilized. As teprotumumab and IVMP were investigated in several trials and pooled data were obtained, all relevant trials are reported in Table 15. This includes two relevant studies for teprotumumab and eight relevant studies for IVMP.

Table 15. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Study design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
Phase 2 (7) NCT01868997	Global, randomized, double-masked, placebo-controlled, phase 2 multicenter trial	The study consisted of three phases: A screening phase of 4 weeks duration (± 2 weeks), a double-masked treatment phase of 6 months, and an off-treatment follow-up phase of 12 months	Patients with active moderate to severe TED	Teprotumumab: Q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. Starting treatment dose of 10 mg/kg, escalated to 20 mg/kg in week 3 and kept constant for the remainder of the study	Placebo (saline): Q3W by IV infusion over a period of 24 weeks for a total of 8 infusions	Primary outcome: Overall response: Reduction of 2 points or more in the CAS and a reduction of 2 mm or more in proptosis in the study eye in the absence of a corresponding amount of worsening in the non-study eye at week 24 Secondary outcomes: Average change of proptosis in the study eye from baseline to week 24. Average change of CAS from baseline to week 24. Average change in GO-QOL, including overall scores and two subscales measuring limitations in visual functioning and psychosocial functioning
OPTIC Phase 3 (8) NCT03298867	Global, phase III, multicenter, double-	The study consisted of three	Patients with active	Teprotumumab:	Placebo (saline):	Primary outcome:

	masked, randomized placebo-controlled trial	phases: A screening phase of 2 to 6 weeks, a double-masked treatment phase of 24 weeks, and an off-treatment follow-up phase of 48 weeks	moderate to severe TED	Q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. Starting treatment dose of 10 mg/kg, escalated to 20 mg/kg in week 3 and kept constant for the remainder of the study	Q3W by IV infusion over a period of 24 weeks for a total of 8 infusions. Starting treatment dose of 10 mg/kg, escalated to 20 mg/kg in week 3 and kept constant for the remainder of the study	Proptosis response: Percentage of participants who were proptosis responders defined as participants with a ≥2 mm reduction from baseline in proptosis in the study eye, without deterioration (≥2 mm increase) of proptosis in the fellow eye at week 24 Secondary outcomes: Percentage of participants who were overall responders, defined as participants with a ≥2 mm reduction in proptosis AND a ≥2 point reduction in CAS from baseline in the study eye, without deterioration (≥2 mm increase in proptosis or ≥2 point increase in CAS) in the fellow eye at week 24 Percentage of participants who were CAS categorical responders, defined as participants with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) in study eye at week 24 Change in proptosis in the study eye from baseline to week 24 Percentage of participants who were diplopia responders, defined as participants with baseline diplopia Subjective Diplopia Score grade > 0 in the study eye who had a reduction of ≥1 grade with no corresponding deterioration (≥1 grade worsening) in the fellow eye at week 24 Mean change in overall score on the GO-QOL
Bartalena et al. (2012) (56)	Randomized, double-blind, multicenter trial	All three intervention groups received infusions of	Patients with active moderate to severe TED	IVMP low dose: Cumulative dose of 2.25 g. Starting dose at 250 mg, maintained for the first six infusions	N/A	Primary outcomes: Overall ophthalmic change from baseline to week 12: Defined as follows: 1) Improvement, when at least two of the following outcome measures improved in one eye, without deterioration in any of these measures in either eye: i) reduction in palpebral aperture by at least 3 mm; ii) reduction in any of the class 2 signs

	IVMP for 12 weeks	and then halved to 125 mg for the remaining six infusions. IVMP middle dose: Cumulative dose of 4.98 g. Starting dose at 540 mg, maintained for the first six infusions and then halved to 290 mg for the remaining six infusions. IVMP high dose: Cumulative dose of 7.47 g. Starting dose at 830 mg, maintained for the first six infusions and then halved to 415 mg for the remaining six infusions	of NOSPECS by at least two grades; iii) reduction in exophthalmos by at least 2 mm; iv) improvement of >8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); v) improvement in CAS by at least 2 points. 2) Deterioration, when DON or two of the following occurred: i) increase in palpebral aperture by at least 3 mm; ii) increase in any of the class 2 signs of NOSPECS by at least two grades; iii) increase in exophthalmos by at least 2 mm; iv) deterioration of >8 degrees in motility or worsening of diplopia (appearance or change in the degree). 3) No change. When there were no changes or changes smaller than previously defined in any of the mentioned parameters Change in QoL from baseline to week 12: 1) Improvement, if there was an increase of 6 or more points on either one (or both) the GO-QOL scales (functioning and appearance). 2) Deterioration, if there was a decrease of 6 or more points on any one of the two scales. 3) No change, if there were no changes or changes smaller than previously defined in either scale. Secondary outcomes: Change of CAS from baseline to week 12 Change in palpebral aperture from baseline to week 12 Change in class 2 signs of NOSPECS from baseline to week 12 Change in proptosis (exophthalmos) from baseline to week 12 Change in subjective ocular motility from baseline to week 12 Change in subjective diplopia from baseline to week 12 Change in soft tissue signs from baseline to week 12

						Change in GO-QOL visual functioning subscale from baseline to week 12 Change in GO-QOL appearance subscale from baseline to week 1
Aktaran et al. (2007) (55)	Prospective, randomized, single-blinded clinical trial	The study consisted of two phases: A treatment phase of 6 weeks followed by a taper-week of 6 weeks.	Patients with active, moderate to severe TED	IVMP: Cumulative dose of 4.5 g. Starting dose at IV infusion of 500 mg methylprednisolone in 100 ml physiological saline once a week for a total of 6 weeks. This was followed by 6 weeks wherein the dose was tapered by 250 mg per week.	Oral methylprednisolone: Cumulative dose of 4 g. Administered in decreasing doses once a week for a total of 6 weeks; 72 mg for the first 2 weeks, 64 mg/day for 2 weeks, 56 mg/day for 2 weeks. This was followed by 6 weeks wherein the dose was tapered off by 8 mg per week.	Primary outcomes: • Overall treatment responders at 3 months, defined by patients showing an improvement in at least two major criteria (variations in proptosis and lid width of ≥ 2 mm; appearance, disappearance or changes in the degree of diplopia; changes in the CAS ≥ 2 points; and changes on one-tenth or more in visual acuity) and one minor criterion (soft tissue changes, self-assessment evaluation). • Change in CAS from baseline to 3 months. • Percentage of participants who were diplopia responders at 3 months. • Change in lid width fissure from baseline to 3 months. • Change in proptosis from baseline to 3 months. • Change in visual acuity from baseline to 3 months. • Change in intraocular pressure from baseline to 3 months. • Changes in extraocular muscle thickness from baseline and after 3 months. Secondary outcomes:

						• Change in GO-QOL visual functioning subscale from baseline to 3 months. • Change in GO-QOL appearance subscale from baseline to 3 months.
He et al. (2017) (60) [81] ChiCTR-IPR-15006848	Prospective, parallel-group, randomized-controlled trial	The study included two groups consisting of an MR and a WR of IVMP. Both regimen groups were followed for 12 weeks.	Patients with active moderate to severe TED	IVMP MR: Cumulative dose of 6.0 g. Administered as 0.5 g IVMP daily for three consecutive days every 4 weeks over a period of 12 weeks for a total of 12 infusions. IVMP WR: Cumulative dose of 4.5 g. Starting treatment dose of 0.5 IVMP weekly for 6 weeks, followed by a reduction to 0.25 g IVMP weekly for 6 weeks over a total period of 12 weeks for a total of 12 infusions.	N/A	Primary outcomes: Overall rate of response at week 12, defined as an overall improvement on the same eye by showing at least one major criterion or two minor criteria in any eye. The major criteria were as follows: 1) Improvement in diplopia by at least 1 grade according to the adapted NOSPECS classification 4. 2) Improvement of eye movement in any direction of 8° or more. 3) Improvement in CAS by at least 2 points. The minor criteria were as follows: 1) Reduction of proptosis by at least 2 mm. 2) Improvement in the grade of soft tissue involvement, according to the modified NOSPECS class 2. 3) Improvement in visual acuity by at least 1.0 Snellen line. 4) Decrease in CAS of 1 point. 5) Decrease in palpebral aperture by at least 2 mm. 6) Improvement in duction or diplopia failing to meet 1 grade. Secondary outcomes: • Change in CAS from baseline to week 12. • Change in diplopia from baseline to week 12. • Change in palpebral aperture from baseline to week 12. • Change in proptosis from baseline to week 12. • Change in ocular motility (eyeball duction) from baseline to week 12. • Change in visual acuity from baseline to week 12.

						• Change in intraocular pressure from baseline to week 12. • Percentage of participants with improved, deteriorated or unchanged above-mentioned ophthalmic measures from baseline to week 12. • Percentage of participants with mild, moderate and severe soft tissue involvement from baseline to week 12. • Percentage of participants with overall deteriorated or unchanged above-mentioned ophthalmic measures from baseline to week 12.
Zhu et al. (2014) NCT01969019 (61)	Prospective, randomized trial of two protocols of IVMP (daily or weekly) for a cumulative dose of 4.5 g.	Overall ophthalmic assessment was performed before therapy and in the fourth and 12th weeks after therapy.	Patients with active moderate to severe TED	Weekly IVMP: Starting treatment dose of 0.5 IVMP weekly for 6 weeks, followed by a reduction to 0.25 g IVMP weekly for 6 weeks over a total period of 12 weeks for a total of 12 infusions. Daily IVMP: Starting treatment dose of 0.5 IVMP daily for three consecutive days weekly for 2 weeks, followed by a reduction to 0.25 g	N/A	Primary outcome: • Overall response rate at week 4 and 12, defined by the following: “Responsive” was defined as at least three of the outcome measures: 1) reduction in lid width by at least 3 mm; 2) reduction in any of the class 2 NOSPECS signs by at least two grades; 3) reduction in proptosis by at least 2mm;4) reduction in intraocular pressure by at least 2 mmHg; 5) improvement in CAS by at least two points; 6) improvement in diplopia (disappearance or decrease in degree); and 7) improvement in visual acuity by 1 Snellen line. “Deterioration” of each parameter was defined as follows: 1) increase in lid width by at least 3 mm; 2) increase in any of the class 2 NOSPECS signs by at least two grades; 3) increase in proptosis by at least 2 mm; 4) increase in intraocular pressure by at least 2 mmHg; 5) increase in CAS by at least two points; 6) increase in diplopia (new onset or increase in degree); and 7) decrease in visual acuity by 1 Snellen line. “Unchanged” was defined as no change or changes

				IVMP daily for three consecutive days weekly for 2 weeks over a total period of 4 weeks for a total of 12 infusions. This was followed by tapering oral prednisone: Starting dose of 60 mg/day for one week, followed by a reduction of 10 mg less/week compared to the previous week for 3 weeks. This was followed by 20 mg/week for one week, followed by a reduction of 5 mg/less compared to the previous week for 3 weeks. The total period was 12 weeks.		smaller than previously defined in any of the mentioned parameters. Secondary outcomes: • Change in CAS from baseline to week 4 and week 12. • Retreatment-free survival after 6 months of therapy.
Kahaly et al. (2005) (62)	Prospective, randomized, single-blinded, and controlled trial	The study consisted of two phases: A treatment phase of 12	Patients with active, moderately severe TED	IVMP: Cumulative dose of 4.5 g.	Oral prednisolone: Cumulative dose of 4.0 g. Starting treatment dose of 0.1 g daily,	Primary outcome: • Overall response at week 12, defined as a relevant improvement of at least three clinically objective parameters including proptosis, lid fissure width, and rate of diplopia in primary gaze, intraocular pressure in

		weeks followed by a 6-month follow-up period		Starting treatment dose of 0.5 g IVMP weekly for 6 weeks, followed by a reduction to 0.25 g IVMP weekly for 6 weeks for a total period of 12 weeks and 12 infusions.	followed by tapering the dose by 0.01 g/week for a total period of 12 weeks.	up gaze, the sum of the ultrasonically measured rectus muscle thickness, and evaluation of QoL. Secondary outcome: • Change in CAS from baseline to week 12. • Change in proptosis from baseline to week 12. • Change in lid width from baseline to week 12. • Change in visual acuity from baseline to week 12. • Change in intraocular pressure from baseline to week 12. • Change in extraocular muscle thickness from baseline to week 12. • Number of participants who were diplopia responders at week 12. • Number of participants who were chemosis responders at week 12. • Change in QoL from baseline to week 12.
Kahaly et al. (2018) (52) MINGO trial EudraCT number: 2008-002123-93	Block-randomized, multicenter, observer-masked, center-stratified, open-label trial	The study conducted outcome assessment at week 12, 24, and 36.	Patients with active moderate to severe TED	IVMP: Cumulative dose of 4.5 g. Starting treatment dose of 500 mg IVMP weekly for 6 weeks, followed by a reduction to 250 mg IVMP weekly for 6 weeks for a total	IVMP + mycophenolate: Cumulative dose of 4.5 g and 120 g. Starting treatment dose of 500 mg IVMP weekly for 6 weeks, followed by a reduction to 250 mg IVMP weekly for	Primary outcomes: • Response rate at week 12: “Response” was defined as an improvement in the most affected eye, defined as a reduction of at least two measures of a composite index without simultaneous deterioration of any of the ophthalmic parameters of the index. Prespecified improvement of GO was defined as reduction of at least two measures in the composite index in at least one eye, without deterioration in any of the same measures in either eye. The composite index measures

				period of 12 weeks and 12 infusions.	6 weeks for a total period of 12 weeks and 12 infusions. Additionally, patients were administered with 360 mg mycophenolate orally twice per day for 24 weeks.	were as follows: 1) improvement of eyelid swelling in accordance with the EUGOGO color atlas, 2) improvement in CAS of at least 2 points, 3) improvement in proptosis of at least 2 mm, 4) improvement in lid width of at least 2 mm, 5) improvement in diplopia (disappearance or change in the degree), 6) and improvement of at least 8° in eye muscle motility. • Relapse rate at week 24 and week 36: Prespecified deterioration of GO (recurrence or relapse relative to baseline) was defined as change in two of the following outcome measures in at least one eye: 1) worsening of inflammatory eyelid swelling, 2) worsening of CAS of at least 2 points, 3) worsening of proptosis of more than 2 mm, 4) worsening of lid width of at least 2 mm, 5) worsening of diplopia, 6) deterioration of eye muscle motility, and 7) occurrence of dysthyroid optic neuropathy. Secondary outcomes: • Response rate at week 24. • Overall treatment response at week 24 and week 36, defined post-hoc as an improvement of ophthalmic symptoms and signs compared with baseline, without any deterioration of any ophthalmic findings.
Shen et al. (2022) (15) ChiCTR1800015912	Prospective, randomized, observer-masked, single center clinical trial	The study conducted outcome assessment at week 12	Patients with active moderate to severe TED	IVMP: Starting treatment dose of 0.5 g IVMP weekly for 6 weeks, followed by a	Reduced IVMP + MTX: Treatment dose of 0.25 g IVMP weekly for 12 weeks. MTX was	Primary outcome: • CAS response at week 12. Secondary outcome:

	reduction to 0.25 g IVMP weekly for 6 weeks for a total period of 12 weeks and 12 infusions. IVMP + MTX: Full-dose IVMP was administered equally to intervention arm. MTX was administered equally to the group receiving reduced IVMP + MTX	administered orally on the next day following IVMP as 10 mg weekly for the first 2 weeks and then regulated to 12.5 mg weekly for 10 weeks.	• Change in CAS at week 12, with improvement defined as CAS decreasing by at least 2 points. • Change in proptosis at week 12, with improvement defined as a reduction of at least 2 mm. • Change in eyelid width at week 12, with improvement defined as a reduction by at least 2 mm. • Change in Gorman diplopia score at week 12, with improvement defined as a decrease in Gorman score (from constant to inconstant, inconstant to intermittent, and intermittent to absent). • Change in intraocular pressure at week 12, with improvement defined as a reduction by at least 2 mmHg. • Change in visual acuity at week 12, with improvement defined as an increase by 1 Snellen line. **For all above-mentioned parameters, exacerbation was defined as an increase by the same extent in the above parameters.* • Overall response at week 12, defined as being responsive in at least two of the four ophthalmic parameters including CAS, proptosis, lid width, and Gorman score. Responsiveness was defined as an improvement in at least one eye without exacerbation in the other eye. Deterioration was defined as exacerbation in at least one eye without improvement in the other eye. Conditions that fit in neither responsiveness nor deterioration were defined as unchanged.

						• Change in QoL from baseline to week 12, with improvement defined as an increase by 6 points or more on the GO-QOL Questionnaire.
Mu et al. (2020) (61)	Prospective, randomized, single-center, open-label trial of two regimens of IVMP (daily or weekly)	The study conducted outcome assessment at a 12-week follow-up visit	Patients with active moderate to severe TED	Weekly IVMP: Cumulative dose of 4.5 g. Starting treatment dose of 0.5 g IVMP weekly for 6 weeks, followed by a reduction to 0.25 g IVMP weekly for 6 weeks for a total period of 12 weeks and 12 infusions. Daily IVMP: Cumulative dose of 4.3 g. Treatment dose of 0.5 g IVMP daily for five consecutive days, followed by oral methylprednisolone for three months. Starting treatment dose of 32 mg/day oral methylprednisolone,	N/A	Primary outcome: • Overall response rate at week 12: “Response” was defined as an improvement in at least two major criteria and one minor criterion. Otherwise, the outcome was considered “non-response”. The major criteria included the following: 1) Improvement in CAS by ≥2 points, 2) improvement in diplopia (disappearance or reduction in degree), 3) improvement in visual acuity by ≥1/10, and 4) reduction in proptosis or lid width of ≥2 mm. The minor criteria were favorable changes in soft tissues and improvement in the patient's self-assessment. Secondary outcome: • Remission rate of major ophthalmic manifestations at week 12. • Average changes in CAS at week 12.

									followed by dose tapered by 4 mg/day Q2W

Abbreviations: CAS, clinical activity score; DON, dysthyroid optic neuropathy; GO, garves' orbitopathy; GO-QOL, graves' ophthalmopathy quality of life questionnaire; IV, intravenous; IVMP, intravenous methylprednisolone; MR, monthly regimen; N/A, not applicable; NOSPECS, no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle signs, corneal involvement, and sight loss score; QoL, quality of life; Q2W, every two weeks; Q3W, every three weeks; TED, thyroid eye disease; WR, weekly regimen.

Ongoing trials

A search for active or unpublished studies that include the intervention and comparator in patients with active moderate to severe TED was conducted on June 2026 on Clinicaltrials.gov and the EU Clinical Trials Register. The searches resulted in three hits for this specific population and treatment options, with one being the completed Phase 2 trial, one being an ongoing trial investigating the use of teprotumumab through subcutaneous administration, and one being a US post-marketing requirement study, investigating the efficacy and safety of IV teprotumumab at different numbers of doses and different treatment lengths. As the two ongoing trials are not expected to be completed before the Q3 of 2026 at the earliest, these studies were not deemed relevant to this current application.

6.1.1 Comparability of Studies

This section will provide details on the comparability of studies of teprotumumab and studies of IVMP. The clinical evidence base for this application comprises a series of RCTs investigating IVMP and teprotumumab, respectively.

All included IVMP studies administered high-dose weekly IVMP over a 12-week period, typically 4.5 g in total, and were conducted primarily in European and Asian settings. In contrast, the two teprotumumab trials used a fixed 24-week dosing regimen and were multinational, with primarily Caucasian (85.4% in the OPTIC Phase 3 trial).

While the studies to some extent vary in study design and geographical context, they are similar in terms of study type, population characteristics, treatment regimen, and outcome definitions, which allow for a comparative analysis of efficacy.

6.1.1.1 Comparability of Patients Across Studies

To reflect both similarities and differences in baseline characteristics between the evidence base for IVMP and teprotumumab, a summary is provided for each treatment group to present the comparability. Thus, a comparability assessment will not be performed for each IVMP study against each teprotumumab study. However, baseline characteristics are presented in each relevant study in Table 16.

The average age for patients in the IVMP trials was within a range of 35-52 years compared to 51.6 years for patients in both teprotumumab trials. Most patients were female, while the proportion of male participants varied more widely in the IVMP trials (21-61%) than in the teprotumumab trials (29-35%).

In terms of baseline proptosis, it was comparable across most studies, with mean values typically ranging from 21 to 23 mm. This suggests a similar degree of disease stage across populations. The duration of TED symptoms before enrolment also fell within a consistent range (6-13 months), further supporting comparability in terms of disease stage at baseline. 40-90% had diplopia (any degree) across the studies at baseline.

Smoking prevalence was higher in the IVMP studies (up to 60%) compared with teprotumumab trials (approximately 21–26%). Race was not reported in all IVMP studies, but when reported, most participants were Asian. Ethnicity was more diverse in the teprotumumab studies, however, with most patients being Caucasian. It is important to reflect these differences as both ethnicity and smoking have been suggested to influence the clinical course of treatment response in TED. Thus, adjustments will be performed in terms of the indirect treatment comparison (ITC) to account for specific differences in baseline characteristics.

Table 16. Patients' baseline characteristics in included studies used in the comparative analysis of effectiveness and safety

Study	Bartalena et al. 2012 (56)	He et al. 2017 (60)	Zhu et al. 2014 (63)	Shen et al. 2022 (15)	Mu et al. 2020 (61)	Aktaran et al. 2007 (55)	Kahaly et al. 2005 (62)	MINGO – Kahaly et al. 2018 (52)	Phase 2 – Smith et al. 2017 (7)	OPTIC Phase 3 – Douglas et al. 2020/ CSR) (8)
Study design	Phase NR, RCT	Phase NR, RCT	Phase 4, RCT	Phase NR, RCT	Phase NR RCT	Phase NR, RCT	Phase NR, RCT	Phase NR, RCT	Phase 2 RCT	Phase 3, RCT
Treatment of interest	Weekly IVMP 4.98g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Weekly IVMP 4.5 g	Teprotumumab (10 mg/kg of body weight for the 1st infusion and 20 mg/kg for subsequent infusions)	Teprotumumab (10 mg/kg of body weight for the 1st infusion and 20 mg/kg for subsequent infusions)
N	54	18	39	30	46	25	35	81 (73 at week 12)	42	41
Treatment duration	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	24 weeks	24 weeks
Mean age	50	41.2	45.3	46.5	35.2	44.3	52	50.6	51.6	51.6
Male (%)	42.59	44.44	38.46	30	60.87	44	28.57	21	35	29.3

Race	NR	Asian 100%	NR	NR	NR	NR	NR	NR	NR	White 85.4% Black 9.8% Asian 4.9% Other 0%
Smokers %	54	22.2	13.51	0	34.8	40	60	51	26	22
Mean duration of TED symptoms (months)	12.4	NR	13.63	NR	12.64	NR	4	8.5	8.5	6.2
Mean baseline proptosis in mm	22.2	17.2	21.66	22.3	17.25	22.2	NR	21.27	23.4	22.62
Any diplopia at baseline, n (%)	74 (40)	12 (66.6)	28 (71.79)	21 (70)	16 (34.8)	11 (44)	26 (75)	52 (66.7)	38 (90)	28 (68.29)
Constant, n (%)	17 (9)	4 (22.2)	7 (17.95)	11 (36.7)	NR	2 (18)	23 (66)	9 (11.5)	15 (35)	NR
Inconstant, n (%)	37 (20)	6 (33.3)	15 (38.46)	7 (23.3)	NR	4 (36)	3 (9)	23 (29.6)	7 (17)	NR
Intermittent, n (%)	20 (11)	2 (11.1)	6 (15.38)	3 (10)	NR	5 (45)	0	20 (25.6)	16 (38)	NR
RIT (%)	9	33.3	10.26	20	NR	NR	NR	20	NR	NR
FT3	NR	NR	4.42 pmol/L	4.7	12.39 pmol/L	2.7 pg/mL	NR	NR	4.8 pmol/L	5.1 pmol/L

FT4	NR	NR	13.43 pmol/L	12.6	31.08 pmol/L	1.5 ng/dL	NR	NR	16.3 pmol/L	16.46 pmol/L
TSH	1.1 mU/L	NR	0.41 uIU/mL	NR	0.26 mU/L	1.9 uU/mL	NR	0.52 mIU/L	NR	1.754 mIU/L

Abbreviations: CSR, clinical study report; FT3, free triiodothyronine; FT4, free thyroxine; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; n, number; N, number; N/A, not applicable; NR, not reported; RCT, randomized controlledtrial; RIT, radioiodine therapy; TED, thyroid eye disease; TSH, thyroid stimulating hormone.

6.1.2 Comparability of Study Population(s) with Danish Patients Eligible for Treatment

In the health economic model, patient characteristics are based on data from the study population pooled from Phase 2 and OPTIC 3 (7, 8). According to the clinical expert consulted for this application, these characteristics reflect the Danish treatment population with active moderate to severe TED. While detailed national data for the past years for all variables are limited, the estimates applied in the model have been validated as presenting a reasonable approximation. The patient characteristics for the Danish population and health economic model are presented in Table 17.

Potential uncertainty remains regarding the exact values for the Danish population. However, the population assumptions used in the model are deemed appropriate and consistent with real-world clinical practice in Denmark and are also validated by the clinical expert.

Table 17: Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population (29)	Study population	Health economic model (7, 8)
Age	53	51.58	51.58
Sex (female)	84.31%	72.97%	72.97%
Body weight	70 kg	78.07 kg	74.67 kg

6.1.3 Analysis Method

Analysis methods for all studies are presented in the below sections together with the results.

6.1.4 Effect – Results per Phase 2

The Phase 2 trial was a multicenter, double-masked, randomized, placebo-controlled trial to determine the efficacy and safety of teprotumumab. 45 patients were included in the placebo group and 42 in the teprotumumab group.

In the intention to treat (ITT) population, 69% (29 out of 42) of patients receiving teprotumumab compared to 20% (9 out of 45) of patients receiving placebo had a response in the study eye at week 24, presenting an adjusted odds ratio (OR) (95% CI) of 8.86 (3.29, 23.8; $p<0.001$). Response was defined as patients who met the composite primary endpoint, being a reduction of 2 points or more in CAS and a reduction of 2 mm or more in proptosis in the study eye at week 24. The time-to-response was found to be

11.2 weeks (SD 6.6) for the teprotumumab group and 18.7 (SD 7.6) for the placebo group (7).

Regarding proptosis at baseline, values were similar for the two groups, with 23.4 mm (SD 3.2) and 23.1 mm (SD 2.9) for the teprotumumab and placebo group, respectively. The change from baseline was -2.46 mm (SD 0.20) in the teprotumumab group and 0.15 mm (SD 0.19) in the placebo group, representing a statistically significant difference (p<0.001). Change in the CAS was found to be -3.43 mm (SD 0.18) for teprotumumab compared to -1.85 (SD 0.17) for placebo, showing a statistically significant difference (p<0.001). Subjective diplopia was assessed based on four grades, and a change of one grade or more was defined as clinically relevant. Treatment with teprotumumab resulted in a statistically significant improvement in subjective diplopia compared to placebo. At baseline, 90% of patients in the teprotumumab group reported some degree of diplopia. After 24 weeks of treatment, 50% of patients in the teprotumumab group reported no diplopia, compared to 40% in the placebo group. The proportion of patients experiencing constant diplopia decreased from 35% at baseline to 10% in the teprotumumab group, whereas it increased slightly from 9% to 13% in the placebo group. The overall response rate, defined as any improvement in diplopia grade, was 68% (26/38) for teprotumumab vs. 26% (10/39) for placebo. This difference was statistically significant, with an odds ratio of 3.78 (95% CI: 1.68–8.54; *p* = 0.001) (7).

6.1.5 Effect – Results per OPTIC Phase 3

OPTIC Phase 3 was a randomized, double-masked, placebo-controlled, phase 3 multicenter trial, among patients with active TED completed in 2020. Patients were assigned to a ratio of 1:1 receiving either teprotumumab or placebo. A total of 41 patients were assigned to the teprotumumab group and 42 were assigned to the placebo group. Confidence intervals (CI) and standard deviations (SD) are reported where applicable.

At week 24 for the ITT population, 83% (34 of 41) of the patients in the teprotumumab group had a proptosis response, as compared to 10% (4 of 42) of the patients in the placebo group (73% difference (95% CI: 59, 88), p<0.001) (8).

Regarding secondary outcomes in the ITT population, an overall response at week 24 was 78% (32 out of 41) for the teprotumumab group and 7% (3 out of 42) for the placebo group, indicating a difference of 71% (56 out of 86) with a p value <0.001. In the teprotumumab group, 59% (24 out of 41) of patients reported a CAS of 0 or 1 at week 24, compared to 21% (9 out of 42) for the placebo group, indicating a difference of 36% (95% CI: 17, 55), p<0.001. The mean change from baseline in proptosis among the patients in the teprotumumab group was -2.82 mm (SD 0.19), which was greater compared to placebo with -0.54 mm (SD 0.19) at week 24 (-2.28 mm difference (95% CI: -2.77, -1.80), p<0.001). In terms of diplopia response, 68% (19 out of 28 [total number of patients with diplopia at baseline]) of patients in the teprotumumab group had a response, compared to 29% (8 out of 28) of patients in the placebo group, representing a difference of 39% (95% CI: 16, 63), p=0.001 (8).

For the health economic model, the number of patients experiencing disease flare in the follow-up period from week 24-72 was utilized. In the teprotumumab arm, 9/34 (26%) patients who responded and participated in the follow-up period experienced a disease flare for proptosis, while 4/19 (21%) patients who responded and participated in the follow-up period experienced a disease flare in diplopia.

6.1.6 Effect – Results per Bartalena et al. 2012

A multicenter, double-blind, randomized trial was performed to determine the efficacy and safety of IVMP in three different doses, 2.25, 4.98, or 7.47 g in 12 weekly infusions. As this application follows the guidelines for IVMP dosage, this section will primarily focus on the medium dose (MD) of 4.98 g (56).

Patients receiving the medium cumulative dose (MD: 4.98 g) of IVMP for active moderate to severe GD showed modest improvements in ocular outcomes at week 12. For proptosis, the mean reduction at week 12 from baseline for MD was –0.4 mm (-0.8, 0) and 20% (11 of 54) of patients in the MD group were classified as improved. Regarding diplopia, 26% (14 of 54) of patients in the MD group had improved extraocular motility at 12 weeks from baseline. No significant difference between groups was observed in the subjective diplopia score based on the Bahn and Gorman grading scale. CAS improved by at least two points in 83% of the patients receiving MD (56).

6.1.7 Effect – results per Aktaran et al. 2007

A prospective, randomized, single-blind clinical trial investigated the efficacy, tolerability, and impact on QoL of intravenous glucocorticoid pulse therapy (IVGC) in patients with moderately severe, active TED. IVGC is a term for high doses of IVMP used for a limited time. The patients received 500 mg of methylprednisolone in 100 ml of physiological saline per week for 6 weeks, then 250 mg per week for 6 weeks. A total of 25 patients received IVGC (55).

At the 3-month follow-up, 72% (18 out of 25) of patients demonstrated a higher treatment response compared with 49% (13 out of 27) of patients in the comparator arm. Clinical outcomes, including CAS, diplopia, and proptosis, were assessed at baseline and at 3 months.

The mean CAS decreased from 5.2 (SD 0.8) at baseline to 2.1 (SD 0.6) at 3 months. Diplopia severity also improved: at baseline, 18% of patients had constant diplopia, 36% had inconstant, and 45% had intermittent diplopia. After 3 months, these figures improved to 9%, 18%, and 36%, respectively. Proptosis was reduced over the treatment period, with the mean value decreasing from 22.2 mm (SD 2.0) at baseline to 21.0 mm (SD 1.5) at 3 months—a statistically significant reduction ($p = 0.038$) (55).

6.1.8 Effect – results per He et al. 2017

A prospective RCT assessed the efficacy and safety of two IVMP regimens—weekly and monthly administration—in patients with active TED over a 3-month treatment period

(60). For this application, only outcomes from the weekly regimen (WR) are reported, as this dosing schedule aligns with the dose reflected in Danish clinical practice.

In total, 18 patients were enrolled in the WR group, and outcome data was available for 17 patients at week 12. The endpoints of interest were changes in CAS, proptosis, and diplopia. At baseline, the mean CAS in the WR group was 3.6 (SD 1.1), which declined modestly to 3.0 (SD 1.5) by week 12. Proptosis was improved in 5 of the 15 patients evaluated at week 12. The baseline estimate was 17.2 (SD 2.1), whereas the estimate at week 12 was 16.0 (SD 3.1). Regarding diplopia, the mean score improved slightly from 1.5 (SD 1.4) at baseline to 1.3 (SD 1.3) at follow-up (60).

6.1.9 Effect – results per Mu et al. 2020

A 12-week, single-center, prospective, randomized, open-label trial evaluated treatment outcomes of two IVMP dosing protocols: a weekly and a daily regimen. For this application, only data from the WR group are presented, as this is the dosing regimen relevant for Danish clinical practice (61).

In the weekly group, 46 patients were enrolled. Proptosis increased slightly over the study period, with mean values rising from 17.25 mm (SD 1.80) at baseline to 17.94 mm (SD 2.08) at week 12. For CAS, a clinically meaningful reduction was observed. The median CAS declined from 4.0 (SD 1.0) at baseline to 2.0 (SD 1.0) at week 12, reflecting a marked reduction in inflammatory activity following weekly IVMP treatment (61).

6.1.10 Effect – results per Zhu et al. 2014

A prospective randomized trial was conducted to compare the efficacy and safety of two protocols of 4.5 g IVMP, either weekly or daily. To reflect Danish clinical practice, only outcomes for the weekly dose will be presented (63). A 12-week prospective protocol of IVMP treatment demonstrated clinically and statistically significant improvements in key ophthalmological outcomes, including CAS, proptosis, and diplopia. Thirty-nine patients were included in the 12-week protocol.

For CAS, the median score decreased from 4 (IQR 3–5) at baseline to 2 (IQR 1–4) at week 12 ($p < 0.0001$). By the end of treatment, 64.1% (25 patients) showed improvement in CAS from baseline, 33.33% (13 patients) remained unchanged, and only 2.56% (1 patient) experienced deterioration. Proptosis decreased modestly from a baseline mean of 22.06 mm (SD 3.17) to 20.81 mm (SD 3.01) at week 12 ($p < 0.0001$). Improvement was observed in 28.2% of patients, while 69.2% remained stable, and 2.6% showed worsening. For diplopia, 71.8% of patients reported diplopia at baseline, primarily intermittent (15.38%), inconstant (38.46%), and constant (17.95%). By week 12, 43.59% of patients showed improvement, 36.9% were unchanged, and 20.51% experienced worsening. The proportion of patients without diplopia remained stable at 28.2% (63).

6.1.11 Effect – results per Shen et al. 2022

A prospective, randomized, observer-masked, single-center clinical trial was designed to evaluate the therapeutic effects and safety of methotrexate (MTX) plus reduced (3.0 g)

or full-dose (4.5 g) IVMP compared to full-dose IVMP alone over 12 weeks (15). 30 patients were included in the IVMP alone group.

The outcomes of interest were CAS, diplopia, and proptosis. In the group treated with IVMP monotherapy, the CAS score changed from 4.5 (3-5) at baseline to 2 (1-4) post-treatment. For proptosis, the mean reduction was 0.9 mm (from 22.3 mm (SD 2.3) to 21.4 mm (SD 2.4)), and 33.3% of patients met the response criterion of a ≥2 mm decrease. This change was statistically significant (p = 0.027), although the proportion of responders was relatively limited. Diplopia was assessed by the Gorman score. Among patients presenting with diplopia at baseline (n = 21), 57.1% showed improvement by week 12. No new cases of diplopia were reported in patients who had no diplopia at baseline (15).

6.1.12 Effect – results per Kahaly et al. 2018

An observer-masked, multicenter, block-randomized, center-stratified trial exploring the effect and safety of IVMP and IVMP together with mycophenolate mofetil (MMF). Within this application, the interest is in IVMP as the comparator, thus only efficacy estimates of IVMP will be presented. The study used a total IVMP dose of 4.5 g, administered as 500 mg weekly for 6 weeks, followed by 250 mg weekly for 6 weeks. 81 patients received IVMP alone (52).

CAS showed a statistically significant reduction over time. In the left eye, the mean CAS decreased from 3.66 (SD 1.28) at baseline to 2.20 (SD 1.34) at week 12, 2.05 (SD 1.49) at week 24, and 1.68 (SD 1.25) at week 36. A statistically significant improvement was observed already at week 12 (p = 0.047 for the left eye vs. baseline). In the right eye, the mean CAS decreased from 3.66 (SD 1.28) at baseline to 1.87 (SD 1.31) at week 12, 1.95 (SD 1.55) at week 24, and 1.65 (SD 1.46) at week 36 (52).

The mean Gorman diplopia score decreased from 1.19 (SD 1.04) at baseline to 0.87 (SD 0.99) at week 12 and remained stable at week 24 (mean 1.00) and week 36 (mean 0.98). Proptosis was part of the composite response criteria, but specific numerical values for proptosis changes in mm for the monotherapy group were not reported separately. However, the definition of treatment response included a ≥2 mm reduction in proptosis, and 49% of patients met the composite response criteria at week 12 (52).

6.1.13 Effect – results per Kahaly et al. 2005

A prospective, randomized, single-blind trial investigated the efficacy and optimal administration route of steroid monotherapy (IV compared to oral) in patients with GO. Thirty-five patients received IVMP. Patients received either once weekly IVMP (0.5 g, then 0.25 g, 6 weeks each) or oral prednisolone starting with 0.1 g/d, then tapering the dose by 0.01 g/wk. (62). For this submission, only outcomes from the IVMP arm are reported, focusing specifically on response in diplopia, proptosis, and CAS.

At baseline, 66% of patients (23 of 35) presented with constant diplopia. Following 12 weeks of treatment, the proportion had decreased to 29% (10 of 35), corresponding to a statistically significant improvement ($p < 0.001$). Median proptosis was reduced from 24

mm (range: 19–28 mm) at baseline to 22 mm (range: 17–25 mm) at week 12. This reduction was statistically significant (p = 0.02) (62).

7. Comparative Analyses

7.1 Analysis Method

To estimate the comparative efficacy of teprotumumab compared to IVMP in patients with moderate to severe active TED, an unanchored MAIC was conducted. In the absence of head-to-head studies, this approach was chosen in accordance with the best practices outlined in NICE Decision Support Unit Technical Support Document 18 (TSD 18) (64). IPD from two RCTs of teprotumumab, namely the Phase 2 and OPTIC Phase 3 trials, were pooled and re-weighted to match aggregate-level data from eight IVMP studies identified through the SLR, see Section 5.1. Specific inclusion and exclusion criteria were applied to define which clinical trials captured in the SLR were relevant to include in the MAIC. These specific population, intervention, comparison, outcomes (PICOs) inclusion and exclusion criteria can be found in Appendix H.

The Phase 2 and OPTIC Phase 3 trials were pooled to increase the sample size and enhance the robustness of the analysis. The pooling was deemed feasible due to the similar design of the trials. The Phase 2 trial consisted of 42 patients, and the OPTIC Phase 3 trial included 41 patients receiving teprotumumab, resulting in 83 patients in total after pooling.

For IVMP, meta-analyses were conducted to estimate the pooled effect size. This was performed using a random-effects model to account for the heterogeneity between studies. For both change-from-baseline proptosis and diplopia response, treatment effects were meta-analyzed to obtain a pooled treatment effect to be used in the MAIC.

The effect measures used in the MAIC of teprotumumab versus IVMP were (27):

- Mean difference in change from baseline proptosis (mm)
- Odds ratio for diplopia response

In the analysis of change in baseline proptosis, seven IVMP RCT studies were included (15, 55, 56, 60-63). The pooled baseline characteristics of the seven IVMP studies were calculated using a weighted average based on the study sample size. The pooled treatment effect is presented in a Forest plot in Appendix D, demonstrating a mean change from baseline proptosis of -0.49 mm. The results were non-significant as the CIs crossed 0 (95% CI: -1.06, 0.07).

In terms of diplopia response rate, four IVMP RCT studies were included (15, 60, 61, 63). The pooled baseline characteristics of the four IVMP studies were calculated using a weighted average based on the study sample size. The pooled proportion of diplopia responders is presented with a mean rate of 57%. There is minimal overlap between the

studies included as demonstrated in a Forest plot in Appendix D. The pooled treatment effect is statistically significant, as the CI does not cross 0 (95% CI: 0.46, 0.67).

The unanchored MAIC assumes that differences between absolute outcomes observed in each study are explained by imbalances in the observed prognostic factors (PFs) and treatment effect modifiers (TEMs). To create pooled baseline characteristics from included studies for use in the MAIC, a weighted average of each baseline characteristic was calculated based on the sample size of the study.

The covariates were selected based on relevance and feasibility across studies, with the effective sample size (ESS) used to ensure adequate overlap and model stability. The TEMs and PFs were arranged in order of importance based on the reports from clinicians (from UK). The following characteristics were arranged in order of importance:

- Smoking (very important)
- Baseline proptosis (very important)
- Diplopia at baseline % (very important)
- Radioiodine therapy (RIT) of GD (very important)
- Thyroid function (FT3 and FT4 biomarkers) (very important)
- Thyroid-stimulating hormone (TSH)/ Thyroid-stimulating immunoglobulin (TSI)/ Thyrotropin receptor antibody (TRAb) levels (very important)
- Diabetes (somewhat important)
- Duration of TED symptoms (somewhat important)
- Age (somewhat important)
- Sex (somewhat important)
- High cholesterol levels (not important)

An ESS of 30 was set as a reasonable threshold, since smaller ESS values can lead to increased variability, less stable estimates, and wider CIs, compromising the reliability of the analysis. Thus, only four or five of the most important factors identified were to be included in the MAIC based on the availability of baseline characteristics reported in the IVMP dataset and the ESS threshold of > 30. For change-from-baseline proptosis, the baseline characteristics were, proportion of smokers (mean, %), baseline diplopia (mean, %), baseline proptosis (mean, mm), and RIT (mean, %). Accordingly, the covariate baseline diplopia was excluded as all patients had baseline diplopia. Thus, for the diplopia response rate the baseline characteristics were proportion of smokers (mean, %), baseline proptosis (mean, mm), RIT (mean, %), age (years), and sex (% male). Statistical adjustment was performed to account for differences in these baseline characteristics between the teprotumumab and IVMP populations. Propensity score weighting was used to match the covariates.

Histograms of the rescaled weights were used to assess whether certain individuals or groups were disproportionately represented in the weighted analysis, see Appendix D. Scaled weights help with interpretability: values greater than 1 suggest that a patient contributes more to the weighted sample than to the original sample, while values below 1 indicate less contribution.

To assess the reliability of the weighted analyses, the ESS was estimated. ESS reflects the number of unweighted individuals needed to achieve the same statistical precision as the weighted sample. A low ESS relative to the original sample size suggests high variability in the weights—often due to limited overlap between populations—which can undermine the stability of the estimates. Furthermore, to reflect that the weights are estimated and not fixed, the uncertainty associated with the weight estimation was incorporated into the overall uncertainty surrounding the estimated relative treatment effects (27).

Robust sandwich estimators were used to calculate standard errors and CIs, thereby accounting for the uncertainty introduced through the reweighting procedure. Regression models were utilized to calculate the adjusted and unadjusted outcomes. For diplopia response, a weighted logistic regression was used to estimate adjusted odds ratios, and for mean change from baseline in proptosis score, a weighted linear regression was used to estimate the adjusted mean differences (27).

All statistical analyses were performed in R using validated scripts based on the MAIC package and the metafor package for meta-analyses (27). In cases of missing baseline characteristics, a sensitivity analysis was conducted to test the inclusion and exclusion of these covariates if they were considered for TEMs or PFs. Strengths and limitations for the MAIC are described in Appendix D.

Differences in definitions of outcomes between studies

The combined data formed the basis for the matching-adjusted indirect comparison (MAIC). Among the available outcomes reported across studies, this submission focuses on proptosis and diplopia, which are considered the most clinically relevant endpoints for assessing efficacy in TED. They represent clinically meaningful and patient-relevant manifestations of TED, both of which have a substantial impact on QoL and functional status. For proptosis, the outcome definition was consistent across most included studies and was measured as the mean change from baseline in mm exophthalmometry. Regarding diplopia, definitions varied slightly across the studies included. However, improvement was generally assessed using the Gorman scale. In some studies, patients presented with no diplopia at baseline, making it impossible to assess improvement. Consequently, patients without diplopia at baseline were excluded from the analysis. The approach taken ensures that the results accurately reflect the treatment effect on the population at risk.

The time points of assessment differed. In the teprotumumab trials, proptosis was evaluated at week 24, corresponding to the end of treatment. In the IVMP studies, it was assessed at week 12, aligning with the standard 12-week tapering protocol recommended by EUGOGO and ATA guidelines. Although the time points differ, both reflect the expected maximum treatment effect and are thus considered clinically comparable for the purposes of the MAIC. In Appendix D, details for the timepoints, measurements, and outcome definitions for each relevant study are depicted.

A key methodological distinction is the availability of IPD, as opposed to aggregated summary data. IPD was available for teprotumumab, allowing for robust statistical

adjustment through weighting and regression modelling. For IVMP, only aggregate-level data from published studies were accessible.

Table 18: Overview of outcomes definitions across included studies

Outcome	Teprotumumab (Phase 2 + OPTIC Phase 3)	IVMP studies (eight RCTs)	Assessment
Proptosis (mm)	Measured using exophthalmometry at Week 24	Measured using exophthalmometry at Week 12	Same method - timing aligned with treatment end.
Diplopia response	≥1 grade improvement on Gorman scale	≥1 grade improvement on Gorman scale (where reported)	Same scale - only studies with usable data included.

Abbreviations: IVMP, intravenous methylprednisolone; RCT, randomized controlled trial.

Source: (7, 8, 55, 56, 60, 61)

The outcomes included in the MAIC were changes from baseline in proptosis (mm) and diplopia response rate, defined as an improvement of ≥1 grade on the Gorman scale.

The selected endpoints also align with the parameters used in the composite responder definitions across the clinical trials and are therefore appropriate for comparative effectiveness. For IVMP, outcomes at week 12 were used, reflecting the full treatment duration and capturing the maximum expected effect. This timepoint was chosen to ensure a consistent and fair comparison across interventions with varying treatment lengths.

7.2 Results of the Comparative Analysis

For teprotumumab, 83 patients were included for change-from-baseline proptosis and diplopia response rate, whereas for IVMP, 282 patients were included for change-from-baseline proptosis and 87 for diplopia response rate before matching.

The MAIC showed that teprotumumab provides significant clinical benefit compared to IVMP for patients with active moderate to severe TED, see Table 21. The specific results for the mean change from baseline proptosis and diplopia response rate results can be found in the sections below. In Table 19 and Table 20, the unadjusted and adjusted baseline characteristics for teprotumumab and the baseline characteristics for IVMP are depicted.

Table 19: Baseline characteristics before and after MAIC (studies included for the change from baseline proptosis) - teprotumumab compared to IVMP

Covariate	Teprotumumab baseline characteristics

	Unadjusted	Adjusted	IVMP baseline characteristics
Smoker (%)	[redacted]	[redacted]	[redacted]
Baseline diplopia (%)	[redacted]	[redacted]	[redacted]
Baseline proptosis (mm)	[redacted]	[redacted]	[redacted]
RIT (%)	[redacted]	[redacted]	[redacted]

Abbreviations: IVMP, intravenous methylprednisolone; MAIC, matching-adjusted indirect comparison; RIT, radioiodine therapy.

Table 20: Baseline characteristics before and after MAIC (studies included for the diplopia response rate) - teprotumumab compared to IVMP

Covariate	Teprotumumab baseline characteristics		IVMP baseline characteristics
	Unadjusted	Adjusted	
Smoker (%)	[redacted]	[redacted]	[redacted]
Baseline proptosis (mm)	[redacted]	[redacted]	[redacted]
RIT (%)	[redacted]	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]

Abbreviations: IVMP, intravenous methylprednisolone; MAIC, matching-adjusted indirect comparison; RIT, radioiodine therapy.

XTable 21. Results from the comparative analysis of teprotumumab vs. IVMP in patients with active moderate to severe TED

	Pooled Phase 2 and OPTIC 3 (unweighted)	Pooled Phase 2 and OPTIC 3 (weighted)		
Outcome	Teprotumumab (N=83)		IVMP (N=282 /87)	Result
Change in baseline proptosis (mm), 24 weeks for	[redacted]	[redacted]	[redacted]	[redacted]

	Pooled Phase 2 and OPTIC 3 (unweighted)	Pooled Phase 2 and OPTIC 3 (weighted)		
Outcome	**Teprotumumab (N=83)**		**IVMP (N=282 /87)**	**Result**
teprotumumab 12 weeks for IVMP				
Diplopia response (OR), 24 weeks for teprotumumab 12 weeks for IVMP	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IVMP, intravenous methylprednisolone; N, number; TED, thyroid eye disease.

7.3 Effect – Results per mean change from baseline proptosis

The studies were matched on the four mentioned covariates. The distribution of the weights for the base case is presented in a histogram in Appendix D, showing the rescaled weights ranging from 0.10 to 8.26, with the median skewed towards 1 (0.71). After reweighting, the ESS dropped from 78 to 35.36.

A summary of the analysis is presented in

Table 22. Results show that teprotumumab is associated with a statistically significant [redacted] compared to IVMP on [redacted] (27).

Table 22: MAIC results – mean change from baseline proptosis

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

Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N/A, not applicable; RIT, radioiodine therapy; SE, standard error.

7.4 Effect – Results per diplopia response rate

The four IVMP studies were compared with the pooled IPD from the two teprotumumab trials and were matched based on the five baseline characteristics.

The distribution of rescaled weights is presented in a histogram in Appendix D, ranging from 0.05 to 3.58, with the median skewed towards 1 (0.73). Three patients had noticeably larger weights, indicating a greater influence on the overall treatment effect. Application of these weights to the dataset caused the ESS to decrease from 75 to 38.95.

A summary of the analysis is presented in

Table **23**. The results indicate that the odds of diplopia response for patients treated with teprotumumab are [redacted] than those treated with IVMP [redacted].

Table 23: MAIC results – base case diplopia response rate

	ESS	OR	95% Lower CI	95% Upper CI
Base case (smoking, , baseline proptosis and RIT, age and sex)				
Adjusted results	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted results	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OR, odds ratio; RIT, radioiodine treatment.

8. Safety

Safety for teprotumumab was evaluated based on data from the Phase 2 trial and the OPTIC Phase 3 trial in patients with moderate to severe active TED. Safety analyses were conducted in the safety population, defined as all patients who received at least one dose of study drug. Safety endpoints were analyzed descriptively.

Safety for IVMP was evaluated based on the eight randomized and prospective clinical studies and described in 8.3.

Across the Phase 2 and OPTIC Phase 3 trials, the incidence of any adverse event (AE) ranged from 74–85% in the teprotumumab groups and from 69–73% in the placebo groups. Most AEs were mild, required no treatment and resolved while patients continued treatment. Commonly reported AEs included muscle spasms, alopecia, nausea, diarrhoea, dry skin, dysgeusia and hearing impairment (7, 8).

Serious adverse events (SAEs) were infrequent, occurring in 2.4–12% of teprotumumab-treated patients compared with 2–5% of placebo-treated patients. No deaths or anaphylactic reactions occurred in any of the trials. Six patients in each treatment group discontinued treatment (7, 8).

Definitions of AEs and SAEs were consistent across the Phase 2 and Phase 3 studies and are described in Appendix K.

8.1 Phase 2

In the Phase 2 trial, most AEs were mild and self-limiting. The most frequently reported AEs in the teprotumumab group were nausea and muscle spasms (7).

Table 24. Overview of adverse events (Phase 2 study; 24-week treatment period)

	Teprotumumab (N = 44)	Placebo (N = 43)	Difference, %-points	Difference, RR (95% CI)
All adverse events (AE), n (%)	32 (74.4)	32 (72.7)	1.7	1.02 (0.80-1.31)
Serious AE (SAE), n (%)[1]	5 (11.6)	1 (2.3)	9.3	5.12 (0.62-42.07)
AE grade ≥ 3, n (%)[2]	4 (9.3)	0	9.3	Not estimable
Dose reduction due to AE, n (%)	NA	NA	NA	NA

	Teprotumumab (N = 44)	Placebo (N = 43)	Difference, %-points	Difference, RR (95% CI)
Treatment discontinuation due to AE, n (%)	5 (11.6)	1 (2.3)	9.3	5.12 (0.62-42.07)

AE = adverse event; CI = confidence interval; RR = risk ratio; SAE = serious adverse event. Source: Smith et al. (2017) (7), Data on file (27)

Hyperglycaemia was the only AE considered related to teprotumumab. In non-diabetic patients, hyperglycaemia occurred as grade 1 events, whereas grade 2 or 3 events were observed in patients with diabetes and were managed by adjustment of antidiabetic therapy. Glycaemic control returned to baseline after six months (7).

No deaths occurred. Six patients in each treatment group discontinued treatment. SAEs were reported in 12% (5/43) of teprotumumab-treated patients and 2% (1/45) of placebo-treated patients. Diarrhoea and mental confusion in the teprotumumab group were considered possibly treatment-related, while other SAEs were assessed as unrelated to study treatment (7).

In Table 25, no individual grade ≥3 AE occurred in ≥3% of patients in either treatment arm. Therefore, grade ≥3 AE are presented in aggregate.

Table 25. Proportion of patients with adverse events (Phase 2 study; 24-week treatment period)

	Teprotumumab (N = 43)		Placebo (N = 44)	
	All	**Grade ≥ 3 or SAE**	**All**	**Grade ≥ 3 or SAE**
Nausea, n (%)	8 (18.6)	NA	4 (9.1)	NA
Muscle spasms, n (%)	8 (18.6)	NA	2 (4.5)	NA
Diarrhea, n (%)	4 (14.0)	NA	2 (4.5)	NA
Hyperglycemia, n (%)	5 (11.6)	NA	2 (4.5)	NA
AE grade ≥ 3 in ≥ 3%, n (%)[1]		5 (12.0)		1 (2.3)

SAE = serious adverse event; NA = not applicable; AE = adverse event; [1] No individual AE grade ≥3 occurred in ≥3% of patients in either treatment arm. However, the overall proportion of patients experiencing at least one AE grade ≥3 was ≥3%, and AE grade ≥3 in ≥3% are therefore presented in aggregate. Source: Smith et al. (2017) (7), Data on file (27)

8.2 OPTIC Phase 3

In the OPTIC Phase 3 trial, AEs were observed in at least 5% of patients in either trial group within 21 days after the final dose. Most AEs were grade 1 or 2. Muscle spasms, alopecia, nausea and fatigue were the most common AEs in the teprotumumab group.

Potential infusion-related reactions were reported in six teprotumumab-treated patients and four placebo-treated patients (8).

Table 26. Overview of adverse events (OPTIC Phase 3; 24-week treatment period)

	Teprotumumab (N = 41)	Placebo (N = 42)	Difference, %-points	Difference, RR (95% CI)
All adverse events (AE), n (%)	35 (85.4)	29 (69.0)	16.4	1.24 (0.99-1.56)
Serious AE (SAE), n (%)[1]	2 (4.9)	1 (2.4)	2.5	2.05 (0.19
AE grade ≥ 3, n (%)[2]	1 (2.4%)	1 (2.4%)	0.0	1.02 (0.07-15.9)
Dose reduction due to AE, n (%)	NA	NA	NA	NA
Treatment discontinuation due to AE, n (%)	1 (2.4)	1 (2.4)	0.0	1.02 (0.07-15.9)

AE = adverse event; CI = confidence interval; RR = risk ratio; SAE = serious adverse event. Source: Douglas et al. (2020) (8), Data on file (27)

AEs of special interest, including infusion-related reactions, hyperglycaemia, muscle spasms, diarrhoea and hearing impairment, were of grade 1 or 2 and, with the exception of a single infusion-related reaction, did not lead to treatment discontinuation (8).

Hyperglycaemia was reported in two patients (<5%) and was mild. Hearing impairment was reported in five teprotumumab-treated patients (hypoacusis, deafness, autophony and patulous eustachian tube). All auditory events occurring during the double-blind treatment period resolved. No auditory AEs were reported in the placebo group. Five teprotumumab-treated patients (four women) experienced a body-weight loss of at least 5 kg, including one case of intentional weight loss of 19 kg. No AEs related to decreased body weight were reported (8).

No deaths occurred. Two SAEs were reported in the teprotumumab group including pneumothorax (likely unrelated to the trial drug) and an infusion reaction leading to trial withdrawal, and one SAE occurred in the placebo group (visual field defect requiring decompression surgery). No anti-drug antibodies were detected (8).

Table 27. Proportion of patients with adverse events (OPTIC Phase 3; 24-week treatment period)

	Teprotumumab (N = 43)		Placebo (N = 44)	
	All	**Grade ≥ 3 or SAE**	**All**	**Grade ≥ 3 or SAE**
Muscle spasms, n (%)	13 (31.7)	NA	4 (9.5)	NA

	Teprotumumab (N = 43)		Placebo (N = 44)	
Alopecia, n (%)	8 (19.5)	NA	5 (11.9)	NA
Nausea, n (%)	6 (14.6)	NA	4 (9.5)	NA
Fatigue	5 (12.2)	NA	1 (2.4)	
Diarrhea, n (%)	4 (9.8)	NA	5 (11.9)	NA
AE grade ≥ 3 in ≥ 3%, n (%)[1]		2 (4.9)		1 (2.4)

SAE = serious adverse event; NA = not applicable; AE = adverse event; [1] No individual AE grade ≥3 occurred in ≥3% of patients in either treatment arm. However, the overall proportion of patients experiencing at least one AE grade ≥3 was ≥3%, and AE grade ≥3 in ≥3% are therefore presented in aggregate. Source: Douglas et al. (2020) (8), Data on file (27)

8.2.1 Auditory adverse events

Auditory AEs have emerged as a relevant safety consideration in the evaluation of teprotumumab for the treatment of TED. Hearing impairment has been identified as a potential risk, with tinnitus and hypoacusis being the most frequently reported conditions. In a prospective case series, 22 of 27 patients (81.5%) reported otologic symptoms during treatment, including hearing loss, muffled hearing and impaired speech discrimination. Among patients reporting hearing loss, 45.5% experienced complete resolution after treatment cessation, indicating partial reversibility, although persistent symptoms have also been reported (65). Importantly, auditory dysfunction is not exclusive to patients treated with teprotumumab. A retrospective study reported that 20% of TED patients who had not received teprotumumab had a diagnosis of hearing loss or ototoxicity (66). This highlights the importance of baseline audiometric evaluation to differentiate disease-related from treatment-related effects.

Further prospective evidence supports this recommendation. In a study including baseline audiometry, one of 32 patients with normal baseline hearing developed new-onset hearing loss at six-month follow-up after completing teprotumumab therapy. Additionally, four of 20 patients with pre-existing hearing impairment experienced further deterioration (67). These findings suggest that while teprotumumab-associated hearing events occur, they may be confounded by pre-existing vulnerability in a subset of patients with TED.

8.2.2 Alopecia

Alopecia was reported in 13% of teprotumumab-treated patients and 8% of placebo-treated patients (7, 8). Some patients also reported eyelash or eyebrow thinning and other hair growth abnormalities (27). All alopecia events were non-serious, mild to moderate in severity and did not lead to treatment discontinuation.

Two additional alopecia events were reported after study closure, relating to the double-blind period and ongoing at last follow-up(68) . Due to limited follow-up,

reversibility cannot be fully assessed. As hair loss is common in thyroid disorders, underlying disease may contribute to the observed findings.

8.3 IVMP

Across the eight randomized and prospective clinical studies, IVMP demonstrated an overall acceptable safety profile in the treatment of moderate to severe active TED. Most AEs were mild to moderate in severity and dose-dependent (15, 52, 55, 56, 60-63).

The most frequently reported AEs included weight gain (8–46%), sleep disturbances (11–18%), fatigue (11–14%), palpitations (up to 15%), gastrointestinal complaints (7–17%), transient hypertension (up to 26%), hyperglycaemia (5–12%) and hypokalaemia (up to 22%). These events were generally self-limiting or manageable with supportive care (15, 52, 55, 56, 60-63).

SAEs such as psychosis, major depression, severe liver enzyme elevations and cardiovascular events were reported but remained rare (typically <5%), with higher incidence observed at higher cumulative doses (15, 52, 55, 56, 60-63). In the study by Bartalena et al. (2012), one myocardial infarction occurred in one patient; however, the patient received a low dose IVMP, which is not considered in this application (56).

Importantly, the occurrence was limited when the doses of IVMP were held lower or around 4.5 g. Overall, the safety profile of IVMP is well-characterized and manageable, though the risk of systemic complications necessitates monitoring (15, 52, 55, 56, 60-63).

Due to heterogeneity in study designs, dosing regimens, outcome definitions, and reporting formats, IVMP safety data are summarized narratively rather than in comparative tables. Detailed study-level safety data for IVMP are provided in Appendix F.

8.4 Comparability of safety in teprotumumab compared to IVMP

IVMP is associated with a well-characterized safety profile dominated by steroid-related AEs that are generally mild to moderate, dose-dependent and manageable. Teprotumumab is also primarily associated with mild to moderate AEs, although the types of AEs differ.

Across the Phase 2 and OPTIC Phase 3 trials, teprotumumab was generally well tolerated. The main safety differences between teprotumumab and IVMP were the occurrence of auditory AEs and alopecia, which were observed only with teprotumumab. According to the Danish clinical expert, these were the only AEs of specific concern, whereas other AEs were expected in patients with moderate to severe TED. Overall, apart from these treatment-specific differences, the general AE profiles were considered similar.

9. Extrapolation of patient transitions

9.1 Clinical Data Used for Extrapolation of Patient Transitions

Extrapolation in the model is informed by the clinical outcomes for proptosis and diplopia, which together define the health state structure and individual patient transitions. These outcomes are sourced from pooled IPD from the Phase 2 trial and the OPTIC Phase 3 trial for teprotumumab, and from the ITCs and published literature for IVMP.

Up to week 24, treatment-specific transition probabilities are estimated based on observed changes in proptosis and diplopia. For IVMP, transition probabilities are applied over the initial treatment period only, reflecting the shorter treatment duration for treatment with IVMP and the timing of outcome assessment in the ITC. Due to the absence of robust long-term follow-up data beyond week 24 for both treatments, extrapolation is implemented using transition probabilities.

Beyond the active treatment period, a remain-in-state assumption is applied, whereby patients are assumed to remain in their current health state. For teprotumumab, this assumption is applied from week 24 onwards, while for IVMP it is applied from week 12 onwards, consistent with the completion of treatment. Disease flares are modelled separately and are not subject to the remain-in-state assumption.

No surrogate outcomes are used in the model, as proptosis and diplopia directly define the clinical health states and outcomes of primary interest.

Table 28: Clinical outcomes and extrapolation approaches

Transition type	Clinical outcome	Data source	Extrapolation approach
Health state transitions (≤ week 24)	Proptosis, diplopia	Phase 2 + OPTIC Phase 3 (teprotumumab); ITCs (IVMP)	Observed transition probabilities
Health state transitions (> week 24)	Proptosis, diplopia	Assumption based on limited long-term data	Remain-in-state
Disease flare transitions	Proptosis flare, diplopia flare	OPTIC Phase 3 follow-up; Burch et al. (2022)	Transition probabilities

Discontinuation	All-cause discontinuation	Phase 2 + OPTIC; Kahaly et al. (2018)	Constant per-cycle probability

9.2 Extrapolation Using Parametric Extrapolation Models

9.2.1 Extrapolation of [Clinical Outcomes 1]

NA

Table 29. Overview of assumptions related to extrapolation of [clinical outcome]

Method/approach	Description/assumption
Data	NA
Selected distribution	NA
Models examined	NA
Assumptions	NA
Proportional hazards between intervention and comparator	NA
Flexible parametric models	NA
Cure point and/or share	NA
Treatment waning	NA
Other assumptions	NA
Internal validity	NA
Distribution with best AIC fit	NA
Distribution with best BIC fit	NA
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	NA
Distribution(s) with best visual fit according to evaluation of smoothed hazards	NA
External validity	NA

Method/approach	Description/assumption
Sources for validating external validity	NA
Distribution with highest external validity	NA

9.2.2 Extrapolation of [Clinical Outcome 2]

NA

9.3 Extrapolation Using Transition Probabilities

The clinical outcomes used to inform extrapolation in the model are proptosis and diplopia, which together define the health state structure and patient transitions. The use of proptosis and diplopia is considered clinically relevant, as they are key indicators of disease severity and functional impairment in patients with active moderate-to-severe TED.

Up to week 24, efficacy for teprotumumab is based on pooled IPD from the Phase 2 trial and the OPTIC Phase 3 trial. Reduction in proptosis from baseline and diplopia response rates are used to estimate transitions between health states. These outcomes are combined in order to model treatment efficacy, as described in Section 4.2. In the absence of head-to-head comparative evidence, efficacy for IVMP is derived indirectly by applying results from de novo ITCs to the teprotumumab transition probabilities. Given the shorter treatment duration for IVMP and the timing of outcome assessment in the ITCs, IVMP specific transition probabilities are applied over the initial 12-week treatment period only. This approach is considered appropriate and internally consistent given the available evidence base.

Transition probability matrices were derived by categorizing subjects at each of their visits at the different timepoints based on their diplopia score and proptosis severity. Diplopia was classified as ‘no diplopia’ (score 0), ‘intermittent/inconstant diplopia’ (score 1 or 2), or ‘constant diplopia’ (score 3). Proptosis was classified as ‘small’ or ‘large’ based on the difference the observed proptosis value and the upper limit of normal for a non-TED patient of the same sex and race; a difference of <3 mm corresponds to ‘small proptosis’, and ≥3 mm corresponds to ‘large proptosis’. This health state definition is validated by TED clinical experts during the development of the model and is clinically plausible and reflective of meaningful differences in disease severity.

The starting distribution of patients across health states is derived from pooled Phase 2 and OPTIC Phase 3 trial data (Table 30). This distribution is considered representative of the target population modelled, since it is based on IPD from RCTs in patients with active moderate-to-severe TED.

Table 30: Distribution of patients across included health states at model beginning

SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
12%	14%	20%	33%	9%	12%

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Extrapolation beyond week 24

Extrapolation of transition probabilities beyond week 24 is required due to limitations in the availability and robustness of long-term follow-up data for both treatment arms. For teprotumumab, although the OPTIC Phase 3 trial includes follow-up data extending to week 72, only 20 patients completed the full follow-up period. This small sample size is insufficient to derive robust long-term transition probabilities and would result in substantial uncertainty, including structurally unstable transition matrices with zero-occupancy health states. Extended follow-up data from the Phase 2 trial was not available and could therefore not be used to inform extrapolation.

For IVMP, no sufficient published long-term follow-up data beyond week 24 is available. Applying long-term transition probabilities for teprotumumab only would result in asymmetric use of evidence across treatment arms and could introduce bias. To ensure consistency and avoid bias, the model therefore assumes that, beyond week 24, patients in both treatment arms remain in their current health states.

Several extrapolation approaches were evaluated, including last observation carried forward and averaging across observed transition matrices. A last observation carried forward approach was not considered clinically plausible, since it would repeatedly apply a transition matrix reflecting peak treatment efficacy. Averaging across transition matrices was also deemed inappropriate due to heterogeneity in patient responses across treatment phases. Given these considerations, a “remain in state” assumption beyond week 24 was selected for both treatment arms. This assumption is applied symmetrically across treatment arms to ensure consistency and to avoid bias arising from asymmetric data availability. The remain-in-state assumption does not apply to disease flares, which are modelled separately.

Disease flare

Disease flares are explicitly modelled as exceptions to the remain-in-state assumption. For teprotumumab, flare probabilities are informed by follow-up data from the OPTIC Phase 3 trial between weeks 24 and 72. During this period, 26.47% of patients (9/34) experienced a flare of proptosis and 21.05% (4/19) experienced a flare of diplopia (27, 68) These observed proportions are used to inform flare-related transitions in the model.

For IVMP, flare probabilities are sourced from Burch et al. (2022), which reports flare proportions 12 weeks after treatment completion (35). The model applies flare transition matrices from this source for two cycles, corresponding to a 12-week period starting

from cycle three. The flare probability is assumed to be the average of the minimum and maximum values reported, resulting in an estimated probability of 30.5% for both proptosis and diplopia over this period. To ensure comparability between treatment arms, it is assumed that the flare rate for IVMP after week 24 mirrors that observed for teprotumumab during the corresponding OPTIC follow-up period. Based on this assumption, the cumulative probability of experiencing a flare in the IVMP arm is estimated at 50.35% for proptosis and 46.29% for diplopia.

Discontinuation

The probability of discontinuation for teprotumumab was derived from pooled IPD on all-cause discontinuations from the pooled Phase 2 and OPTIC Phase 3 trials. As trial data covered a 24-week period, discontinuation rates were converted to 6-week probabilities to align with the cycle length in the health economic model. For IVMP, discontinuation rates were sourced from Kahaly et al. (2018), which is considered relevant due to its sample size (N=164) and dosing regimen aligned with model assumptions (52). All-cause discontinuation rates were reported for the 12-week and 24-week periods and, as with teprotumumab, were converted to 6-week probabilities. Due to limited availability of time-dependent discontinuation data, a constant probability was assumed across all cycles. The resulting per-cycle probability of discontinuation was 2.18% for teprotumumab and 1.34% for IVMP.

Transition probabilities applied in the initial model cycle

Table 31 and Table 32 present the initial transition probabilities applied in the health economic model for teprotumumab and IVMP. These transition probabilities illustrates the transition from baseline to cycle 1. The transition probabilities for the teprotumumab arm are derived from pooled data from the Phase 2 study and the OPTIC Phase 3 study (7, 8). The transition probabilities for the IVMP treatment arm are estimated based on the de novo ITCs (27).

Table 31. Transition probabilities in the health economic model for Teprotumumab from baseline to cycle 1

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
Small Proptosis, No Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
	LP, CD	[redacted]		
Large Proptosis, No Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		
	LP, CD	[redacted]		
Small Proptosis, Intermittent/Inconstant Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		
	LP, CD	[redacted]		
Large Proptosis, Intermittent/Inconstant Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		
	LP, CD	[redacted]		
Small Proptosis, Constant Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		
	LP, CD	[redacted]		
Large Proptosis, Constant Diplopia	SP, ND	[redacted]		Pooled Phase 2 and OPTIC
	LP, ND	[redacted]		
	SP, ID	[redacted]		
	LP, ID	[redacted]		
	SP, CD	[redacted]		
	LP, CD	[redacted]		

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Table 32. Transition probabilities in the health economic model for IVMP from baseline to cycle 1

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
Small Proptosis, No Diplopia	SP, ND	87%		De novo ITCs
	LP, ND	0%		
	SP, ID	13%		
	LP, ID	0%		
	SP, CD	0%		
	LP, CD	0%		

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
Large Proptosis, No Diplopia	SP, ND	23%		De novo ITCs
	LP, ND	64%		
	SP, ID	4%		
	LP, ID	10%		
	SP, CD	0%		
	LP, CD	0%		
Small Proptosis, Intermittent/Inconstant Diplopia	SP, ND	41%		De novo ITCs
	LP, ND	0%		
	SP, ID	52%		
	LP, ID	0%		
	SP, CD	7%		
	LP, CD	0%		
Large Proptosis, Intermittent/Inconstant Diplopia	SP, ND	11%		De novo ITCs
	LP, ND	30%		
	SP, ID	14%		
	LP, ID	38%		
	SP, CD	2%		
	LP, CD	5%		
Small Proptosis, Constant Diplopia	SP, ND	12%		De novo ITCs
	LP, ND	0%		
	SP, ID	36%		

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
	LP, ID	0%		
	SP, CD	53%		
	LP, CD	0%		
Large Proptosis, Constant Diplopia	SP, ND	3%		De novo ITCs
	LP, ND	9%		
	SP, ID	9%		
	LP, ID	26%		
	SP, CD	14%		
	LP, CD	39%		

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Table 31 and Table 32 present the corresponding transition matrices for teprotumumab and IVMP for the first transition from baseline to cycle 1. Transition matrices for subsequent cycles (cycle 2 to 4) are provided in Appendix E.2.4.

Table 33. Transition matrix for Teprotumumab: Baseline to cycle 1

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Table 34. Transition matrix for IVMP: Baseline to cycle 1

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	87%	0%	13%	0%	0%	0%
LP, NP	23%	64%	4%	10%	0%	0%
SP, ID	41%	0%	52%	0%	7%	0%
LP, ID	11%	30%	14%	38%	2%	5%
SP, CD	12%	0%	36%	0%	53%	0%
LP, CD	3%	9%	9%	26%	14%	39%

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Internal validity

The internal validity of the transition probabilities is supported by the close alignment between the clinical data used and the structure of the model. Patient movement between health states is driven by observed transitions in proptosis and diplopia, with transition probabilities applied to the distribution of patients across health states in each model cycle to derive subsequent state occupancy. This ensures that modelled transitions during the observed study period reflect empirically observed changes in disease severity.

For teprotumumab, transition probabilities up to week 24 are derived from pooled individual patient data from the Phase 2 and OPTIC Phase 3 trials. Pooling data across trials increases the robustness and representativeness of the transition estimates and allows differences in transition patterns across health states to reflect observed heterogeneity in patient response. Transitions are based on observed movements between proptosis and diplopia categories at six-weekly visit time points, ensuring consistency between the clinical data and the model structure.

For IVMP, transition probabilities during the treatment period are derived through de novo ITCs and applied within the same health-state framework as teprotumumab. This approach is used in the absence of head-to-head comparative evidence and maintains internal consistency by ensuring that differences between treatment arms are driven by relative treatment effects rather than structural differences in the model or health-state definitions.

Internal validity is further supported by the explicit consideration of alternative extrapolation approaches and their subsequent rejection. Methods such as last observation carried forward and averaging across available transition matrices were explored but not selected due to small sample sizes, heterogeneity across timepoints, and the risk of generating structurally unstable transition matrices. By avoiding reliance

on uncertain or implausible long-term transition estimates, the selected approach preserves consistency within the model.

In addition, the transition probability calculations and overall model implementation have been subject to systematic internal quality checks, including verification of calculations and review of methodological assumptions. Comparator transition derivations have also been reviewed independently to ensure methodological accuracy.

External validity

The assessment of external validity focuses on the clinical plausibility of the transition probabilities in relation to evidence from external sources. Robust long-term follow-up data beyond week 24 are not available for either teprotumumab or IVMP. Rather than extrapolating long-term transition probabilities based on limited or asymmetric evidence, the model adopts a conservative approach in which patients are assumed to remain in their current health states beyond the observed trial period unless a disease flare occurs.

This approach is considered clinically plausible in the context of the available evidence and avoids over-extrapolation of treatment effects based on small sample sizes. Applying the same long-term assumption across treatment arms ensures that comparative results are not biased by differential availability of follow-up data and supports the external validity of the comparison.

Where external evidence is available, it is incorporated to inform clinically relevant transitions. In particular, published evidence on disease flaring following IVMP treatment is used to inform flare-related transitions, ensuring that long-term disease worsening is anchored in observed clinical patterns.

9.4 Summary and Validity of Extrapolated Patient Transitions

Table 35 summarizes the modelled mean time (years) spent in each health state for the intervention arm (teprotumumab) and the comparator arm (IVMP). The estimates are undiscounted, incorporate half-cycle correction, and are adjusted for background mortality. In both arms, total life years are identical (32.29 years), reflecting that mortality in the model is applied as general population mortality and does not differ by treatment arm.

The distribution of time across the TED health states differs between arms and is consistent with the patterns observed in the Markov traces. In Table 27, teprotumumab is associated with more time in less severe symptom states, in particular “Small proptosis, no diplopia” (10.23 vs 3.00 life years) and “Small proptosis, intermittent/inconstant diplopia” (7.08 vs 4.86). Conversely, IVMP accrues more time in the more severe “large proptosis” states and in the post-surgical pathway. For example, teprotumumab accrues fewer life years in “Large proptosis, intermittent/inconstant diplopia” (1.85 vs 4.75) and “Large proptosis, constant diplopia” (0.58 vs 2.95), and fewer years in the post-surgery state (5.62 vs 8.76) as well as fewer years in the surgery state itself (0.73 vs 1.13). These differences are driven by the underlying transition structure of

the model, whereby patients in worse proptosis and diplopia health states have higher probabilities of transitioning to surgery, resulting in a greater proportion of patients in the IVMP arm entering the surgery and post-surgery health states. Duration of treatment is longer for teprotumumab than IVMP (0.43 vs 0.23 years), which is consistent with the modelled treatment course settings.

Table 35. Modelled means in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	Teprotumumab	IVMP	Difference
Total life years	[redacted]	32,29	[redacted]
Life years in SP, ND	[redacted]	3,00	[redacted]
Life years in LP, ND	[redacted]	4,96	[redacted]
Life years in SP, ID	[redacted]	4,86	[redacted]
Life years in LP, ID	[redacted]	4,75	[redacted]
Life years in SP, CD	[redacted]	1,88	[redacted]
Life years in LP, CD	[redacted]	2,95	[redacted]
Life years in Surgery	[redacted]	1,13	[redacted]
Life years in Post surgery	[redacted]	8,76	[redacted]
Duration of treatment	[redacted]	0,23	[redacted]

Abbreviations: SP, ND, small proptosis, no diplopia; LP, ND, large proptosis, no diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; SP, CD, small proptosis, constant diplopia; LP, CD, large proptosis, constant diplopia.

Figure 2 and

Figure 3 show the modelled health-state occupancy over the lifetime horizon for teprotumumab and IVMP, illustrating how the cohort is distributed across the six proptosis/diplopia health states, the surgery and post-surgery states, and the absorbing state of death. As background mortality is applied equally across treatment arms, the proportion of patients in the “Dead” state increases over time and approaches the full cohort by the end of the horizon in both arms.

During the observation period (weeks 0–24), the Markov traces reflect redistribution across proptosis and diplopia states based on trial-informed transitions, capturing on-treatment changes in symptom severity. Beyond this period, the base-case extrapolation assumes that patients remain in their achieved proptosis/diplopia health state, with subsequent movement driven primarily by background mortality and, where applicable, transitions into surgery and post-surgery according to the model structure. This conservative “remain in state” approach was selected to avoid implausible long-term behaviour when extrapolating from limited observed data.

Overall, the resulting transition patterns are clinically plausible. Identical life years across arms are consistent with the assumption that TED does not affect mortality, while the greater time spent in less severe health states and reduced time in severe and surgical states under teprotumumab align with the modelled symptom improvements. The explicit timing and sequencing of surgery further ensure stable and interpretable

health-state occupancy over time without introducing speculative long-term disease dynamics.



Figure 2: Distribution of patients across health states over the model time horizon – teprotumumab



Figure 3: Distribution of patients across health states over the model time horizon – IVMP

10. Health-Related Quality of Life

10.1 Overview

Table 36. Overview of included instruments for measuring health-related quality of life

Instrument	Median follow-up time and data-cut	Use	Source	Reference to description
EQ-5D-5L	Week 24 (June 14, 2023)	Clinical effectiveness	OPTIC-J (27)	Section 10.2.1
GO-QOL	Week 24 (February 19, 2019)	Clinical effectiveness	OPTIC Phase 3 (8)	Section 10.2.2

Table 37. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
TTO	Health state utilities	Smith et al. (2023) (59)	Systematic literature search
TTO	Disutilities	Matza et al. (2013) (6)	Systematic literature search

10.2 Instruments

10.2.1 EQ-5D-5L

10.2.1.1 Study Design and Instrument EQ-5D-5L

EQ-5D data has only been gathered in a study of teprotumumab named OPTIC-J, which were conducted in a strictly Japanese patient population consisting of 54 patients in total with active moderate to severe TED, as described in the study by Hiromatsu et al. (2025) (69). It has not been possible to identify any other teprotumumab studies, which included the collection of EQ-5D data.

The study was a randomized, double-blinded placebo-controlled multicenter phase 3 trial, where patients were randomly assigned 1:1, stratified by smoking status, to receive either teprotumumab or placebo. Patients were screened 4 weeks before the baseline visit and received teprotumumab or placebo once every three weeks at week 3, 6, 9, 12, 15, 18 and 21. Last patient visit occurred at week 24. Patient baseline characteristics are presented in Appendix G.6.

EQ-5D data from OPTIC-J has not been used in this application due to several challenges. First, EQ-5D-5L was included only as an exploratory efficacy endpoint in OPTIC-J, since the tool was not expected to be sensitive to changes in HRQoL. It is well documented that EQ-5D-5L lacks sensitivity for diseases causing visual impairment. EQ-5D-5L includes only five broad domains and does not contain any vision-specific or appearance-related dimensions. This is a major limitation for patients withTED. The most burdensome symptoms for TED patients include visual disturbances, orbito-facial changes which often results in patients with TED withdrawing themselves from activities that involve contact with other persons and diminished self-esteem. Existing literature further confirms the lack of sensitivity of EQ-5D for diseases causing visual impairment; Luo et al. (2015), Gandhi et al. (2020), and Rajagopalan et al. (2005) concluded that EQ-5D, in conditions involving visual impairment, was considered to be inferior to disease-specific alternatives (70-72). This is supported by the NICE DSU, as they acknowledge that EQ-5D is probably not appropriate for assessing specific forms of visual impairment QoL (73). However, beyond visual impairment, orbito-facial changes can also substantially affect the HRQoL of patients with TED, yet these effects may not be adequately captured by the EQ-5D-5L either. As a result, reliance on EQ-5D-5L alone risks underestimating both disease burden and treatment benefits, supporting the need for incorporation of TED-specific QoL instruments.

Secondly, TED presents differently in Japanese/East Asian and Caucasian patients despite sharing the same underlying autoimmune pathophysiology. In Japanese and other East Asian populations, TED often appears less externally dramatic, with less pronounced proptosis and subtler eyelid changes, even in patients with clinically significant orbital disease. This is thought to be largely related to anatomical differences, including smaller orbital volume and greater apical crowding, which may predispose East Asian patients to compressive complications such as dysthyroid optic neuropathy (DON) at lower degrees of proptosis. Several Asian cohort studies have also reported relatively greater

extraocular muscle involvement, more restrictive myopathy, and a higher frequency of diplopia. These phenotypic differences are clinically important because severe disease in Japanese/East Asian patients may be underestimated if clinicians rely primarily on visible proptosis or classic external appearance (74, 75).

10.2.1.2 Data Collection EQ-5D-5L

At baseline, week 6, week 12, and week 24, patients filled out the EQ-5D-5L questionnaire, both in the placebo group and the active treatment group. All participants filled out the questionnaire at all four visits, which shows that data represents the answers for all participants in the ITT population. Since all patients answered the questionnaire at all four planned visits, no table showing missing observations, percentage completed, etc. is shown. All data were collected and transformed using the Japanese tariff for EQ-5D-5L (73).

Table 38. Overview of responses

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Measurement time point 1	NA	NA	NA	NA
Measurement time point 2	NA	NA	NA	NA
Measurement time point 3	NA	NA	NA	NA

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 39. Overview of responses by health states

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Health state 1	NA	NA
Health state 2	NA	NA

10.2.1.3 Results EQ-5D-5L

EQ-5D-5L data was collected throughout the entire study period to reflect any change in HRQoL during treatment. The baseline value of patients in the teprotumumab treatment group was statistically significantly lower than the same value measured in the placebo treatment group. No explanation can be found in baseline patient characteristics, indicating a skewing which could lead to one group having a significantly lower QoL at baseline. Values for all other timepoints indicate no difference between the two treatment groups, and no difference over time within each treatment group from week 6 and forward. The lack of differences over time and across treatment arms for most timepoints highlights the lack of sensitivity of the EQ-5D for visual impairments alongside orbito-facial changes leading to disfigurement, as the results for the primary endpoint of the OPTIC-J study showed a significant difference in proptosis response (24/27 patients in the teprotumumab treatment group vs. 3/27 patients in the placebo treatment group) (69). As described in Section 10.1, using EQ-5D for measuring HRQoL in TED and from OPTIC-J is not considered relevant for this application.

EQ-5D-5L results from the OPTIC-J study were not estimated based on the health states included in the health economic model. Therefore, these data cannot be used in a sensitivity analysis exploring the impact of utilizing EQ-5D data for estimating the HRQoL. Results are presented in Table 40.

Table 40. Results for EQ-5D-5L

	Teprotumumab	Placebo	Difference
	Mean (SD)	Mean (SD)	Difference (95% CI)
Baseline	0.787 (0.1799)	0.871 (0.1194)	-0.084
Week 6	0.889 (0.1017)	0.880 (0.1188)	0,009
Week 12	0.873 (0.1649)	0.884 (0.1465)	-0,011
Week 24	0.879 (0.1799)	0.882 (0.1287)	-0,003

95% CI is not available

10.2.2 GO-QoL

10.2.2.1 Study Design and Instrument GO-QoL

The Graves' ophthalmopathy - quality of life (GO-QoL) questionnaire is the most widely used disease-specific QoL instrument for patients with TED, making it highly relevant for use in this application (4). The GO-QoL is a valid QoL instrument, with good reliability and high-face validity of both subscales included in the instrument. Construct validity and internal consistency of the disease-specific questionnaire have been assessed, further showing good reliability and high-face validity, while correlations with other measures support construct validity in the specific patient population considered for this application (76). The minimal clinically important difference (MCID) has been estimated at approximately 6 points, underlining the instrument's sensitivity to detecting meaningful changes in PROs. GO-QoL is recommended in international guidelines for the evaluation of TED and is an appropriate measure of disease impact (1, 76).

In the OPTIC trials, patients' HRQoL was assessed through the GO-QoL questionnaire, as recommended by the ETA guidelines (1). GO-QoL is a 16-item self-administered questionnaire divided into 2 subsets and used to assess the perceived effects of TED by the subjects on their daily physical activity as it relates to visual function, and their psychosocial functioning. Each subset consists of 8 questions, and answers to these questions are transformed to a 0-100 point scale for each of the two subsets. GO-QoL was included in the study, as the EQ-5D scale was not considered to be sensitive enough for TED patients.

Both subscales were evaluated and presented separately, while an overall score was also calculated. The GO-QoL overall score was estimated by calculating the sum of scores from each set of 8 questions and transforming these to a scale from 0 to 100 – one for the subscale for visual functioning, one for the subscale for appearance and one for the overall combined score. Higher values correspond to better QoL.

10.2.2.2 Data Collection GO-QoL

At baseline, week 6, week 12, and week 24, patients filled out the two subscales of the GO-QoL questionnaire, both in the placebo group and the active treatment group. The number of missing observations was very low, indicating that the results of the GO-QoL questionnaire are representative of almost all patients initially included in the clinical study. A mixed model for repeated measure (MMRM) analysis was conducted for all continuous secondary endpoints, including GO-QoL. The mixed model does not impute missing data or delete incomplete subject records; it uses maximum likelihood methodology, which does not require a balanced design unlike other methods. The estimates from the mixed models are more stable and are unbiased if the used correlation is correct. The mixed model is robust for missing data at random.

[redacted]patients were prematurely discontinued from the 24-week double-masked treatment period: [redacted]from the placebo arm and [redacted]from the teprotumumab arm. [redacted]patient in the placebo group discontinued after the [redacted]. The other patient who discontinued from placebo did

so after [redacted]. Of the [redacted] patients from the teprotumumab treatment arm who discontinued treatment, [redacted] did so due to an [redacted] at the [redacted] of teprotumumab. [redacted] discontinued due to [redacted] of teprotumumab. As [redacted] out of [redacted] of these patients discontinued due to [redacted], the missing data is not expected to result in bias of GO-QoL results.

Table 41. Overview of responses

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Baseline	83	83	100%	100%
Week 6	83	80	96%	96%
Week 12	80	79	99%	95%
Week 24	79	78	99%	94%

* Number of patients "at risk": Patients who have not died or been censored before time point *t* and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 42. Overview of responses by health states

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Health state 1	NA	NA
Health state 2	NA	NA

10.2.2.3 Results GO-QoL

GO-QoL data was collected throughout the entire study period to reflect any change in HRQoL during treatment. Mean GO-QoL questionnaire overall transformed score at

baseline was 63.26 in the teprotumumab treatment arm and 60.92 in the placebo treatment arm. With least squares (LS) mean change from baseline of 13.79 in the teprotumumab treatment arm and 4.43 in the placebo treatment arm, a statistically significant difference in the LS mean of 9.36 was estimated (95% CI: 4.08, 14.64, p <0.001), see Figure 4. LS mean changes for each treatment arm at all assessed timepoints are presented in Table 43, as well as the difference between the two treatment arms.

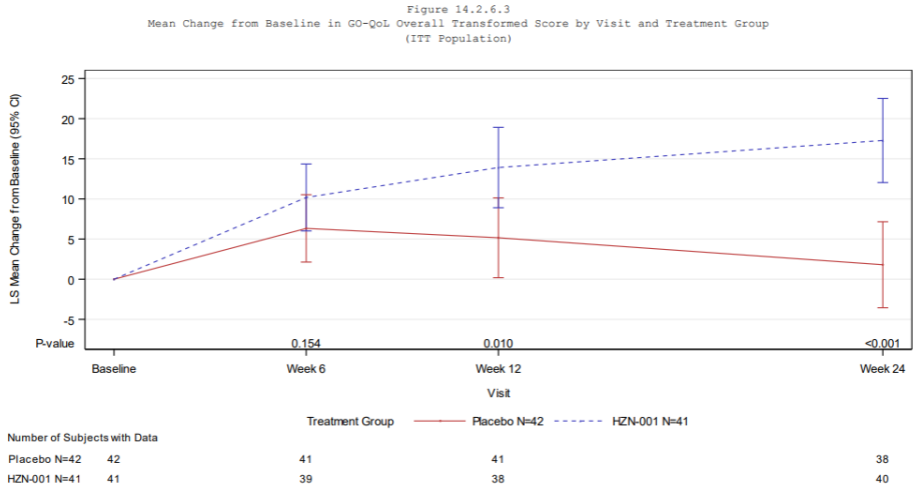


Figure 4: Depiction of the LS mean change from baseline through the different data collection time points for both teprotumumab and placebo

Abbreviations: CI, confidence interval; GO-QOL, graves' orbitopathy quality of life; HZN-001, teprotumumab; ITT, intention to treat; LS, least square; N, number; P-value, probability value.

Table 43. Results for GO-QoL

	Teprotumab	Placebo	Difference
	Mean (SD)	Mean (SD)	Difference (95% CI)
Baseline	63.26 (22.13)	60.92 (19.44)	2,34
Week 6	63.36 (21.89)	60.88 (19.68)	2,48
Week 12	77.50 (21.90)	68.40 (16.55)	9,1
Week 24	80.91 (17.63)	64.60 (18.65)	16,31

95% CI is not available

10.2.3 Summary when reporting multiple instruments

NA

10.3 Utility Values

10.3.1 Data Sources

Utility values for the health economic model were derived from a dedicated time trade-off (TTO) study, as no validated mapping algorithm exists to convert GO-QOL outcomes to EQ-5D, and no relevant EQ-5D data were identified for estimating utility values associated with the health states included in the model. EQ-5D was not collected in the Phase 2 and OPTIC Phase 3, as it was considered insufficiently sensitive to detect relevant changes in HRQoL in patients with active moderate to severe TED.

A targeted literature review was conducted to identify alternative sources of utility data. Several studies were identified; however, none provided sufficient or appropriate data to inform the health states defined in the health economic model. Consequently, utilities values for the active phase of disease were derived from a de novo TTO study conducted in a general population sample (59).

The TTO study was conducted in the United States between April 2020 and April 2021 and included members of the general public without TED (59). Although utilities were elicited in a US population, the resulting values were reviewed and validated by a Danish clinical expert, who considered them reflective of the HRQoL of patients with TED in Denmark. The utility values were age-adjusted in accordance with Section 7.3 of the Danish Medicines Council's methodological guideline (77).

In addition to the utility values applied during the active phase of disease, a separate set of health-state utility values was applied for patients entering the chronic phase of TED. A targeted literature review did not identify published utility values for chronic TED aligned with the health-state definitions used in the model. Therefore, chronic utility values were derived by applying adjustments to the TTO-based utility values reported by Smith et al. (2023) (59) , informed by published evidence demonstrating an association between disease activity and quality of life by Wang et al. (2021) (25) and supported by clinical expert input. This approach reflects evidence and clinical feedback indicating that patients experience improvements in underlying quality of life following transition to the chronic phase, primarily due to reduced inflammation and pain, while maintaining similar levels of proptosis and diplopia.

Utility values for surgery and post-surgery health states were not directly elicited in the TTO study, nor were suitable values identified in the literature. Therefore, proxy estimates were derived based on averages of the four lowest and four highest utility values reported in Smith et al. (2023) (59).

Calculation of Utility Values

Utility values were elicited using a vignette-based time trade-off (TTO) approach with a finite 10-year time horizon. The Measurement and Valuation of Health TTO protocol was applied, whereby respondents traded off years lived in a defined health state against a shorter duration in full health. Utility values were anchored at 1 for perfect health and 0 for death and were calculated directly from respondents' TTO valuations.

The TTO interviews were conducted by trained interviewers who were independent of the study authors. As utility values were directly elicited for each health state included in the health economic model, no regression-based estimation was required. Age adjustment was applied to the estimated utility values in accordance with Section 3.4.2. of the Danish Medicines Council's guideline for Health-related quality of life (78).

Utility values were applied in a phase-specific manner in the model. During the active phase of disease, utilities derived from the TTO study were applied directly to each health state. Upon transition to the chronic phase of TED, a separate set of chronic utility values was applied to reflect improvements in underlying quality of life associated with reduced inflammation and pain, while maintaining similar levels of proptosis and diplopia.

Entry into the chronic phase was assumed to occur from cycle 26 onwards. Patients entering the chronic phase were assumed to remain in the same proptosis and diplopia health states, with the only change being the utility values applied. Chronic utilities were applied only to patients who did not undergo surgery; patients receiving surgery transitioned directly to the post-surgery health state and were therefore not subject to chronic utility adjustments.

Full methodological details, including the TTO protocol, statistical analyses, clinical validation of chronic utilities, and resulting utility estimates with associated uncertainty, are provided in Appendix G.

10.3.2 Adverse Events, Comorbidity and Other State-Specific Adjustments to Utility Values

Utility values applied in the health economic model were adjusted to account for treatment-related adverse events (AEs) and intravenous (IV) administration, as these impacts were not expected to be fully captured by the health-state utility values elicited through the TTO study. No additional adjustments were applied for comorbidities beyond those implicitly captured within the health-state definitions.

IV administration disutility

A disutility associated with IV administration was applied to reflect the temporary reduction in quality of life experienced during treatment administration. Disutility estimates were based on published values reported by Matza et al. (2013), which assessed disutility associated with different durations of monthly IV infusion (6). These estimates were adapted to reflect the administration schedules relevant to teprotumumab and comparators by interpolating between reported infusion durations and converting the resulting values to daily disutilities. The daily disutility was multiplied by the number of IV administrations per model cycle to derive the total IV administration disutility applied in each cycle.

Adverse event disutilities

All disutilities have been sourced from external clinical trials. Disutilites for grade ≥3 AEs occurring in ≥5% of the population were sourced directly from a number of different publications, as listed and presented in Appendix G. As described in G.4, only three AEs were included in the base-case health economic model. Two of these AE, 10-fold increase of aminotransfera5-fold 5-fold increase of gamma-glutamyl transferase, were assumed to entail such a low disutility, that it was not included in the health economic model. The last included AE, hyperglycemia, was assumed to entail a disutility of -0.01, based on study data from Drummond et al. (2018) and Aktaran et al. (2007) (55, 79).

10.3.3 Results for Utility Values

Utility values applied in the base case health economic model are presented in Table 44. The table summarizes the utility values used for each health state, including utilities applied during the active and chronic phases of disease, as well as utility values for surgery and post surgery health states, where applicable. In addition, Table 44 presents the disutilities applied for intravenous administration and selected adverse events.

Uncertainty around utility values was explored through one-way sensitivity analyses (OWSA), in which individual utility and disutility parameters were varied within predefined bounds. No additional scenario analysis using alternative sets of utility values were conducted, as no suitable alternative utility sources aligned with the model health-state definitions were identified.

Table 44. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Main analysis			
SP, ND (Acute HS)	0.60 [0.54-0.67]	TTO	Smith et al 2023 (59), Section 10.3Smith et al 2023 (80), Section 10.3
LP, ND (Acute HS)	0.46 [0.40-0.52]	TTO	Smith et al 2023 (59), Section 10.3
SP, ID (Acute HS)	0.52 [0.45-0.58]	TTO	Smith et al 2023 (59), Section 10.3
LP, ID (Acute HS)	0.43 [0.36-0.49]	TTO	Smith et al 2023 (59), Section 10.3
SP, CD (Acute HS)	0.34 [0.29-0.40]	TTO	Smith et al 2023 (59), Section 10.3
LP, CD (Acute HS)	0.30 [0.24-0.36]	TTO	Smith et al 2023 (59), Section 10.3

	Utility value [95% CI]	Instrument, preference weight	Source and reference
SP, ND (Chronic HS)	0.72 [0.65-0.81]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
LP, ND (Chronic HS)	0.55 [0.48-0.63]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
SP, ID (Chronic HS)	0.63 [0.54-0.70]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
LP, ID (Chronic HS)	0.47 [0.40-0.54]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
SP, CD (Chronic HS)	0.37 [0.32-0.44]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
LP, CD (Chronic HS)	0.33 [0.26-0.40]	TTO	Smith et al 2023 and Wang et al. 2021 (25, 59), Section 10.3
Surgery	0.38	N/A	Smith et al 2023 (59).
Post-surgery	0.50	N/A	Smith et al 2023 (59).
IV administration, 1 hour	-0.0009	TTO	Matza et al. 2013 (6)
IV administration, 1.5 hours	-0.0011	TTO	Matza et al. 2013 (6)
Hyperglycemia	-0.01	Literature-derived model disutilities; non-preference-based QoL instrument	Drummond et al. 2018 and Aktaran et al. 2007 (55, 79)

Abbreviations: LP, CD, large proptosis, constant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; LP, ND, large proptosis, no diplopia; SP, CD, small proptosis, constant diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; SP, ND, small proptosis, no diplopia; HS, health state

11. Calculations of Costs

11.1 Drug Costs

11.1.1 Drug Costs for Intervention and Comparator

Teprotumumab is dosed at 10 mg/kg bodyweight for the first infusion, followed by a dose of 20 mg/kg of bodyweight for all subsequent infusions. Teprotumumab is infused Q3W for the entire treatment period. Teprotumumab is only available as a 500 mg vial at a preliminary pharmacy purchase price (PPP) of 44,868.60 Danish Krone (DKK), with no expected possibility of vial sharing. The RDI of teprotumumab was based on the recorded compliance in the Phase 2 and OPTIC Phase 3 trials, showing a pooled compliance of 98.21% (7, 8).

IVMP is dosed at 500 mg infusions for the first six weeks, followed by 250 mg infusions for the last six weeks, representing a cumulative dose of 4.5 g, as recommended in the EUGOGO guidelines (1). IVMP is infused once weekly for the entire treatment period. As no compliance data were reported for IVMP, it is assumed that IVMP has the same compliance rate as teprotumumab, being 98.21%. The cost of IVMP is based on official Danish price listings from Medicinpriser.dk, using the pharmacy purchasing price (PPP) (81).

In the base case analysis, an average patient weight of 74.67 kg was utilized, based on the average weight of patients included in all five teprotumumab studies (7, 8, 41, 68, 82).

A Danish register study of moderate to severe TED by Laurberg et al. (2012) reported a mean body weight of 70 kg based on 75 Danish patients from the period 2001-2009, with approximately 81% being women (29). This female predominance is consistent with the epidemiology of TED and aligns with the modelled population, in which approximately 73% of patients are women. To further support the reduction in average patient weight, more recent Danish population-level data from Statens Institut for Folkesundhed (2021) show a mean body weight of 71.4 kg among adult women and 86.4 kg among adult men (83). When interpreting these data in the context of a predominantly female TED population, greater emphasis is placed on the female mean body weight. Overall, the Laurberg et al. study and the more recent Danish population data support the average patient weight applied in the base case analysis.

Overall, the selected base case weight of 74.67 kg is considered appropriate for a Danish population with moderate to severe TED and has further been validated by a Danish clinical expert.

Two approaches have been applied for calculating wastage: (1) the rounding method and (2) the method of moments. In the rounding method, all individual infusions are rounded up to the nearest whole vial, ensuring that no partial vials are considered. The method of moments is used in the model as it is considered more accurate, as it accounts for the

distribution of patient weights. It is based on a lognormal transformation of the mean and SD of the average patient weights of all five teprotumumab studies. When using the average patient weight options from the pooled Phase 2 and OPTIC Phase 3 trials the method is based on the individual mean and SD of patient weights reported in the two studies. From this, a lognormal distribution of vial usage is derived, and a weighted average number of vials per infusion is calculated.. While the underlying calculations for the method of moments for the weight of OPTIC 3 and Pooled data are hardcoded in the model, they cannot be presented in detail, as they rely on confidential IPD.

11.1.2 Drug Costs for Subsequent Treatment

After receiving their 1L treatment, some patients may need further treatment. Therefore, the model considers a course of 2L treatment for a proportion of non-responders, following EUGOGO guidelines (1). Only the cost of subsequent treatment is included in the model, applied to 100% of patients in the four most severe health states (excludes 'Small proptosis, no diplopia', and 'Small proptosis, intermittent/inconstant diplopia'). Hence, all patients who are not in the 'Small proptosis, no diplopia' (SP, ND) or 'Small proptosis, intermittent/inconstant diplopia' (SP, ID) health states at the time they finish their 1L treatment will receive 2L treatment. The cost of subsequent treatment is applied as a one-off cost in the cycle after patients complete their 1L treatment (cycle 5 for teprotumumab and cycle 3 for IVMP). In addition, subsequent treatment costs are also applied for any patients that discontinue their initial 1L treatment course before completion, or for patients experiencing their first flare after treatment completion, applied as a one-off cost in the cycle at which discontinuation or first flare occurs. A RDI of 100% is assumed for tocilizumab, rituximab, and MMF, while 98.21% is used for IVMP, as expected for the 1L treatment described in section 11.1.1. No waste was assumed for rituximab, IVMP, and MMF, as the dose of these treatments all correspond to the packaged dosing. The method of rounding was used for calculating waste associated with tocilizumab treatment.

Table 45: Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Tocilizumab (IV infusion)	8 mg/kg	100%	Administered once	No
Rituximab (IV infusion)	500 mg	100%	Administered once	No
IVMP (IV infusion)	500 mg for first six weeks 250 mg for last six weeks	98.21%	Weekly	No
MMF (oral administration)	1,000 mg	100%	Daily for 24 weeks	No

For the distribution of subsequent treatments, input was obtained from a Danish clinical expert. In accordance with the treatment guidelines used in Denmark, the estimates from the Danish clinical expert were applied in the model, see Table 46. In patients experiencing significant proptosis at the stage of 2L treatment, tocilizumab treatment is considered. However, the proportion of patients for whom this applies is highly uncertain and expected to be very low. Therefore, it is not included in the calculation of costs of subsequent treatment.

Table 46: Distribution of subsequent treatments

2L treatment	Teprotumumab	IVMP
Tocilizumab	0%	10%
Rituximab	0%	10%
IVMP	95%	55%
MMF	5%	25%

2L, second-line; IVMP, intravenous methyprednisolone; MMF, mycophenolate mofetil.

11.2 Hospital Costs

11.2.1 Administration

Administration costs associated with IV infusions have been included for both teprotumumab and IVMP. The frequency of administration costs follows the dosing frequencies described in section 11.1.

Table 47. Assumptions regarding administration costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
IV infusion	A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (BVAA62) Medicingivning ved intravenøs infusion	02MA01 Øvrige kontakter ved øjensygdomme	1773

*Include other patient information if relevant for the choice of DRG group; A = action diagnosis

11.2.2 Disease Management

Disease management costs are included to reflect the costs and healthcare resource use associated with routine monitoring and disease management.

Healthcare resource use categories included are artificial tears, ophthalmic gels/ointments, computed tomography (CT) scans, magnetic resonance imaging (MRI), ophthalmologist visits, and endocrinologist visits. These categories were identified through a targeted literature review, and their frequency of use per cycle were estimated by a Danish clinical expert. The frequency of some included categories varies depending on disease severity and is therefore described for each included health state individually. For very few patients, CT and MRI scans may be performed more than once during their lifetime. However, as this number is expected to be very low and uncertain, based on the opinion of a Danish clinical expert, an average of one CT scan and one MRI scan per patient is assumed. All disease management costs in the surgery health state are assumed to equal the average of the four most severe health states. For the post-surgery health state, management costs are assumed to equal the average of the four least severe health states.

Table 48. Assumptions regarding disease management costs

Activity/pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Artificial tears (84)		Lifetime	NA	NA	107.45 DKK /60 = 1.79 DKK
SP, ND	4 x day				
LP, ND	8 x day				
SP, ID	4 x day				
LP, ID	8 x day				
SP, CD	4 x day				
LP, CD	8 x day				
Ophthalmic gels/ointments (85)	1 x day	Lifetime	NA	NA	97 DKK/ (300/2)=0.65 DKK
CT scan	1 x per patient in entire time horizon		A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (UXCA20) CT-skanning af orbita	30PR06 CT-scanning, kompliceret (2026)	2,861 DKK
MRI scan	1 x per patient in entire time horizon		A (DH052B) Eksoftalmi forårsaget af ødem i øjenhule	30PR03 MR-scanning, ukompliceret (2026)	2,264 DKK

Activity/pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
			T (DH506) Strabismus mechanicus P: (UXMA20) MR-skanning af orbita		
Ophtalmologist visit		Lifetime	NA	Takstkort 14b, Øjenspecialet, Senere konsultation (2026)	241.07
SP, ND	Every 5 months				
LP, ND	Every 3 months				
SP, ID	Every 10 weeks				
LP, ID	Every 10 weeks				
SP, CD	Every 2 months				
LP, CD	Every 2 months				
Endocrinologist visit		Lifetime	A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (BVAA91) Samtale med speciallæge	01MA01 Øvrige kontakter ved øjensygdomme	1,773 DKK
SP, ND	Every 3 months				
LP, ND	Every 3 months				
SP, ID	Every 3 months				
LP, ID	Every 3 months				
SP, CD	Every 10 weeks				
LP, CD	Every 10 weeks				

Abbreviations: LP, CD, large proptosis, constant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; LP, ND, large proptosis, no diplopia; SP, CD, small proptosis, constant diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; SP, ND, small proptosis, no diplopia

11.2.3 Treatment Monitoring

Hearing appointments were included in the model as part of treatment monitoring for patients receiving teprotumumab. A total of three hearing appointments per patient are assumed, corresponding to assessments before, during, and after treatment to monitor potential hearing-related adverse events. In the health economic model, these hearing appointments are captured as a one-off cost applied in the first model cycle and are applied to all patients treated with teprotumumab, regardless of health state. No costs for hearing appointments are included for the IVMP treatment arm.

Table 49. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Hearing appointment	One hearing appointment before, during, and after treatment			Takstkort 11A, Øre-, næse- og halsspecialet, Undersøgelse af høreevnen for rene toner (Toneaudiometri) (2026)	293,8 DKK

11.2.4 Management of adverse events

Costs for management of AE are applied in the model during cycles in which patients receive active treatment. For teprotumumab, this includes the first four cycles and for IVMP, this constitutes the first two cycles. AE costs are not applied to patients who have discontinued treatment. The AEs included in the model, along with their per-cycle probabilities, are described in Appendix F.1.4.

The DRG-tariff 07MA06 (Akut infektiøs eller toksisk leversygdom) has been used for both a 10-fold increase of aminotransferase and a 5-fold increase of gamma-glutamyl transferase, based on the diagnosis code DK719 (Toksisk leversygdom UNS). The DRG-tariff 23MA03 (Symptomer og fund, u. kompl. bidiag.) is based on the diagnosis code DR739 (Hyperglykæmi UNS).

Table 50. Assumptions regarding costs for the management of adverse events

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	Teprotumumab	IVMP			
Hyperglycemia	0%	6.25%	A: (DR739) Hyperglykæmi UNS B: (DH506) Strabismus mechanicus B: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule P: (BBHF32) Behandling med højdosis binyrebarkhormon	23MA03 Symptomer og fund, u. kompl. bidiag. (2026)	5,737 DKK

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	Teprotumumab	IVMP			
10-fold increase of aminotransferase	0%	6.25%	A: (DK719) Toksisk leversygdom UNS B: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule B: (DH506) Strabismus mechanicus P: (BBHF32) Behandling med højdosis binyrebarkhormon Varighed: >=12 timer (lang)	07MA06 Akut infektiøs eller toksisk leversygdom (2026)	47,074 DKK
5-fold increase of gamma-glutamyl transferase	0%	6.25%	A: (DK719) Toksisk leversygdom UNS B: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule B: (DH506) Strabismus mechanicus P: (BBHF32) Behandling med højdosis binyrebarkhormon Varighed: >=12 timer (lang)	07MA06 Akut infektiøs eller toksisk leversygdom (2026)	47,074 DKK

11.2.5 Other Hospital Costs

As described in section 4.2, three types of surgery are utilized for the treatment of TED once the disease reaches the chronic state. These surgeries are orbital decompression surgery, strabismus surgery, and eyelid surgery. The probabilities that a patient needs these different surgeries once the disease is chronic depends on the disease severity of the patient, since the surgeries aim directly at reducing disease severity by minimizing proptosis and diplopia. Hence, the proportion of patients undergoing surgery depends on the health state they are in. On average, it takes patients 1.5 years to reach the

chronic health state. However, no data is available to inform the proportion of patients moving to surgery from each of the health states. Therefore, assumptions for the proportion of patients in each health state that undergoes surgery is based on input from UK clinical experts, which were then validated by the Danish clinical expert consulted for this application (27). The probabilities of moving to the surgery health state after 1.5 years, corresponding to approximately 14 cycles in the model, are presented in Table 51.

Table 51: Proportion of patients from each health state transitioning to the surgery health state

	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Proportion of patients	5.0%	38.1%	5.0%	41.3%	43.8%	43.8%

Abbreviations: LP, CD, large proptosis, constant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; LP, ND, large proptosis, no diplopia; SP, CD, small proptosis, constant diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; SP, ND, small proptosis, no diplopia

Surgical procedure costs are applied as a one-off cost (lumpsum) during the cycle in which patients enter the surgery state. Since TED patients typically undergo more than one surgery, the average number of surgeries per eligible patient, calculated by health state, is used to determine the total surgical procedure cost. The number of surgeries for each health state was estimated from a UK clinician consultation and is presented in Table 52 (27). During consultation with a Danish clinical expert, it was assessed that the average number of surgeries in Danish clinical practice may be higher than those reported in the UK. To address this uncertainty, a deterministic sensitivity analysis was conducted in which the average number of surgeries per patient was increased by 20%. The number of surgeries was assumed to be independent of health states, and the treatment arm.

Table 52: Number of surgeries for all health states

Average number of surgeries per patient	SP, ND	LP, ND	SP, ID	LP, ID	SP, CD	LP, CD
Orbital decompression	0.66	0.66	0.66	0.66	0.66	0.66
Strabismus	0.88	0.88	0.88	0.88	0.88	0.88
Eyelid	1.00	1.00	1.00	1.00	1.00	1.00
Total	**2.53**	**2.53**	**2.53**	**2.53**	**2.53**	**2.53**

Abbreviations: LP, CD, large proptosis, constant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; LP, ND, large proptosis, no diplopia; SP, CD, small proptosis, constant diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; SP, ND, small proptosis, no diplopia.

The costs associated with each type of surgery were sourced from the interactive DRG system. The rates used for estimating the costs of each surgery are presented in Table 53.

Table 53: Surgery costs used in the model

Surgery	Unit cost [DKK]	DRG code	Reference
Orbital decompression	83,734	26MP15	Kraniekirurgi og kranioplastik, kompliceret A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (KCAC44) Kombineret dekompression af øjenhule
Strabismus	2,993	02MP08	Store operationer, øjenhule, øjenmuskler, konjunktiva og linse, u. generel anæstesi A: (DH506) Strabismus mechanicus T: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule P: (KCEC10) Recession og resektion af øjenmuskel
Eyelid	3,012	02MP18	Mindre operationer, øjenlåg, øjenmuskler, konjunktiva, nethinde og glaslegeme, u. generel anæstesi A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (KCBD00) Rekonstruktion af øjenlåg med sutur

Abbreviations: DKK, danish krone; DRG, diagnosis related group.

11.2.5.1 Surgical complication

The costs of complications associated with each type of surgery are included in the base case as a one-off cost (lumpsum) during the cycle in which patients transition to the surgery health state. These surgical complications are treated separately from AEs, since they apply only to the surgery state and are therefore captured under disease management in the health economic model.

Data for surgery complications were sourced from three publications identified through a targeted literature search, informing complications associated with each type of surgery respectively (86-88). Costs associated with each complication were identified through the DRG system.

Table 54: Probability of complication by surgery type

Surgical complications	Incidence complication per surgery		
Complication	**Orbital decompression**	**Strabismus surgery**	**Eyelid surgery**
New post-operative diplopia	19.00%	0.00%	0.00%
Hematoma	0.00%	0.00%	0.50%

Chemosis	0.00%	0.00%	6.00%
Lowerlid malpositioning	0.00%	0.00%	3.00%

Table 55: Costs for complications reflected after undergoing surgery

Complication	Unit cost (DKK)	DRG-code and assumptions
New post-operative diplopia	2,993	02MP08 Store operationer, øjenhule, øjenmuskler, konjunktiva og linse, u. generel anæstesi A: (DH506) Strabismus mechanicus T: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule P: (KCEC10) Recession og resektion af øjenmuskelPatient will have to undergo strabismus surgery
Hematoma	1,773	**02MA01 Øvrige kontakter ved øjensygdomme**A: (DH506) Strabismus mechanicus T: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule P (KCWD00) Reop. for overfl. blødn. eft. op. på øje el. øjenomgivelser
Chemosis	1,773	02MA01, Øvrige kontakter ved øjensygdomme (2026) A: (DH506) Strabismus mechanicus T: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule P (KCWD00) Reop. for overfl. blødn. eft. op. på øje el. øjenomgivelser
Lowerlid malpositioning	3,012	02MP18 Mindre operationer, øjenlåg, øjenmuskler, konjunktiva, nethinde og glaslegeme, u. generel anæstesi (2026) A: (DH052B) Eksoftalmi forårsaget af ødem i øjenhule T: (DH506) Strabismus mechanicus P: (KCBD00) Rekonstruktion af øjenlåg med sutur Patients will have to undergo new eyelid surgery

Abbreviations: DKK, danish krone; DRG, diagnosis related group; UNS, unspecified

11.3 Patient Costs

Patient costs were included for administration, monitoring, and surgeries. The patient costs were included as described in the DMC's supplementary guidelines of costs, with a unit cost for patient time of 200 DKK/hour and travel costs of 3.81 DKK/km (89). Based on an assumed average distance to the hospital of 20 km, transportation costs of 150 DKK were estimated per visit (89). A total travel time of 90 minutes for each visit was assumed according to the DMC's supplementary guidelines of Cost Calculation (89)

Administration of teprotumumab occurs over the span of 90 minutes for the first two administrations and 60 minutes for the remaining administrations in accordance with the

approach of the OPTIC Phase 3 study and SmPC for teprotumumab (8, 58). IVMP administration occurs over approximately two hours, based on Danish regional treatment guidelines (90). For subsequent treatment with tocilizumab or rituximab, 60 minutes for administration was assumed.

Based on the experience of a Danish clinical expert, decompression surgery lasts for 1-3 hours, strabismus surgery lasts for 1-3 hours, and eyelid surgery lasts for 30-120 minutes. Average values of 2 hours, and lastly 1 hour and 15 minutes respectively were used in the model. Patients undergoing decompression surgery in Denmark are hospitalized for 24-48 hours, 24 hours of patient time are included in the model for all such surgeries.

Assumed time estimates for monitoring activities, as well as all other patient costs included in the model, are presented in Table 56.

Table 56. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transport time	Note
Teprotumumab administration	Administration 1-2: 2 times Administration 3-8: 6 times	Administration 1-2: 1.5 hours Administration 3-8: 1 hour	90 minutes	
IVMP administration	500 mg: 6 times 250 mg: 6 times	2 hours	90 minutes	
Tocilizumab/Rituximab administration	One time	1 hour	90 minutes	
Decompression surgery	One time	2 + 24 hours	90 minutes	
Strabismus surgery	One time	2 hours	90 minutes	
Eyelid surgery	One time	75 minutes	90 minutes	
CT scan	One time	1.5 hours	90 minutes	
MRI scan	One time	1.5 hours	90 minutes	
Ophthalmologist visit	See Table 48	1 hour	90 minutes	
Endocrinologist visit	See Table 48	1 hour	90 minutes	

11.4 Other Costs

NA

12. Results

The base case results for the health economic comparison of teprotumumab vs. IVMP are presented in Table 57.

Table 57. Results, discounted estimates, half-cycle corrected (where relevant), and adjusted for background mortality

	Teprotumumab	IVMP	Difference
Drug costs	1,072,616.82	390.13	1,072,226.70
Drug costs for subsequent treatment	5,961.41	14,030.56	-8,069.15
Administration	12,979.73	19,943.81	-6,964.08
Disease management	224,973.09	237,996.25	-13,023.16
Treatment monitoring	881.13	0.00	881.13
Management of adverse events	0.00	3,051.64	-3,051.64
Patient costs	94,250.31	101,260.82	-7,010.51
Other costs, e.g., co-medication	0.00	0.00	0.00
Total costs	**1,411,662.49**	**376,673.21**	**1,034,989.28**
Life years in SP, ND	[redacted]	[redacted]	[redacted]
Life years in LP, ND	[redacted]	[redacted]	[redacted]
Life years in SP, ID	[redacted]	[redacted]	[redacted]
Life years in LP, ID	[redacted]	[redacted]	[redacted]

	Teprotumumab	IVMP	Difference
Life years in SP, CD	[redacted]	[redacted]	[redacted]
Life years in LP, CD	[redacted]	[redacted]	[redacted]
Life years in Surgery	[redacted]	[redacted]	[redacted]
Life years in Post-surgery	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs in SP, ND	[redacted]	[redacted]	[redacted]
QALYs in LP, ND	[redacted]	[redacted]	[redacted]
QALYs in SP, ID	[redacted]	[redacted]	[redacted]
QALYs in LP, ID	[redacted]	[redacted]	[redacted]
QALYs in SP, CD	[redacted]	[redacted]	[redacted]
QALYs in LP, CD	[redacted]	[redacted]	[redacted]
QALYs in Surgery	[redacted]	[redacted]	[redacted]
QALYs in Post-surgery	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained			**NA**
Incremental costs per QALY gained (ICER)			[redacted]

Abbreviations: LP, CD, large proptosis, constant diplopia; LP, ID, large proptosis, intermittent/inconstant diplopia; LP, ND, large proptosis, no diplopia; SP, CD, small proptosis, constant diplopia; SP, ID, small proptosis, intermittent/inconstant diplopia; SP, ND, small proptosis, no diplopia.

Table 58. Results per drug in combination treatments

	Drug costs
Intervention: Drug A	NA
Intervention: Drug B	NA

	Drug costs
Comparator: Drug C	NA
Comparator: Drug D	NA

12.1 Sensitivity Analyses

12.1.1 Deterministic Sensitivity Analyses

Across the scenarios assessed, the ICER ranges from approximately [redacted] DKK to [redacted] DKK per QALY gained. The greatest variation in ICER is observed when utility values, particularly for acute and chronic health states, are varied, whereas changes to cost assumptions, including the exclusion of subsequent treatment, patient time costs, and wastage, have a more limited impact on the results.

Table 59. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Incremental costs	Incremental QALYs	ICER
All adverse events >5%	1,038,433.41DKK	[redacted]	[redacted]
Lower values for all utility values	1,034,989.28DKK	[redacted]	[redacted]
Upper values for all utility values	1,034,989.28DKK	[redacted]	[redacted]
Lower values for acute utility values	1,034,989.28 DKK	[redacted]	[redacted]
Upper values for acute utility values	1,034,989.28DKK	[redacted]	[redacted]
Lower values for chronic utility values	1,034,989.28DKK	[redacted]	[redacted]
Upper values for chronic utility values	1,034,989.28DKK	[redacted]	[redacted]
Exclude subsequent treatment	1,043,058.42DKK	[redacted]	[redacted]
Exclude wastage	880,053.17DKK	[redacted]	[redacted]
Increase number of surgeries with 20%	1,033,561.44DKK	[redacted]	[redacted]

12.1.2 Probabilistic Sensitivity Analyses (PSA)

A probabilistic sensitivity analysis (PSA) was conducted to assess the total impact of parameter uncertainty across included parameters on the results of the health economic analysis. 10,000 iterations were utilized to ensure a stable mean across iterations.

The incremental cost-effectiveness plane for teprotumumab versus IVMP is presented in the scatter plot of Figure 5.



Figure 5: Incremental cost-effectiveness plane, scatterplot
Abbreviations: DKK, danish krone; QALY, quality-adjusted life years.

All of the iterations fell into the right-hand quadrant, indicating both greater efficacy and greater cost for teprotumumab relative to IVMP. The wide spread of ICER points along the X-axis suggests a low variability in incremental costs and wide variability in incremental QALYs, indicating a wide range of potential effectiveness outcomes (QALYs) for the intervention compared to IVMP. This means that while costs are relatively stable, the clinical effectiveness as reflected in QALYs is variable. This is reflective of the underlying uncertainty in key clinical effectiveness parameters due to the small sample size of the trial data and limitations in the available HRQOL data.

The cost-effectiveness acceptability curve (CEAC) is presented in
Figure 6**Error! Reference source not found.**, showing the probability that teprotumumab is a cost-effective treatment alternative compared to IVMP at different willingness-to-pay thresholds. The CEAC shows that the probability of teprotumumab being cost-effective increases as the cost-effectiveness threshold rises, reaching 50% at a threshold of [redacted] DKK/QALY.



Figure 6: Cost-Effectiveness Acceptability Curve for Teprotumumab vs. IVMP
Abbreviations: DKK, danish krone.

A convergence analysis was conducted to assess the stability of the probabilistic sensitivity analysis results across iterations. As illustrated in Figure 7, the ICER initially shows some variability but gradually stabilizes as the number of iterations increases. After several thousand iterations, the ICER converges towards a stable mean value, indicating that a sufficient number of iterations were used to ensure robust and reliable model results.



Figure 7: Convergence plot
Abbreviations: DKK, danish krone; ICER, incremental cost effectiveness ratio.

13. Budget Impact Analysis

The budget impact analysis is based on the number of patients who will be eligible for treatment with teprotumumab for active moderate to severe TED shown in Table 1 in section 3.1.2. As further described in section 3.1.2 gradual implementation is expected, as clinical adoption requires familiarity with the product's use and alignment with existing care pathways and unit-level practices.

Table 60 presents the results of the budget impact analysis. Total regional costs with a recommendation are DKK 74 million in Year 5, primarily driven by higher drug acquisition costs. In the absence of a recommendation, total regional costs are DKK 10 million. The resulting incremental budget impact is DKK 64 million in Year 5.

Table 60. Budget impact (undiscounted estimates), DKK (million)

	Year 1	Year 2	Year 3	Year 4	Year 5
Regional costs with recommendation					
Drug costs	11	22	43	65	75
Other regional hospital costs	4	6	6	7	7
Total with recommendation	14	28	49	71	82
Regional costs without recommendation					
Drug costs	0	0	0	0	0
Other regional hospital costs	4	6	7	8	9
Total without recommendation	4	6	7	8	9
Total budget impact	10	21	42	63	73

14. List of Experts

Thomas Brix, Clinical Associate Professor, Department of Endocrinology at Odense University Hospital, Denmark.

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Appendix A. Study Characteristics

Table 61. Main characteristics Phase 2

Study name: Phase 2	NCT number: NCT01868997
Objective	The primary objective of the study was to investigate the efficacy, safety, and tolerability of teprotumumab, administered Q3W for 6 months, in comparison to placebo, in the treatment of patients with active TED.
Publications – title, author(s), journal, year	Smith TJ et al., Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med. 2017 May 4;376(18):1748-1761.
Study type and design	A randomized, double-masked, placebo-controlled, phase 2 multicenter trial. Patients were randomly assigned in the double-masked intervention phase to either of two intervention groups in a 1:1 ratio in blocks of two, stratified within each clinical center according to smoking status with the use of an interactive web-response system. Study pharmacists, who were aware of the trial-group assignments, prepared the masked infusion. The on-site principal investigators could identify a patient's intervention only in the case of an emergency.
Number of trial participants (N)	87 (43 for the teprotumumab group)
Primary inclusion criteria	Patients must meet each of the following inclusion criteria to be eligible to take part in the study: 1. Aged 18-75 years (inclusive). 2. Clinical diagnosis of GD associated with active TED with a CAS ≥ 4 (on the 7-point version of the scale) for the most severely affected eye. 3. Fewer than 6 months from the onset of TED, as determined by patient records. 4. No previous medical or surgical therapy for TED, excluding local supportive measures. 5. Euthyroid because of remission after a course of antithyroid drug therapy, or euthyroidism for at least 2 months since commencing antithyroid drug therapy, or after thyroidectomy, or euthyroidism for at least 6 months after radioiodine therapy. Euthyroidism defined as determined by physical examination and normal free thyroxine (FT4) and free triiodothyronine (FT3) levels. Patients to remain euthyroid for the duration of the study. 6. Not requiring immediate surgical ophthalmological intervention 7. ALT/AST ≤ 3 x the ULN for the reference laboratory; serum creatinine < 1.5 x ULN according to age.

	8. Diabetic patients must have a well-controlled disease, demonstrated by no change in the diabetes medication (oral or insulin) greater than 10% for the past 60 days. 9. Women of childbearing potential, including women with an onset of menopause within the past 2 years, will require a negative pregnancy test at baseline and at all treatment visits up to follow up visit 2 (month 9) post randomization, and must be willing and able to use two different methods of contraceptive, one of which must be an oral contraceptive. Male patients must be surgically sterile or must agree to use a barrier contraceptive method.
Primary exclusion criteria	Patients meeting any of the following exclusion criteria will not be eligible to take part in the study. 1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision within the last 6 months of two lines of Snellen chart, new visual field defect or color defect secondary to optic nerve involvement. 2. Corneal decompensation, unresponsive to medical management. 3. Improvement in CAS of ≥ 2 points between screening and baseline. 4. Treatment with oral or IV steroids or any other immunosuppressive agent for any indication in the previous 3 months. Topical steroids for dermatological conditions is not excluded. 5. Any treatment with any investigational agent for any condition in the past 60 days, or treatment with an investigational agent for any condition during the trial. 6. Any previous treatment with rituximab (Rituxan® or MabThera®). 7. Previous orbital irradiation. 8. Identified preexisting ophthalmic disease which, in the judgment of the investigator, would preclude study participation or complicate interpretation of study results. 9. Platelet count < 100 x 109/L at screening or baseline. Patients with platelet count < 35 x 109/L following dosing will be withdrawn. 10. Bleeding diathesis. 11. Hemoglobin concentration > 2 gr/dL below the lower limit of the local laboratory reference range. 12. Malignant condition in the past 12 months (with the exception of successfully treated basal cell of the skin). 13. Pregnant or lactating women.

Study name: Phase 2		NCT number: NCT01868997
	14. 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. 15. Poorly controlled diabetes. 16. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies. 17. Any other condition which, in the opinion of the investigator, would preclude inclusion in the study. Patients who have already been randomized and received treatment under this protocol. Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.	
Intervention	Teprotumumab (n = 43): Participants received teprotumumab once every 3 weeks by IV infusion over a period of 24 weeks for a total of 8 infusions. All participants started treatment at a dose of 10 mg/kg. At Week 3, the dose was escalated to 20 mg/kg and kept constant for the remainder of the study.	
Comparator(s)	Placebo (n = 44): Participants received placebo (saline) once every 3 weeks by IV infusion over a period of 24 weeks for a total of 8 infusions. The same instructions as for the active arm (teprotumumab group) were followed in relation to dose escalation and duration of infusion. To maintain the mask, placebo patients similarly had the "dose" doubled at Week 3.	
Follow-up time	Follow-up was conducted until three weeks after the final dose, which corresponded to week 24 of the study.	
Is the study used in the health economic model?	Yes	
Primary, secondary, and exploratory outcomes	**Endpoints included in this application:** The Phase 2 study reported several endpoints. The primary efficacy endpoint was the assessment of whether the patient is a responder or not at the end of the 24-week treatment phase. A responder was defined as a patient with a decrease in overall CAS ≥ 2 points, OR an improvement in ductions of ≥ 10 degrees, OR a reduction in proptosis ≥ 2 mm. All responses were observed in the study eye without deterioration of CAS in the fellow eye (i.e. increase in CAS ≥ 2 points). Secondary endpoints included overall average change in proptosis of the study eye and CAS from baseline to week 24. **Other endpoints:** Overall average change in GO-QoL from baseline to week 24.	

Study name: Phase 2	NCT number: NCT01868997
	The Phase 2 study also included two subscales of GO-QoL measuring limitations in visual functioning and psychosocial functioning as a consequence of changed physical appearance, visual functioning and appearance) from baseline to week 24.
Analysis method	The ITT population, which included all randomly assigned patients who received at least one infusion, was used to analyze the primary and secondary efficacy outcomes. The safety population, which included all patients who received teprotumumab or placebo, was used for all safety analyses. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute), after database lock. In the primary analysis, a logistic regression model was used with the intervention group as the model effect and smoking as a covariate. Patients who did not have week 24 data for any reason were considered to have treatment failure. Results of a stratified Cochran–Mantel–Haenszel chi-square test, with smoking status as the stratification factor, enabled confirmation of the logistic analysis results. For assessment of the secondary end points (proptosis, CAS, and GO-QoL scores), an MMRM was fit to the individual change from baseline with the use of the PROC MIXED procedure in SAS software. Each baseline score (including smoking status, intervention group, time, time according to intervention, and time according to baseline interaction) was incorporated into the analysis. Responses in the non-study eye were assessed with the use of identical analyses.
Subgroup analyses	N/A
Other relevant information	N/A

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAS, clinical activity score; FT3, free triiodothryonine; FT4, free thyroxine; GD, graves' disease; GO-QOL, graves' ophthalmopathy quality of life; ITT, intention to treat; IV, intravenous; N/A, not applicable; NCT, national clinical trial; MMRM, mixed model repeated measure; PROC MIXED, procedure for mixed models (in SAS software); SAS, statistical analysis system; TED, thyroid eye disease; TED-QOL, thyroid eye disease quality of life; TTO, time trade-off; ULN, upper limit of normal.
Sources: (7)

Table 62: Main characteristics of OPTIC phase 3

Study name: OPTIC Phase 3	NCT number: NCT03298867
Objective	The overall objective was to investigate the efficacy, tolerability, and safety of teprotumumab (a fully human monoclonal antibody inhibitor of the insulin-like growth factor-1 receptor), administered once every 3 weeks for 21 weeks with a final assessment at week 24, in comparison to placebo, in the treatment of participants with moderate to severe active TED.
Publications – title, author(s), journal, year	Douglas RS et al., Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med. 2020 Jan 23;382(4):341-352.
Study type and design	A randomized, double-masked, placebo-controlled, parallel-group, phase 3 multicenter study. Patients were randomized on Day 1 in a 1:1 ratio (stratified by tobacco use status) to receive IV infusion of either teprotumumab or placebo once every 3 weeks for 21 weeks for a total of eight infusions; the last trial visit for this analysis was at Week 24. Randomization was performed with the use of an interactive web-response system. The patients, investigators, and trial-site personnel (excluding the formulating pharmacists) were unaware of the trial-group assignments and remained unaware through the follow-up data analysis and completion of the trial-site closeout visit.
Number of trial participants (N)	83 (41 for the teprotumumab group)
Primary inclusion criteria	Eligible patients must meet/provide all the following criteria: 1. Written informed consent. 2. Patients between the ages of 18 and 80 years, inclusive, at Screening. 3. Clinical diagnosis of GD associated with active TED with a CAS ≥ 4 (on the 7-item scale) for the most severely affected eye at Screening and Baseline. 4. 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. 5. Onset of active TED symptoms (as determined by patient records) within 9 months prior to Baseline. 6. Patients must be euthyroid with the thyroid function under control or have mild hypo- or hyperthyroidism (defined as FT4 and 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. 7. Does not require immediate surgical ophthalmological intervention and is not planning corrective surgery/irradiation during the course of the study. 8. ALT or AST ≤3 times the ULN or serum creatinine <1.5 times the ULN according to age at Screening. 9. Diabetic patients must have HbA1c < 9.0% with no new diabetic medication [oral or insulin] or more than 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening). 10. 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 of less than 1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomized partner. 11. 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. 12. Patients are willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.
Primary exclusion criteria	Patients will be ineligible for study participation if they meet any of the following criteria: 1. 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 color defect secondary to optic nerve involvement within the last 6 months. 2. Corneal decompensation, unresponsive to medical management.

3. Decrease in CAS of ≥ 2 points in the study eye between Screening and Baseline.
4. Decrease in proptosis of ≥ 2 mm in the study eye between Screening and Baseline.
5. Previous orbital irradiation or surgery for TED.
6. Any steroid use (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED. Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to Screening.
7. Corticosteroid use for conditions other than TED within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed).
8. 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.
9. 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.
10. Use of an investigational agent for any condition within 60 days prior to Screening or anticipated use during the course of the trial.
11. Identified pre-existing ophthalmic disease that, in the judgment of the Investigator, would preclude study participation or complicate interpretation of study results.
12. Bleeding diathesis that in the judgment of the Investigator would preclude inclusion in the clinical trial.
13. Malignant condition in the past 12 months (except successfully treated basal/squamous cell carcinoma of the skin).
14. Pregnant or lactating women.
15. 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.
16. 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).

Study name: OPTIC Phase 3	NCT number: NCT03298867
	17. Known hypersensitivity to any of the components of teprotumumab or prior hypersensitivity reactions to monoclonal antibodies. 18. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study. 19. Previous enrollment in this study or participation in a prior teprotumumab clinical trial. 20. HIV, hepatitis C or hepatitis B infections.
Intervention	Teprotumumab (n = 41): Participants received 8 infusions of teprotumumab once every 3 weeks for a total of 21 weeks. Teprotumumab 10 mg/kg was administered on Day 1 and teprotumumab 20 mg/kg was administered once every 3 weeks for the remaining 7 infusions. Teprotumumab was provided in single-dose 20 mL glass vials as a freeze-dried powder. Each vial of teprotumumab was reconstituted with 10 mL of water for injection. Reconstituted teprotumumab solution was further diluted in 0.9% (w/v) NaCl solution prior to administration. Teprotumumab was administered in 100 mL or 250 mL infusion bags (100 mL infusion bags for doses up to 1800 mg and 250 mL infusion bags for doses > 1800 mg).
Comparator(s)	Placebo (n = 42): Participants received 8 infusions of placebo once every 3 weeks for a total of 21 weeks. Placebo consisted of normal saline (0.9% NaCl solution and was administered in 100 mL or 250 mL infusion bags, as would be appropriate, per weight-based dosing volumes (100 mL infusion bags for doses up to 1800 mg and 250 mL infusion bags for doses > 1800 mg).
Follow-up time	Follow-up was conducted until three weeks after the final dose, which corresponded to week 24 of the study.
Is the study used in the health economic model?	Yes.
Primary, secondary, and exploratory outcomes	**Endpoints included in this application:** The OPTIC Phase 3 study reported several endpoints. The primary endpoint was percentage of participants who were proptosis responders at week 24. Proptosis responders were defined as participants with a ≥2 mm reduction from Baseline in proptosis in the study eye, without deterioration (≥2 mm increase) of proptosis in the fellow eye at Week 24. Secondary endpoints:

	1. Percentage of participants who were overall responders at week 24. Overall responders were defined as participants with a ≥2 mm reduction in proptosis AND a ≥2 point reduction in CAS from Baseline in the study eye, without deterioration (≥2 mm increase in proptosis or ≥2 point increase in CAS) in the fellow eye at Week 24. 2. Percentage of participants who were CAS categorical responders at week 24 (study eye). CAS categorical responders were defined as participants with a reduction to a CAS of 0 or 1 (no or minimal inflammatory symptoms) in study eye. 3. Change from baseline in proptosis to week 24 (study eye). 4. Percentage of participants who were diplopia responders at week 24. Diplopia responders were defined as participants with Baseline Diplopia Subjective Diplopia Score grade >0 in the study eye who had a reduction of ≥1 grade with no corresponding deterioration (≥1 grade worsening) in the fellow eye at Week 24. 5. Change from baseline to week 24 in the GO-QOL Questionnaire overall score was included as secondary endpoint in the study, but results are not included in this application.
Analysis method	All efficacy analyses were performed in the ITT population (all patients who underwent randomization). Analyses to evaluate the sensitivity of the ITT analyses were performed in the per-protocol population (all patients who underwent randomization, received ≥1 infusion, had at least one post baseline value, and completed the treatment period). In the primary outcome analysis, the between-group difference was assessed, stratified according to tobacco use, in the percentage of patients who had a proptosis response. Cochran–Mantel–Haenszel weighting was used to estimate the percentage-point differences in risk and the standard error of the risk difference within strata of smoking status To reduce the type I error rate, all outcome measures were tested in a hierarchical stepwise fashion. A mixed-model repeated-measures analysis of covariance was used to assess the secondary outcomes of change from baseline in proptosis and overall score on the GO-QOL questionnaire (continuous variables). Model terms included baseline assessment of proptosis and GO-QOL, tobacco use status (nonuser or user), trial group, visit, and visit-by-trial-group and visit-by-baseline score interactions.
Subgroup analyses	Pre-specified subgroup analyses for the primary endpoint:

Study name: OPTIC Phase 3	NCT number: NCT03298867
	The primary efficacy analysis was repeated separately for each tobacco use status (non-user, user) using an unstratified chi-square test within each status.
Other relevant information	N/A

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAS, clinical activity score; GD, graves' disease; FT3, free triiodothryonine; FT4, free thyroxine; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; GO-QOL, graves ophthalmopathy quality of life; IGF-1, insulin-like growth factor-1; ITT, intention to treat; IUD, intrauterine device; IV, intravenous; N/A, not applicable; NaCl, sodium chloride; NCT, national clinical trial; PROC MIXED, procedure for mixed models (in SAS software); SAS, statistical analysis system; TED, thyroid eye disease; ULN, upper limit of normal.
Sources: (8)

Table 63: Main characteristics of Bartalena et al. 2012

Study name: Bartalena et al. 2012	NCT number: N/A
Objective	The primary objective of the study was to investigate the efficacy and safety of three different cumulative doses of IVMP (2.25, 4.98, 7.47 g) for patients suffering from active moderate-to-severe GO.
Publications – title, author(s), journal, year	Bartalena L et al., Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012 Dec;97(12):4454-63.
Study type and design	A randomized, double-blind, multicenter trial. Enrolled patients were randomized (using sealed envelopes in blocks of six) to receive IVMP to a cumulative dose of 2.25 g [LD group], 4.98 g [MD group], or 7.47 g [HD group], subdivided into 12 weekly infusions. Both ophthalmologists and patients were blinded to treatment assignments.
Number of trial participants (N)	159 (54 receiving middle dose)
Primary inclusion criteria	1. Active GO: patients with CAS ≥ 3/7. 2. Moderate-to-severe GO, defined as having at least one of the following signs: i) moderate-to-severe soft tissue involvement (class 2b-c of the NOSPECS classification, also according to Color Atlas evaluation; ii) extraocular muscle involvement with ductions in any direction of gaze <30° or evident motility impairment; iii) diplopia according to Bahn's and Gorman's score of grades a-c; iv) no previous treatment for TED (glucocorticoids, orbital radiotherapy, immunosuppressive drugs, orbital decompression), except for local measures. 3. Euthyroidism for at least 3 months with antithyroid drugs or following thyroidectomy, or 6 months following radioiodine administration. Euthyroidism was defined as normal serum

Study name: Bartalena et al. 2012	NCT number: N/A
	free thyroxine, total or free triiodothyronine, and thyrotropin levels below 4 mU/L. 4. Age 18-75 years.
Primary exclusion criteria	1. CAS <3/7 2. DON 3. Contraindications to the use of glucocorticoids 4. Pregnancy 5. Lack of informed consent 6. Increased liver enzymes by a factor of 2 or more above upper normal limits
Intervention	Arm A (LD) (n = 53): Starting dose at 250 mg, maintained for the first six infusions, then halved to 125 mg for the remaining six infusions. Arm B (MD) (n = 54): Starting dose at 540 mg, maintained for the first six infusions and then halved to 290 mg for the remaining six infusions. Arm C (HD) (n = 52): Starting dose at 830 mg, maintained for the first six infusions and then halved to 415 mg for the remaining six infusions.
Comparator(s)	N/A
Follow-up time	Follow-up was performed at week 6, 12, and 24.
Is the study used in the health economic model?	Yes.
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The study reported several endpoints. The primary efficacy endpoint was overall ophthalmic change and change in QoL, evaluated with the validated disease-specific GO-QOL questionnaire. Overall ophthalmic outcome was defined as follows: Improvement, when at least two of the following outcome measures improved in one eye, without deterioration in any of these measures in either eye: i) reduction in palpebral aperture by at least 3 mm; ii) reduction in any of the class 2 signs of NOSPECS by at least two grades; iii) reduction in exophthalmos by at least 2 mm; iv) improvement of >8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); v) improvement in CAS by at least 2 points. Deterioration, when DON or two of the following occurred: i) increase in palpebral aperture by at least 3 mm; ii) increase in any of the class 2 signs of NOSPECS by at least two grades; iii) increase in exophthalmos

	by at least 2 mm; iv) deterioration of >8 degrees in motility or worsening of diplopia (appearance or change in the degree). No change. When there were no changes or changes smaller than previously defined in any of the mentioned parameters. For the GO-QOL questionnaire, the following applied: • Improvement, if there was an increase of six or more points on either one (or both) the GO-QOL scales (functioning and appearance). • Deterioration, if there was a decrease of six or more points on any one of the two scales. • No change, if there were no changes or changes smaller than previously defined in either scale. **Other endpoints:** As secondary endpoints, the study considered the individual eye parameters as well as the GO-QOL subscales.
Analysis method	For the two primary outcomes of efficacy, a two-level outcome (improvement vs. no improvement, the latter defined as no change or deterioration) was determined. The overall dose effect, as well as pairwise differences in the probability of improvement between doses were tested by age- and gender-adjusted Wald χ^2 tests from a logistic regression model. The effect of dose on the probability of improvement, no change/deterioration was tested by means of a generalized logistic model; for parameters expressed on a continuous scale, we estimated a 12-week trend over time within groups through repeated-measures linear regression models. Due to the discrete nature of the CAS, time trends and differences at 6 and 12 weeks were tested using a nonparametric approach (Jonckheere-Terpstra test and Kruskall-Wallis test, respectively). Differences in the safety score were analyzed by analysis of covariance (F test), with age and gender as covariates, considering both the total safety scores and major AEs alone. All analyses were done using the SAS Software for Windows, version 9.2. Patients withdrawn from the study prematurely for any reason were included in the analysis if the 6-week evaluation was available; results of their last assessment were carried forward and evaluated as the last visit.
Subgroup analyses	N/A
Other relevant information	N/A

Abbreviations: AE, adverse event; CAS, clinical activity score; DON, dysthyroid optic neuropathy; F-test, fisher's test (analysis of covariance); GO, graves' orbitopathy; GO-QOL, Graves' ophthalmopathy-specific quality-of-life; HD, high dose; IVMP, intravenous methylprednisolone; LD, low dose; MD, middle dose; N/A, not applicable; NCT, national clinical trial; NOSPECS, No physical signs or symptoms, Only signs, Soft tissue involvement,

Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss score; QoL, quality of life; SAS, statistical analysis system; χ^2 test, chi-square test.
Sources: **(56)**

Table 64: Main characteristics of Akratan et al. (2007)

Study name: Aktaran et al. (2007)	**NCT number: N/A**
Objective	A prospective, randomized and single-blind clinical trial. Patients were randomly assigned either IVGC therapy or OGC therapy. Treatment information was sealed in envelopes to ensure randomization with a 1:1 ratio for treatment modalities in blocks of 10 size. A complete ophthalmic examination was performed by the same ophthalmologist, who was blind to the treatment given to the patients, both before and 3 months after the start of therapy.
Publications – title, author(s), journal, year	Aktaran Ş, Akarsu E, Erbağci I, Araz M, Okumuş S, Kartal M. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. Int J Clin Pract. 2007 Jan;61(1):45–51
Study type and design	Prospective randomized controlled trial (RCT). Parallell-group comparative study including patients with GO that were randomized to either IVMP og oral methylprednisolone. The study evaluated efficacy and safety of IV versus oral corticosteroid therapy. Follow-up duration: 12 weeks.
Number of trial participants (N)	52
Primary inclusion criteria	Patients included must meet all the following criteria: 1. All patients must give their informed consent to participate in the study. 2. Patients who had moderately severe and active TED with a duration of <6 months. 3. All patients were enrolled in this study after achievement of stable euthyroidism by use of the thionamide therapy. • Patients must not have been previously treated for TED, except for eye drops without corticosteroids.
Primary exclusion criteria	Patients were ineligible for study participation if they met any of the following criteria: 1. Corneal involvement (exposure keratitis, corneal ulceration, clouding, or necrosis). 2. Contraindication to glucocorticoid therapy. 1. Patients who had been treated with glucocorticoids or any other treatment such as surgery or radiotherapy.

Study name: Aktaran et al. (2007)	NCT number: N/A
Intervention	Arm A (IVGC group) (n = 25): Patients received 500 mg of methylprednisolone in 100 mL of physiological saline as a 30-minute IV infusion per week for 6 weeks, then tapering the dose by 250 mg per week for 6 weeks. The total cumulative dose of IVGC was 4.5 g.
Comparator(s)	Arm B (OGC group) (n = 27): Oral methylprednisolone was given in decreasing doses; 72 mg/day for the first 2 weeks, 64 mg/day for 2 weeks, 56 mg/day for 2 weeks. Thereafter, the dose was tapered by 8 mg per week for 6 weeks. The total cumulative dose of OGC was 4 g.
Follow-up time	Follow-up was performed at Week 12.
Is the study used in the health economic model?	Yes.
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The study reported several endpoints including the following: improvement in CAS, diplopia, lid fissure width, and proptosis at 3 months after the start of treatment. Patients showing improvement in at least two major criteria (variations in proptosis and lid width of ≥2 mm; appearance, disappearance or changes in the degree of diplopia; changes in the CAS ≥2 points; and changes of one-tenth or more in visual acuity) and one minor criterion (soft tissue changes, self-assessment evaluation) were considered responders to therapy. On the contrary, showing no changes or improvement in one major criterion and/or in one or two minor criteria were classified as non-responders. **Other endpoints:** QoL assessment was performed on the day of the start of treatment and 3 months later using the English language translation GO-QOL Questionnaire, modified to suit the Australian population.
Analysis method	Baseline and post-treatment (at 3 months after treatment) values of dependent samples were compared with Wilcoxon's signed-rank test (for metric variables) and the McNemar test (dichotomous variables). Bonferroni correction was made to calculate the final test statistics. Comparisons between two independent samples were analysed by using the Mann–Whitney U-test (metric variables) or Fisher's exact t-test (dichotomous variables). Delta values were used for comparisons between treatment groups. The correlation between data was examined using r_s. $p < 0.05$ was considered to indicate significance. All data were presented as mean ± SD. Range was given for metric values. Frequencies were given for dichotomous variables. Analysis was performed with a statistical software package, SPSS version 10.0.
Subgroup analyses	Improvement in CAS between smokers and non-smokers

Study name: Aktaran et al. (2007)	NCT number: N/A
Other relevant information	N/A

Abbreviations: CAS, clinical activity score; GO, graves' orbitopathy; GO-QOL, graves' ophthalmopathy-specific quality-of-life; IVGC, intravenous glucocorticoid (methylprednisolone pulse); N/A, not applicable; NCT, national clinical trial; OGC, oral glucocorticoid (methylprednisolone); p, probability; QoL, quality of life; r_s, spearman's rank correlation; SD, standard deviation; SPSS, statistical package for the social sciences.
Sources: (55)

Table 65: Main characteristics of He et al. (2017)

Trial name: He et al. (2017)	NCT number: ChiCTR-IPR-15006848
Objective	The overall objective was to compare the efficacy and safety of two different regimens of IVMP. Furthermore, the study aimed to determine the value of CAS and T2RTs and areas of extraocular muscles by magnetic resonance imaging for diagnosis of active GO.
Publications – title, author(s), journal, year	He et al. Comparison of two different regimens of intravenous methylprednisolone for patients with moderate to severe and active Graves' ophthalmopathy: a prospective, randomized controlled trial. Endocr J. 2017 Feb 27;64(2):141-149.
Study type and design	A prospective, parallel-group, randomized controlled trial. Eligible patients meeting the inclusion criteria were randomly assigned to the MR group or WR group according to a random number table. The ophthalmologist and radiologist in the study were both blinded to the grouping and did not consult each other with regards to the results and observations throughout the study period.
Number of trial participants (N)	40
Primary inclusion criteria	The inclusion criteria were as follows: 1. Patients, aged 18–70 years, were included if they had not received any immunosuppressive therapy, orbital radiotherapy, or surgery. 2. Patients could be either hyperthyroid or hypothyroid status upon enrollment, but only patients whose thyroid status was restored to normal levels within 2–4 weeks from antihyperthyroid drugs or levothyroxine with adjustment medication were included in the study. These patients remained in euthyroid status during the treatment. 3. Patients with intracranial diseases and other eye diseases were excluded. 4. Moderate-to-severe TED must meet at least one of the following three items, which was based on the EUGOGO consensus statement: lid retraction ≥ 2 mm, exophthalmos ≥ 3 mm above

Trial name: He et al. (2017)	NCT number: ChiCTR-IPR-15006848
	the upper normal limit of 18 mm, diplopia (inconstant or constant). 5. Active TED (CAS ≥ 3) or inactive TED (1 ≤ CAS < 3) coupled with a prolonged T2RT on at least one of extraocular muscles.
Primary exclusion criteria	The exclusion criteria were as follows: 1. Contraindications to GCs, including active or unexplained gastric disease, active liver disease, a history of pulmonary tuberculosis, heart arrhythmias, uncontrolled hypertension, uncontrolled diabetes mellitus, or glaucoma. 2. Patients that had previously received IVMP. 3. Patients with symptoms and signs of other eye diseases. 4. Patients with recurrent GO. 5. Dysthyroid optic neuropathy (DON).
Intervention	Patients with MR group (n = 22): 0.5 g IVMP daily for three consecutive days (pulse therapy on Days 1, 2, and 3 in Weeks 1, 5, 9, and 13) over 4 cycles at 4-weekly intervals, for a total dose of 6.0 g over 3 months. Patients in the MR group were evaluated at Weeks 1, 5, 9, and 13 within one week after administration of each cumulative dose of 1.5 g IVMP. Patients with WR group (n = 18): Administration of 0.5 g IVMP weekly for 6 weeks, followed by 0.25 g weekly for 6 weeks, for a cumulative dose of 4.5 g IVMP over 12 consecutive weeks. Patients in the WR group were evaluated at weeks 3, 6, 9, and 12 within one week after administration of each cumulative dose of 1.5 g IVMP (former 6 weeks) or 0.75 g IVMP (later 6 weeks).
Comparator(s)	N/A
Follow-up time	The study did not perform follow-up assessments.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** Overall improvement and deterioration were determined for each eye. An improvement was defined as showing at least one major criterion or two minor criteria in any eye. Deterioration was defined as exhibiting one of the following: worsening of diplopia by 1 grade or more, decrease in eyeball duction of 8° or more, increase in palpebral aperture by at least 2 mm, increase in the modified NOSPECS class 2 by at least 2 grades, or increase in exophthalmos by at least 2 mm.

Trial name: He et al. (2017)	NCT number: ChiCTR-IPR-15006848
	The study reported several major endpoint criteria including the following: 1. Improvement in diplopia by at least 1 grade according to the adapted NOSPECS classification 4. 2. Improvement of eye movement in any direction by 8° or more. 3. Improvement in CAS by at least 2 points. **Other endpoints:** Six minor endpoint criteria were also reported: 1. Reduction of proptosis by at least 2 mm. 2. Improvement in the grade of soft tissue involvement, according to the modified NOSPECS class 2. 3. Improvement in visual acuity by at least 1.0 Snellen line. 4. Decrease in CAS of 1 point. 5. Decrease in palpebral aperture by at least 2 mm. 6. Improvement in duction or diplopia failing to meet 1 grade.
Analysis method	Continuous variables were expressed as means ± standard deviation. The t test, Wilcoxon Mann-Whitney test and Kruskal-Wallis test was used to compare continuous variables between groups. Comparisons of sample means between groups were analyzed with one-way ANOVA. Categorical variables were expressed as frequencies or percentages. Fisher's exact test was used to examine differences in categorical variables between groups using 2 × 2 contingency tables. A $p<0.05$ was taken as the minimum level of statistical significance. All data were analyzed using the statistical software package SPSS version 17.0.
Subgroup analyses	N/A
Other relevant information	The criteria for premature termination were: 1. Patients who were allergic to GCs or unable to tolerate IVMP. 2. Patients with aggravated symptoms after treatment. 3. Patients who were not able to complete regular visits to the clinic.

Abbreviations: ANOVA, analysis of variance; CAS, clinical activity score; ChiCTR, chinese clinical trial registry; DON, dysthyroid optic neuropathy; EUGOGO, european group on grave's orbitopathy; GC, glucocorticoid; GO, graves' orbitopathy; IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging; MR, monthly regimen; N/A, not applicable; NCT, national clinical trial; NOSPECS – no signs or symptoms, only signs, no symptoms, soft tissue involvement, proptosis, extraocular muscle involvement, corneal involvement, sight loss; SD, standard deviation; SPSS, staistical package for the social sciences; T2RT, T2 relaxation time; WR, weekly regimen.
Sources: (60)

Table 66: Main characteristics of Zhu et al. (2014)

Trial name: Zhu et al. (2014)	NCT number: NCT01969019
Objective	The primary objective of the study was to compare the efficacy and safety of two protocols of 4.5 IVMP (daily or weekly) for patients suffering from active moderate-to-severe GO.
Publications – title, author(s), journal, year	Zhu et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with Graves' ophthalmopathy. J Clin Endocrinol Metab. 2014 Jun;99(6):1999–2007.
Study type and design	A prospective, randomized trial. Patients were randomized to receive IVMP weekly or daily. Patients were randomized to receive 4.5 g methylprednisolone for 12 weeks or 4 weeks. Patients were randomly assigned following a restricted randomization scheme: computer random number generator, a block size of six, and an allocation ratio of one-to-one. Sealed envelopes were applied for allocation concealment. Overall ophthalmic assessment was performed before therapy and in the 4th and 12th weeks after therapy. Eye examinations were performed by a single ophthalmologist.
Number of trial participants (N)	80
Primary inclusion criteria	Patients should meet the criteria of either a or b, and together with c, d, e, and f, to be included in the study. a) Lid retraction with any one of the following: i) Thyroid dysfunction ii) Proptosis iii) Optic nerve involvement iv) Extraocular muscle involvement. b) Thyroid dysfunction with any one of the following: i) Proptosis ii) Optic nerve involvement iii) Extraocular muscle involvement. c) Exclude cases with such ophthalmological signs caused by other diseases. d) Moderate-to-severe patients defined by EUGOGO. e) CAS ≥ 3/7 f) Normal function of heart, liver, and kidney.
Primary exclusion criteria	1. Orbital decompression surgery needed immediately 2. History of chronic recurrent or active infection 3. History of peptic ulcer 4. Patients with a history of chronic liver disease or liver disorders: ALT or AST above 2.5 times upper limit of normal 5. History of HIV, hepatitis C or hepatitis B positive 6. Clinically significant cardiovascular or cerebrovascular disease

Trial name: Zhu et al. (2014)		NCT number: NCT01969019
	7. Uncontrolled diabetes mellitus 8. Use of corticosteroids during 12 weeks prior to the inclusion period 9. Pregnant patient or patient who is planning to become pregnant during the study	
Intervention	Arm A – IVMP (weekly protocol) (n = 39): Patients received a starting dose at 0.5 g IVMP once every week for 6 weeks, followed by 0.25 g IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone. Arm B – IVMP (daily protocol) (n = 41): Patients received a starting dose of 0.5 g IVMP daily for three consecutive days per week for 2 weeks, then halved to 0.25 g IVMP daily for three consecutive days per week for another 2 weeks. The cumulative dose was 4.5 g methylprednisolone. This was followed by tapering oral prednisone with the following regimen: a starting dose of 60 mg/day for one week, followed by a reduction of 10 mg less/week compared to the previous week for 3 weeks. This was followed by 20 mg/week for one week, followed by a reduction of 5 mg/less compared to the previous week for 3 weeks.	
Comparator(s)	N/A	
Follow-up time	Overall ophthalmic assessment was performed before therapy and in week 4 and week 12 after therapy. The study did not report any further median or mean follow-up time.	
Is the study used in the health economic model?	Yes	
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The primary endpoint was overall response rate at week 4 and week 12. The following definitions were used: • "Responsive": Defined as at least three of the outcome measures: 1) reduction in lid width by at least 3 mm; 2) reduction in any of the class 2 NOSPECS signs by at least two grades; 3) reduction in proptosis by at least 2mm;4) reduction in intraocular pressure by at least 2 mmHg; 5) improvement in CAS by at least two points; 6) improvement in diplopia (disappearance or downgrade in degree); and 7) improvement in visual acuity by 1 Snellen line. • "Deterioration": Defined for *each parameter* as follows: 1) increase in lid) decrease least 3 mm; 2) increase in any of the class 2 NOSPECS signs by at least two grades; 3) increase in proptosis by at least 2 mm; 4) increase in intraocular pressure by at least 2 mmHg; 5) increase in CAS by at least two points;	

Trial name: Zhu et al. (2014)	NCT number: NCT01969019
	6) increase in diplopia (new onset or upgrade in degree); and 7) decrease in visual acuity by 1 Snellen line. • "Unchanged": Defined as no change or changes smaller than previously defined in any of the mentioned parameters. **Other endpoints:** As secondary endpoints, the study assessed the change in CAS from baseline to week 4 and week 12, AEs after 4, 8, and 12 weeks of treatment, as well as retreatment-free survival after 6 months of therapy.
Analysis method	ITT analysis was applied, including all eligible enrolled patients. Continuous variables were expressed as the mean ± SD or median (interquartile intervals, 25–75th percentile). Categorical variables were expressed as frequency and percentage. For each patient, the mean value of the two eyes was presented for each ophthalmological parameter. Student's t test was used to compare the two groups in continuous variables, and the Mann-Whitney U test was used for comparing CAS. χ^2 test or Fisher's exact test was used for comparing proportions. Retreatment-free percentage was depicted with Kaplan-Meier survival curves, and the log-rank (Mantel-Cox) test was used to compare the percentages of the two groups. Hazard ratio and its 95% confidence interval were computed using the Mantel-Haenszel method. All analyses were performed with SAS software for Windows, version 8.1 (SAS Institute Inc) and Prism 5 for Windows, version 5.01 (GraphPad Software Inc).
Subgroup analyses	N/A
Other relevant information	N/A

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAS, clinical activity score; EUGOGO, european group on graves' orbitopathy; GO, graves' orbitopathy; HIV, human immunodeficiency virus; ITT, intention to treat; IVMP, intravenous methylprednisolone; N/A, not applicable; NCT, national clinical trial; NOSPECS, No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss score; SAS, statistical analysis system; SD, standard deviation; χ^2 test, chi-square test.
Sources: (63)

Table 67: Main characteristics of Kahaly et al. (2005)

Trial name: Kahaly et al. (2005)	NCT number: N/A
Objective	The primary objective was to optimize glucocorticoid application by comparing the efficacy and tolerability of IVMP vs. oral prednisolone in patients with active and severe GO.
Publications – title, author(s), journal, year	Kahaly et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005 Sep;90(9):5234-40.
Study type and design	A prospective, randomized, single-blind, and controlled study. Euthyroid patients with TED of recent onset (<6 months) were randomly assigned to receive IVMP once weekly for 12 weeks or oral prednisolone for 12 weeks. The type of therapy was not known to the ophthalmologist. Patients were randomly assigned following a simple randomization scheme.
Number of trial participants (N)	70
Primary inclusion criteria	The study did not specify any inclusion criteria.
Primary exclusion criteria	The study did not specify any exclusion criteria.
Intervention	IVMP (n = 35): Patients received a starting dose at 0.5 g IVMP once every week for 6 weeks, followed by 0.25 g IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone.
Comparator(s)	Oral prednisolone (n = 35): Patients received a starting dose of 0.1 g prednisolone daily, then tapering the dose by 0.0.1 g weekly for a total period of 12 weeks. The cumulative dose was 4.0 g prednisolone.
Follow-up time	Complete ophthalmic investigation was performed before therapy and 12 weeks after starting therapy. The follow-up period was 6 months. The study did not report any further median or mean follow-up time.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The study reported the primary endpoint as the overall response at week 12, defined as a composite, relevant improvement in at least three clinically objective parameters, including proptosis, lid fissure width, rate of diplopia in primary gaze, intraocular pressure in up gaze, the sum of the ultrasonically measured rectus muscle thickness, and evaluation of QoL.

Trial name: Kahaly et al. (2005)	NCT number: N/A
	Other endpoints: The study also reported several secondary endpoints, including the change in CAS, proptosis, lid width, visual acuity, intraocular pressure, extraocular muscle thickness, and QoL from baseline to Week 12. Additionally, the study also reported the number of participants who were diplopia responders and chemosis responders at Week 12.
Analysis method	For metric variables, median values and range were given, and for dichotomous variables, absolute and relative frequencies were shown. For statistical tests concerning eye-specific variables, the mean values of the two eyes were computed for each patient. Comparisons between two independent samples were performed by the Mann-Whitney U test (metric variables) or Fisher's exact test (dichotomous variables). To examine whether a change occurred between baseline and week 12, the Wilcoxon signed-rank test was performed for metric variables, and the McNemar test was performed for dichotomous variables. Significance α was set at 0.05; effects with $0.1 < P < 0.05$ were viewed as a trend. To increase precision, data were entered twice into a computer program, which minimizes the possibility of typing errors. Statistics were calculated using the SPSS/PC software package for MS Windows, release 8.0.
Subgroup analyses	The study did not report any prespecified subgroup analysis. Two post-hoc analyses were conducted: • Subgroup analyses were conducted to assess the effects of smoking, gender, and age on the response to therapy. • Subgroup analyses were conducted for physical components and psychosocial components of the 36-item short form (SF-36). Raw T-values of the questionnaire were transformed into age- and gender-specific z-values.
Other relevant information	N/A

Abbreviations: CAS, clinical activity score; GO, graves' orbitopathy; IVMP, intravenous methylprednisolone; MS, microsoft; N/A, not applicable; NCT, national clinical trial; P, probability; QoL, quality of life; SF-36, 36-item short form health survey; SPSS, statistical package for the social sciences.
Sources: (62)

Table 68: Main characteristics of MINGO

Trial name: MINGO	NCT number: EUDRACT 2008-002123-93
Objective	The primary objective of the study was to compare the efficacy and safety (tolerability) of IVMP vs. IVMP + mycophenolate in patients suffering from active, moderate-to-severe GO.
Publications – title, author(s), journal, year	Kahaly et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018;6(4):287–98.
Study type and design	A block-randomized, multicenter, observer-masked, center-stratified, open-label trial. Eligible patients were randomized to either IVMP or IVMP + mycophenolate in a 1:1 ratio. The randomization schedule was generated by an independent statistician before study activation and was stratified by site in blocks of sixteen. The randomly assigned treatment was communicated via fax to the investigator in each orbital center. All ophthalmologists and the expert statistician at Johannes Gutenberg University were masked to group assignment. Although the thyroid investigators were aware of the medication received, they emphasized that ophthalmologists should not inquire about the medication received and that patients should not inform the observer ophthalmologists regarding their current treatment.
Number of trial participants (N)	164
Primary inclusion criteria	2. Euthyroidism for at least 2 months with antithyroid drugs or following thyroidectomy, or 6 months following radioiodine administration. 3. CAS ≥ 3/7 4. Moderately severe GO: at least one of the following signs: a) moderate-to-severe active soft tissue involvement, also according to color atlas evaluation, b) proptosis ≥ 22 mm, c) eye muscle involvement with mono-ocular ductions in any direction of gaze of less than 30° or evident dysmotility or d) diplopia according to Gorman score of grades a-c. 5. No previous immunosuppressive treatment for GO 6. Age 18-75 years 7. Effective method of contraception during the whole trial and at least six weeks after last intake of trial drugs.
Primary exclusion criteria	1. CAS <3 2. Optic neuropathy 3. Pregnancy or breast-feeding women

	4. No informed consent 5. Acute or chronic viral hepatitis 6. Relevant malignancy 7. Chronic renal failure (GFR < 30) 8. Corticosteroids or other immunosuppressive agents within the last 3 months 9. Recent history of alcoholism or drug abuse
Intervention	IVMP (n = 81): Patients received a starting dose at 500 mg IVMP once every week for 6 weeks, followed by 250 mg IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone.
Comparator(s)	IVMP + mycophenolate (n = 83): Patients received a starting dose at 500 mg IVMP once every week for 6 weeks, followed by 250 mg IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone. Additionally, patients were administered with 360 mg mycophenolate orally twice per day for 24 weeks. The cumulative dose was 120 g mycophenolate.
Follow-up time	Complete ophthalmic and endocrine assessment was conducted at baseline and at weeks 6, 12, 24, and 36 after starting treatment. The study did not report any further median or mean follow-up time.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The study reported one primary endpoint as the rate of response at Week 12, with "response" being defined as an improvement in the most affected eye, defined as a reduction of at least two measures of a composite index without simultaneous deterioration of any of the ophthalmic parameters of the index. Prespecified improvement of TED was defined as reduction of at least two measures in the composite index in at least one eye, without deterioration in any of the same measures in either eye. The composite index measures were as follows: 1. Improvement of eyelid swelling in accordance with the EUGOGO color atlas. 2. Improvement in CAS of at least 2 points. 3. Improvement in proptosis of at least 2 mm. 4. Improvement in lid width of at least 2 mm. 5. Improvement in diplopia (disappearance or change in degree).

	6. Improvement of at least 8° in eye muscle motility. The study also reported another primary endpoint as relapse rates at Weeks 24 and 36 with prespecified deterioration of Graves' orbitopathy (recurrence or relapse relative to baseline) being defined as change in two of the following outcome measures in at least one eye: 1. Worsening of inflammatory eyelid swelling. 2. Worsening of CAS of at least 2 points. 3. Worsening of proptosis of more than 2 mm. 4. Worsening of lid width by at least 2 mm. 5. Worsening of diplopia. 6. Deterioration of eye muscle motility. • Occurrence of dysthyroid optic neuropathy. Prespecified lack of change in orbitopathy was defined as an absence of changes or changes smaller than those defined in any of the previously mentioned parameters. **Other endpoints:** The study also reported post-hoc outcomes including rate of response at week 24 and sustained response at week 36. Additionally, overall response to immunosuppressive treatment in both study groups was defined post-hoc as improvement of ophthalmic symptoms and signs at Weeks 24 and 36 compared with baseline, without any deterioration of any ophthalmic findings.
Analysis method	Prespecified primary outcomes, post-hoc outcomes, and secondary outcomes were analyzed in the modified ITT population, which included all patients assigned to treatment who received at least one infusion of methylprednisolone, when outcome data were available. For the primary outcome, a sample size of 75 patients per group was estimated to have 80% power to detect a difference in response rates between 85% (IVMP + mycophenolate) and 65% (IVMP), with a type I error of 0.05 and a two-sided χ^2 test of trend in proportions based on a logistic model. Statistical analysis was done with SPSS (version 22.0). The distribution of metric variables was characterized by reporting median and quartiles or means and standard deviation when appropriate. For dichotomous variables, absolute and relative frequencies were shown. All outcomes were adjusted for multiple comparisons. Treatment effects at all timepoints were reported as ORs and 95% CIs. For the prespecified primary outcomes and the post-hoc outcomes, the proportions of patients having response or relapse were compared by using Fisher's exact test and the treatment effect was reported as an OR with 95% CIs.

	As a post-hoc analysis, the patients evaluable at Week 36 were classified into three ordered categories according to response at Week 24 and sustained response at Week 36, and treatment groups with respect to this ordinal classification were compared by using the Mantel Haenszel χ^2 test for trend. To assess possible attrition bias, a post-hoc sensitivity analysis was performed by fitting a logistic model for longitudinal binary data to the outcome response at Week 12 and Week 24 and sustained response at Week 36 using the method of generalized estimation equations. - p values for findings were reported at Week 24 only to limit the number of tests and avoid inflation of type I error. All reported p values were two-sided, and the significance level was set at 0.05.
Subgroup analyses	Post-hoc subgroup analyses of treatment effects were conducted with respect to response at week 24 by testing for interaction in a logistic model and were reported non-selectively. Subgroups included gender, age, duration of GO, proportion of smokers, ophthalmic CAS, severity of GO, and serum concentrations of thyroid stimulating hormone and TSHR-Ab. Subgroup specific treatment ORs and 95% CIs were presented as a forest plot. Further post-hoc comparisons were conducted between treatment groups with respect to single variables contributing to the primary composite outcome using the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for dichotomous variables.
Other relevant information	N/A

Abbreviations: CAS, clinical activity score; CI, confidence interval; EUGOGO, european group on graves' orbitopathy; EudraCT, european union drug regulating authorities clinical trial; GEE, generalized estimating equations; GFR, glomerular filtration rate; GO, graves' orbitopathy; ITT, intention to treat; IVMP, intravenous methylprednisolone; N/A, not applicable; NCT, national clinical trial; OR, odds ratio; p value, probability value; PSS, statistical package for the social sciences; TSHR-Ab, thyroid-stimulating hormone receptor autoantibodies; χ^2 test, chi-square test.
Sources: (52)

Table 69: Main characteristics of Shen et al. (2022)

Trial name: Shen et al. (2022)	NCT number: ChiCTR1800015912
Objective	The primary objective of the study was to evaluate the therapeutic effects and safety of IVMP, IVMP + MTX and reduced IVMP + MTX in patients suffering from active, moderate-to-severe GO.
Publications – title, author(s), journal, year	Shen L et al. Methotrexate plus reduced or full-dose glucocorticoids for the treatment of active, moderate-to-severe Graves' orbitopathy. Euro Thyroid J. 2022;11(5):e220017.
Study type and design	Prospective, randomized, observer-masked, single center clinical trial. Patient randomization was generated in random block size with an allocation ratio of 1:1:1 for three groups: IVMP group (group 1), reduced IVMP + MTX group (group 2), and IVMP + MTX group (group 3). The observer ophthalmologist was blinded to the treatment groups. Patients were told not to inform the ophthalmologist about the medication they received.
Number of trial participants (N)	90
Primary inclusion criteria	1. Age 18-65 years 2. Diagnosed with active, moderate-to-severe GO
Primary exclusion criteria	1. Patients who have received any immunosuppressive therapy or radiotherapy or decompression surgery in the previous 3 months. 2. Patients with abnormal heart, liver, and kidney function, other known autoimmune diseases, or with malignancy.
Intervention	IVMP (n = 30): Patients received a starting dose at 0.5 g IVMP once every week for 6 weeks, followed by 0.25 g IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone.
Comparator(s)	IVMP + MTX (n = 30): Patients received a starting dose at 0.5 g IVMP once every week for 6 weeks, followed by 0.25 g IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone. Additionally, MTX was administered orally on the next day following IVMP as 10 mg weekly for the first 2 weeks and then regulated to 12.5 mg weekly for 10 weeks. Folic acid 5 mg was given orally once a week following the next day of MTX for 12 weeks. Reduced IVMP + MTX (n = 30): Patients received 0.25 g IVMP once a week for 12 weeks. The cumulative dose was 3.0 g methylprednisolone. Additionally, MTX was administered orally on the next day following IVMP as 10 mg weekly for the first 2 weeks and then regulated to 12.5

Trial name: Shen et al. (2022)	NCT number: ChiCTR1800015912
	mg weekly for 10 weeks. Folic acid 5 mg was given orally once a week following the next day of MTX for 12 weeks.
Follow-up time	All patients underwent efficacy (ophthalmic and endocrine) and safety assessments at baseline, Week 6 and Week 12. A subset of patients had additional follow-ups at Week 24 and Week 36. The study did not report any further median or mean follow-up time.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The study reported one primary endpoint as the CAS response at Week 12. **Other endpoints:** The study reported several secondary outcomes for other ophthalmic parameters including the following: • Change in CAS from baseline to Week 12, with improvement defined as CAS decreased by at least 2 points. • Change in proptosis from baseline to Week 12, with improvement defined as a reduction by at least 2 mm. • Change in eyelid width from baseline Week 12, with improvement defined as a reduction by at least 2 mm. • Change in Gorman diplopia score from baseline to Week 12, with improvement defined as a degrade of Gorman score (from constant to inconstant, inconstant to intermittent, and intermittent to absent). • Change in intraocular pressure from baseline to Week 12, with improvement defined as a reduction by at least 2 mmHg. • Change in visual acuity from baseline to Week 12, with improvement defined by 1 Snellen line. **For all above mentioned parameters, exacerbation was defined as an increase by the same extent in the above parameters.* The study also reported change in QoL, including two subscales of visual function and appearance, from baseline to Week 12 as a post hoc outcome. Furthermore, the overall response at Week 12 as a post hoc outcome. Overall response was defined as being responsive in at least two of the four ophthalmic parameters including CAS, proptosis, lid width, and Gorman score with the following definitions: • Responsiveness was defined as an improvement in at least one eye without exacerbation in the other eye.

Trial name: Shen et al. (2022)	NCT number: ChiCTR1800015912
	• Deterioration was defined as exacerbation in at least one eye without improvement in the other eye. • Conditions that fit in neither responsiveness nor deterioration were defined as unchanged.
Analysis method	The sample size was calculated based on previous studies, assuming that add-on MTX could achieve 91% CAS response, compared with 60% for IVMP monotherapy. The sample size of 29 patients per group was estimated to provide the trial with 80% power to detect such difference at a two-sided alpha level of 0.05. Continuous variables were expressed as the mean ± SD or median and quartiles; categorical variables were expressed as frequency and percentage. Values of serum FT4, FT3, TSH, TRAb, thyroid peroxidase antibody, and thyroglobulin antibody were shown as median and quartiles of the original values and log10 normal transformed before statistical analysis. For each patient, the worst value of the two eyes was presented for each ophthalmological parameter. Student's t-test was used to compare continuous variables, and the Mann–Whitney U-test was used for comparing CAS. χ2 test or Fisher's exact test was used for comparing proportions. P values were two-sided, and the significance level was set at 0.05. All analyses were performed with SASsoftware for Windows, version 9.4 (SAS Institute Inc) and Prism 9 for Windows, version 9.0 (GraphPad Software Inc).
Subgroup analyses	Post hoc subgroup analyses were tested for interaction in logistic model of CAS response at week 12. Subgroup specific odds ratios and 95% CIs were presented as a forest plot. QoL was analyzed post hoc by both ITT analysis, which analyzed the full data set, and per-protocol analysis, which analyzed patients with QoL questionnaires.
Other relevant information	N/A

Abbreviations: CAS, clinical activity score; CI, confidence interval; ChiCTR, chinese clinical trial registry; GO, graves' orbitopathy; GO-QOL, graves' ophthalmopathy-specific quality-of-life; ITT, intention to treat; IVMP, intravenous methylprednisolone; MTX, methotrexate; N/A, not applicable; NCT, national clinical trial; P value, probability vaue; QoL, quality of life; SAS, statistical analysis system; SD, standard deviation; TSH, thyroid stimulating hormone; TRAb, thyroid-stimulating hormone receptor autoantibodies; χ^2 test, chi-square test.
Sources: (15)

Table 70: Main characteristics of Mu et al. (2020)

Trial name: Mu et al. (2020)	NCT number: N/A
Objective	The primary objective of the study was to compare the treatment effects of two regimens of IVMP (weekly or daily) in patients suffering from active, moderate-to-severe TAO. The secondary objective was to investigate associated cytokines between the two regimens.
Publications – title, author(s), journal, year	Mu et al. Comparison of two regimens for patients with thyroid-associated ophthalmopathy receiving intravenous methyl prednisolone: A single center prospective randomized trial. Exp Ther Med. 2020;20(3):153.
Study type and design	Prospective, randomized, single-center, open-label trial. Patients were randomized at a ratio of 1:1 to receive IVMP therapy for 12 weeks on a weekly protocol or daily scheme. Sealed opaque envelopes, which were arranged in a computer-generated random order prepared by a statistician prior to the study, were opened to determine the patients' treatment assignments. All patients were required to quit smoking, to take oral anti-thyroid drugs, and received local measures for relieving symptoms (including sunglasses, artificial tears, lubricant ointments and prisms) according to advice from specialists.
Number of trial participants (N)	90
Primary inclusion criteria	1. Patients with active, moderate-to-severe TAO
Primary exclusion criteria	1. Patients with infectious diseases, allergies, autoimmune diseases, coronary artery disease, diabetes mellitus, hypertension, liver disease, kidney disease or a history of alcoholism. 2. Previous steroid treatment, orbital radiotherapy or orbital surgery.
Intervention	Arm A – IVMP (weekly regimen) (n = 46): Patients received a starting dose at 0.5 g IVMP once every week for 6 weeks, followed by 0.25 g IVMP once a week for 6 weeks. The cumulative dose was 4.5 g methylprednisolone. Arm B – IVMP (daily regimen) (n = 44): Patients received 0.5 IVMP once a day for five consecutive days, followed by oral methylprednisolone for three months. Starting treatment dose of 32 mg/day oral methylprednisolone, followed by dose tapered by 4 mg/day every two weeks.
Comparator(s)	N/A
Follow-up time	Ophthalmic assessments were performed prior to therapy and at the 12-week follow-up visit. The study did not report any further median or mean follow-up time.

Trial name: Mu et al. (2020)	NCT number: N/A
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Endpoints included in the study:** The primary endpoint was overall response rate at Week 12, with "response" being defined as an improvement in at least two major criteria and one minor criterion. Otherwise, the outcome was considered "non-response". The major criteria included the following: 1. Improvement in CAS by ≥2 points. 2. Improvement in diplopia (disappearance or reduction in degree). 3. Improvement in visual acuity by ≥1/10. 4. Reduction in proptosis or lid width of ≥2 mm. The minor criteria were favorable changes in soft tissues and improvement in the patient's self-assessment. **Other endpoints:** As secondary endpoints, the study assessed the remission rate of major ophthalmic manifestations at Week 12 and the average changes in CAS from baseline to Week 12.
Analysis method	Continuous variables were expressed as the mean ± standard deviation or median (interquartile range, 25th-75th percentile). Categorical variables are expressed as frequencies and percentages. Differences in continuous variables between groups were evaluated by Student's t-test, while differences in categorical variables between groups were analyzed by the χ2 test. Paired Student's t-tests were used to compare continuous variables prior to and after treatment. All statistical analyses were performed with SPSS 18.0.
Subgroup analyses	One-way analysis of variance was applied for comparison of continuous variables among >2 groups, which was followed by Fisher's Least Significant Difference post-hoc test in the case of statistical significance. P<0.05 was considered to indicate a statistically significant difference.
Other relevant information	N/A

Abbreviations: CAS, clinical activity score; IVMP, intravenous methylprednisolone; N/A, not applicable; NCT, national clinical trial; SPSS, statistical package for the social sciences; TAO, thyroid-associated ophthalmopathy; χ^2 test, chi-square test.
Sources: (61)

Appendix B. Results for Clinical effectiveness per Study

B.1 Results per study

In the following section, the relevant efficacy results per study included in this assessment are presented.

Table 71: Results of Phase 2 (teprotumumab)

Results of Phase 2 (teprotumumab) [NCT01868997]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI/SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Response rate in the study eye at week 24	Teprotumumab	42	69% (N/A)	49%	N/A	N/A	OR: 8.86	3.29, 23.8	<0.001	The response rate is based on a logistic regression model with the intervention group as the model effect and smoking as a covariate. The OR was calculated with the use of logistic regression for cumulative logits.	(7)
	Placebo	45	20% (N/A)								(7)

Results of Phase 2 (teprotumumab) [NCT01868997]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI/SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change in proptosis from baseline to week 24	Teprotumumab	42	-2.46 mm (0.20)	-2.31 mm	-2.84, -1.77	<0.001	N/A	N/A	N/A	The change in proptosis was analyzed with the use of MMRMs with smoking as a covariate.	(7)
	Placebo	45	-0.15 mm (0.19)								(7)
Change in CAS from baseline to week 24	Teprotumumab	42	-3.43 (0.181)	-1.58 mm	-2.07, -1.11	<0.001	N/A	N/A	N/A	The change in CAS was analyzed with the use of MMRM with smoking as a covariate.	(7)
	Placebo	45	-1.85 (0.172)								(7)
Subjective diplopia response at week 24	Teprotumumab	42	68% (N/A)	42%	N/A	<0.001	N/A	N/A	N/A	The subjective diplopia response was analyzed with the use of MMRM with smoking as a covariate. The χ^2 test was used to compare data from patients who had a	(7)
	Placebo	45	26% (N/A)								(7)

Results of Phase 2 (teprotumumab) [NCT01868997]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI/SD)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										response with data from those who did not at week 24.	

Abbreviations: CAS, clinical activity score; CI, confidence interval; N, number; N/A, not applicable; NCT, national clinical trial; OR, odds ratio; MMRM, mixed model repeated measure; P value, probability value; SD, standard deviation; χ^2 test, chi-square test.

Results of OPTIC Phase 3

Table 72: Results of OPTIC Phase 3

Results of OPTIC Phase 3 [NCT03298867]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Proptosis response rate at week 24	Teprotumumab	41	83% (N/A)	73%	59, 88	<0.001	N/A	N/A	N/A	The proptosis response rate was assessed by the between-group difference, stratified according to tobacco use, in the percentage of patients who had a proptosis response. Cochran–Mantel–Haenszel weighting was used to estimate the percentage-point differences in risk and the standard error of the risk difference within strata of smoking status.	(8)
	Placebo	42	10% (N/A)								(8)
Overall response	Teprotumumab	41	78% (N/A)	71%	56, 86	<0.001	N/A	N/A	N/A	The overall response rate was analyzed with the use	(8)

Results of OPTIC Phase 3 [NCT03298867]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
rate at week 24	Placebo	42	7% (N/A)							of a MMRM analysis of covariance.	(8)
CAS response rate at week 24	Teprotumumab	41	59% (N/A)	36%	17, 55	<0.001	N/A	N/A	N/A	The CAS response rate was analyzed with the use of Cochran–Mantel–Haenszel weighting to estimate the percentage-point differences in risk and corresponding 95% CIs.	(8)
	Placebo	42	21% (N/A)								(8)
Change in proptosis from baseline to week 24	Teprotumumab	41	-2.82 mm (0.19)	-2.28 mm	-2.77, -1.80	<0.001	N/A	N/A	N/A	The change in proptosis was analyzed with the use of a MMRM analysis of covariance.	(8)
	Placebo	42	-0.54 mm (0.19)								(8)
Diplopia response	Teprotumumab	41	68% (N/A)	39%	16, 63	0.001	N/A	N/A	N/A	The diplopia response rate was analyzed with the use	(8)

Results of OPTIC Phase 3 [NCT03298867]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
at week 24	Placebo	42	29% (N/A)							of Cochran–Mantel–Haenszel weighting to estimate the percentage-point differences in risk and corresponding 95% CI.	

Abbreviations: CAS, clinical activity score; CI, confidence interval; MMRM, mixed model repeated measures; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value.

Results of Bartalena et al. 2012

Table 73: Results of Bartalena et al. 2012

Results of Bartalena et al. 2012 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in exophthalmos from baseline to week 12	IVMP – MD (4.98 g)	54	-0.4 mm (-0.8, 0)	MD vs. LD: 0.4 mm	N/A	MD vs. LD. 0.12	N/A	N/A	N/A	The change in proptosis was estimated by a 12-week trend over time within groups through repeated-measures linear regression models.	(56)
	IVMP – LD (2.25 g)	53	-0.8 mm (-1.2, -0.4)	MD vs. HD: 0.2 mm		MD vs. HD: 0.5					(56)
	IVMP – HD (7.47 g)	52	-0.6 mm (-1, -0.2)								(56)
Improved proptosis at week 12	IVMP – MD (4.98 g)	54	20% (N/A)	MD vs. LD: -12%	N/A	MD vs. LD. 0.12	N/A	N/A	N/A	Improved proptosis was analyzed by means of a generalized logistic model.	(56)
	IVMP – LD (2.25 g)	53	32% (N/A)	MD vs. HD: -1%		MD vs. HD: 0.86					(56)
	IVMP – HD (7.47 g)	52	21% (N/A)								(56)

Results of Bartalena et al. 2012 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Improved diplopia (ocular motility) at week 12	IVMP – MD (4.98 g)	54	26% (N/A)	MD vs. LD: 5%	N/A	MD vs. LD: 0.8	N/A	N/A	N/A	Improved diplopia was analyzed by means of a generalized logistic model.	(56)
	IVMP – LD (2.25 g)	53	21% (N/A)	MD vs. HD: -20%		MD vs. HD: 0.05					(56)
	IVMP – HD (7.47 g)	52	46% (N/A)								(56)
CAS improved by 2 points at week 12	IVMP – MD (4.98 g)	54	83% (N/A)	MD vs. LD: 25%	N/A	MD vs. LD: 0.01	N/A	N/A	N/A	Time trends and differences were tested with a nonparametric approach by the use of Kruskall-Wallis test.	(56)
	IVMP – LD (2.25 g)	53	58% (N/A)	MD vs. HD: 2%		MD vs. HD: 0.91					(56)
	IVMP – HD (7.47 g)	52	81% (N/A)								(56)

Abbreviations: CAS, clinical activity score; CI, confidence interval; HD, high dose; IVMP, intravenous methylprednisolone; LD, low dose; MD, middle dose; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value.

Results of Aktaran et al. 2007

Table 74: Results of Aktaran et al. 2007

Results of Aktaran et al. 2007 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change in CAS from baseline to month 3	IVGC	25	-3.1 (N/A)	-0.8	N/A	0.001	N/A	N/A	N/A	Change in CAS was analyzed by the use of delta values for comparisons between treatment groups. The correlation between data was examined using r_s.	(55)
	Oral methylprednisolone	27	-2.3 (N/A)								(55)
Change in diplopia from baseline to month 3	IVGC	25	Constant: -9% Inconstant: -18% Intermittent: -9%	Constant: -1% Inconstant: -10% Intermittent: 5%	N/A	0.6	N/A	N/A	N/A	Change in diplopia was analyzed by the use of delta values for comparisons between treatment groups. The correlation between data was examined using r_s.	(55)
	Oral methylprednisolone	27	Constant: -8% Inconstant: -8%								(55)

Results of Aktaran et al. 2007 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
			Intermittent: -14%								
Change in proptosis from baseline to month 3	IVGC	25	-1.2 mm (N/A)	-0.6 mm	N/A	0.038	N/A	N/A	N/A	Change in proptosis was analyzed by the use of delta values for comparisons between treatment groups. The correlation between data was examined using r_s.	(55)
	Oral methylprednisolone	27	-0.6 mm (N/A)								(55)

Abbreviations: CAS, clinical activity score; CI, confidence interval; IVGC, intravenous methylprednisolone; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value; r_s, Spearman's rank correlation.

Results of He et al. 2017

Table 75: Results of He et al. 2017

Results of He et al. 2017 [ChiCTR-IPR-15006848]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change in CAS from baseline to week 12	IVMP (WR)	18	-0.6 (N/A)	0.1	N/A	>0.05	N/A	N/A	N/A	The change in CAS was analyzed by the use of the t test, Wilcoxon Mann-Whitney test and Kruskal-Wallis test to compare continuous variables between groups. Comparisons of sample means between groups were analyzed with one-way ANOVA.	(60)
	IVMP (MR)	22	-0.7 (N/A)								(60)
Change in exophthalmos from baseline to week 12	IVMP (WR)	18	-1.2 mm (N/A)	-0.1 mm	N/A	>0.05	N/A	N/A	N/A	The change in proptosis was analyzed by the use of the t test, Wilcoxon Mann-Whitney test and Kruskal-Wallis test to compare continuous variables between groups. Comparisons of sample means between groups	(60)
	IVMP (MR)	22	-1.1 mm (N/A)								(60)

Results of He et al. 2017 [ChiCTR-IPR-15006848]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										were analyzed with one-way ANOVA.	
Change in diplopia from baseline to week 12	IVMP (WR)	18	-0.2 (N/A)	-0.1	N/A	>0.05	N/A	N/A	N/A	The change in diplopia was analyzed by the use of the t test, Wilcoxon Mann-Whitney test and Kruskal-Wallis test to compare continuous variables between groups. Comparisons of sample means between groups were analyzed with one-way ANOVA.	(60)
	IVMP (MR)	22	-0.1 (N/A)								(60)

Abbreviations: ANOVA, analysis of variance; CAS, clinical activity score; ChiCTR, chinese clinical trial registry; CI, confidence interval; IVMP, intravenous methylprednisolone; MR, monthly regimen; N, number; N/A, not applicable; P value, probability value; WR, weekly regimen.

Results of Mu et al. 2020

Table 76: Results of Mu et al. 2020

Results of Mu et al. 2020 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median change in CAS from baseline to week 12	IVMP (WR)	46	-2.0 (N/A)	0.0	N/A	>0.05	N/A	N/A	N/A	Differences in CAS variables between groups were evaluated by Student's t-test, while differences in categorical variables between groups were analyzed by the χ2 test. Paired Student's t-tests were used to compare continuous variables prior to and after treatment.	(61)
	IVMP (DR)	44	-2.0 (N/A)								(61)
Change in proptosis from baseline to week 12	IVMP (WR)	46	0.69 mm (N/A)	0.53 mm	N/A	>0.05	N/A	N/A	N/A	Differences in proptosis variables between groups were evaluated by Student's t-test, while differences in categorical variables between groups were analyzed by the χ2 test. Paired Student's t-tests were used to compare continuous	(61)
	IVMP (DR)	44	0.16 mm (N/A)								(61)

Results of Mu et al. 2020 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										variables prior to and after treatment.	

Abbreviations: CAS, clinical activity score; CI, confidence interval; DR, daily regimen; IVMP, intravenous methylprednisolone; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value; WR, weekly regimen, χ^2 test, chi-square test.

Results of Zhu et al. 2014

Table 77: Results of Zhu et al. 2014

Results of Zhu et al. 2024 [NCT01969019]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median change in CAS from baseline to week 12	IVMP (WR)	39	-2.0 (N/A)	-1.0	N/A	0.82	N/A	N/A	N/A	Student's t test was used to compare the two groups in CAS variables, and a Mann-Whitney U test was used for comparing CAS. χ2 test or Fisher's exact test was	(63)
	IVMP (DR)	41	-1.0 (N/A)								(63)

Results of Zhu et al. 2024 [NCT01969019]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										used for comparing proportions.	
Change in proptosis from baseline to week 12	IVMP (WR)	39	-1.25 mm (N/A)	-1.15 mm	N/A	N/A	N/A	N/A	N/A	Student's t test was used to compare the two groups in proptosis variables, and a Mann-Whitney U test was used for comparing CAS. χ2 test or Fisher's exact test was used for comparing proportions.	(63)
	IVMP (DR)	41	-0.10 mm (N/A)								(63)
Change in diplopia from baseline to week 12	IVMP (WR)	39	Constant: 2.56% Inconstant: -23.08% Intermittent: 17.95% Absent: 0%	Constant: 0.64% Inconstant: -17.5% Intermittent: 21.03	N/A	Constant: N/A Inconstant: 0.003 Intermittent: 0.06	N/A	N/A	N/A	Student's t test was used to compare the two groups in diplopia variables, and a Mann-Whitney U test was used for comparing CAS. χ2 test or Fisher's exact test was used for comparing proportions.	(63)

Results of Zhu et al. 2024 [NCT01969019]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	IVMP (DR)	41	Constant: 1.92% Inconstant: -5.58% Intermittent: -3.08% Absent: 6.73%	Absent: -6.73%		Absent: 0.03					(63)

Abbreviations: CAS, clinical activity score; CI, confidence interval; DR, daily regimen; IVMP, intravenous methylprednisolone; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value; WR, weekly regimen; χ^2 test, chi-square test.

Results of Shen et al. 2022

Table 78 Results of Shen et al. 2022

Results of Shen et al. 2022 [ChiCTR1800015912]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CAS response rate at week 12	IVMP	30	53.3% (N/A)	IVMP vs. IVMP + MTX: -23.4% IVMP vs. Reduced IVMP + MTX: -23.4%	N/A	IVMP vs. IVMP + MTX: 0.1 IVMP vs. Reduced IVMP + MTX: 0.1	N/A	N/A	N/A	A Mann–Whitney U-test was used for comparing CAS. χ2 test or Fisher's exact test was used for comparing proportions.	(15)
	IVMP + MTX	30	76.7% (N/A)								(15)
	Reduced IVMP + MTX	30	76.7% (N/A)								(15)
Change in proptosis from baseline to week 12	IVMP	30	-0.9 mm (N/A)	IVMP vs. IVMP + MTX: -0.5 mm IVMP vs. Reduced IVMP + MTX: -0.1 mm	N/A	IVMP vs. IVMP + MTX: 0.9 IVMP vs. Reduced IVMP + MTX: 1.0	N/A	N/A	N/A	Student's t-test was used to compare proptosis variables. χ2 test or Fisher's exact test was used for comparing proportions.	(15)
	IVMP + MTX	30	-0.4 mm (N/A)								(15)
	Reduced IVMP + MTX	30	-0.8 mm (N/A)								(15)

Results of Shen et al. 2022 [ChiCTR1800015912]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Diplopia response rate at week 12	IVMP	30	57.1% (N/A)	IVMP vs. IVMP + MTX: +12.7% IVMP vs. Reduced IVMP + MTX: +7.1%	N/A	IVMP vs. IVMP + MTX: 0.6 IVMP vs. Reduced IVMP + MTX: 0.2	N/A	N/A	N/A	Student's t-test was used to compare diplopia variables. χ2 test or Fisher's exact test was used for comparing proportions.	(15)
	IVMP + MTX	30	44.4% (N/A)								(15)
	Reduced IVMP + MTX	30	50% (N/A)								(15)

Abbreviations: CAS, clinical activity score; ChiCTR, chinese clinical trial registry; CI, confidence interval; IVMP, intravenous methylprednisolone; MTX, methotrexate; N, number; N/A, not applicable; P value, probability value; χ^2 test, chi-square test.

Results of MINGO

Table 79 Results of MINGO

Results of MINGO [EUDRACT 2008-002123-93]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Change in CAS from baseline to week 12	IVMP	75	-1.46 (N/A)	0.16	N/A	N/A	Adjusted mean difference: 0.43	0.01, 0.85	0.047	Mann-Whitney U test was used to compare CAS variables.	(52)
	IVMP + MMF	79	-1.62 (N/A)								(52)
Change in diplopia from baseline to week 12	IVMP	75	-0.32 (N/A)	-0.2	N/A	N/A	Adjusted mean difference: 0.18	-0.10, 0.46	0.21	Mann-Whitney U test was used to compare diplopia variables.	(52)
	IVMP + MMF	79	-0.12 (N/A)								(52)
	IVMP	75	49% (N/A)	-14%	N/A	N/A	OR: 1.76	0.92, 3.39	0.089		(52)

Results of MINGO [EUDRACT 2008-002123-93]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Response rate at week 12	IVMP + MMF	79	63% (N/A)							The response rate was analyzed by the use of Fisher's exact test.	(52)

Abbreviations: CAS, clinical activity score; CI, confidence interval; EUDRACT, european union drug regulating authorities clinical trials database; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; N, number; N/A, not applicable; P value, probability value.

Results of Kahaly et al. 2005

Table 80 Results of Kahaly et al. 2005

Results of Kahaly et al. 2005 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Diplopia response rate at week 12	IVMP	35	Overall improvement: 45.71% Constant: -37.14% Inconstant: 11.43% Intermittent: 8.57%	Overall improvement: 31.42% Constant: 11.43% Inconstant: -2.86% Intermittent: -2.86%	N/A	Overall improvement: N/A Constant: 0.112 Inconstant: 1.000 Intermittent: 0.614	N/A	N/A	N/A	To examine whether a change occurred between baseline and week 12, the Wilcoxon signed-rank test was performed for diplopia variables. Comparisons between two independent samples were performed by the Mann-Whitney U test.	(62)
	Oral methylprednisolone	35	Overall improvement: 14.29% Constant: -20.0%								(62)

Results of Kahaly et al. 2005 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
			Inconstant: 11.43% Intermittent: 2.86%								
Proptosis response rate at week 12	IVMP	35	60% (N/A)	20%	N/A	<0.02	N/A	N/A	N/A	To examine whether a change occurred between baseline and week 12, the Wilcoxon signed-rank test was performed for proptosis variables. Comparisons between two independent samples were performed by the Mann-Whitney U test.	(62)
	Oral methylprednisolone	35	40% (N/A)								(62)
CAS response	IVMP	35	77% (N/A)	26%	N/A	<0.01	N/A	N/A	N/A	To examine whether a change occurred between	(62)

Results of Kahaly et al. 2005 [NCT number: N/A]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
rate at week 12	Oral methylprednisolone	35	51% (N/A)							baseline and week 12, the Wilcoxon signed-rank test was performed for CAS variables. Comparisons between two independent samples were performed by the Mann-Whitney U test.	(62)

Abbreviations: CAS, clinical activity score; CI, confidence interval; IVMP, intravenous methylprednisolone; N, number; N/A, not applicable; NCT, national clinical trial; P value, probability value.

Appendix C. Subsequent Treatment

N/A

Appendix D. Comparative Analyses

The primary methodology of the MAIC is described in Section 7.

Regarding the SLR strict inclusion and exclusion criteria were defined to capture relevant RCTs and RWE for the ITC, these specific criteria can be found in Table 81.

Table 81: PICOs inclusion and exclusion criteria used to define which RCT and RWE evidence identified in the SLR will be considered in the ITC

PICOS Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with moderate to severe active TED	Disease other than moderate to severe active TED
Interventions/ Comparators	Teprotumumab IVMP: IV administered cumulative dose of 4.5 g – 5.0 g	A cumulative dose that is not IVMP 4.5 g – 4.98 g indicated by EUGOGO, and ATA/ETA guidelines.
Outcomes	Studies reporting adequate information (including baseline patient characteristics) on one of the following outcomes of interest including mean change from baseline proptosis or diplopia response (reduction in diplopia of ≥1 grade) and treatment discontinuation (number of patients and reasons for discontinuation).	N/A
Study design	RCTs, single-arm, RWE	Case reports/case series
Publication	Full text	Abstracts

Abbreviations: ATA, American thyroid association; ETA, European thyroid association; EUGOGO, European group on graves' orbitopathy; ITC, indirect treatment comparison; IVMP, intravenous methylprednisolone; N/A, not applicable; PICOS, populations, interventions/comparators, outcomes, and study design; RCT, randomized controlled trial; RWE, real-world evidence; SLR, systematic literature review; TED, thyroid eye disease.

Source: (1, 35)

For the MAIC, eight IVMP studies and two teprotumumab studies were included for the mean change from baseline proptosis outcome. In Table 82, specific information for each relevant study can be found.

Table 82: Change from baseline proptosis

Author	Trial name	Treatment	Outcome definition	Timepoint	Measurement	Mean change from baseline (mm)
Smith et al. (2017) (7)	NCT01868997	Tepezza	Mean change in proptosis (mm) from baseline through Week 24	Week 24	Hertel exophthalmometer	-2.46 (0.20)
Douglas et al. (2020) (8)	NCT03298867 (OPTIC Phase 3)	Tepezza	Mean change in proptosis (mm) from baseline through Week 24	Week 24	Hertel exophthalmometer	-2.82 (0.19)
Bartalena et al. (2012) (56)	NR	IVMP	Change in exophthalmos (mm) week 12	Week 6 and 12	NR	-0.4
Aktaran et al. (2007) (55)	NR	IVMP	Proptosis (mm) at baseline and 3 months	3 months	Hertel exophthalmometer	-1.2

He et al. (2017) (60)	ChiCTR-IPR-15006848	IVMP	Mean exophthalmos (mm) at baseline and week 12	Week 12	NR	-1.2
Zhu et al. (2014) (63)	NR	IVMP	Mean proptosis (mm) at baseline and week 12	Week 4 and 12	Hertel exophthalmometer	-1.25
Kahaly et al. (2018) (52)	NR	IVMP	Mean proptosis (mm) at baseline and week 12	Week 12	Hertel exophthalmometer	-0.12
Shen et al. (2022) (15)	NR	IVMP	Mean proptosis (mm) at baseline and week 12.	Week 12	Hertel exophthalmometer	-0.9
Mu et al. (2020) (61)	NR	IVMP	Mean proptosis (mm) at baseline and week 12	Week 12	Hertel exophthalmometer	0.69

Abbreviations: ChiCTR, chinese clinical trial registry; IVMP, intravenous methylprednisolone; N/A, not applicable; NCT, national clinical trial; NR, not reported.

For the analysis of diplopia response rate, four IVMP studies and two teprotumumab studies were considered. In Table 83, specific information for each study can be found.

Table 83: Comparability assessment of diplopia response rate

Trial	Treatment	Diplopia at baseline n (%)	Outcome definition	Timepoint	Diplopia responders n (%)
Smith et al. (2017) (7)	Tepezza	Absent: 4 (10) Intermittent: 16 (38) Inconstant: 7 (17) Constant: 15 (35)	NR	Week 24	26 (68)
Douglas et al. (2020) (8)	Tepezza	68.29	Reduction in diplopia of ≥1 grade	Week 24	19 (67.86)
He et al. (2017) (60)	IVMP	Absent: 6 (33.3) Intermittent: 2 (11.1) Inconstant:6 (33.3) Constant:5 (22.2)	Improvement in diplopia by at least one grade according to the adapted NOSPECS classification 4	Week 12	4 (26.7)
Zhu et al. (2014) (63)	IVMP	Absent: 11 (28.21) Intermittent:6 (15.38) Inconstant: 15 (38.56) Constant: 7 (17.95)	Improvement in diplopia (disappearance or degrade in degree)	Week 4 and 12	17 (43.59)
Kahaly et al. (2005) (62)	IVMP	Constant: 23 (66.00) Inconstant: 3 (9.00)	Intermittent, inconstant, and constant diplopia in primary position	NR	Intermittent: 4 (36) Inconstant: 2(18)

		Intermittent: 0 (0)			Constant: 10 (28.57)
Shen et al. (2022) (15)	IVMP	Absent: 9 (30) Intermittent: 3 (10) Inconstant: 7 (23.3) Constant: 11 (36.7)	Improvement was defined by degrade of Gorman score (from constant to inconstant, inconstant to intermittent, and intermittent to absent)	Week 12	Intermittent: 6(20) Inconstant: 4 (13.3) Constant: 5 (16.7)

Abbreviations: IVMP, intravenous methylprednisolone; NR, not reported; NOSPECS, no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle signs, corneal involvement, and sight loss score.

Strengths and limitations of the comparative analysis of efficacy

The comparative analysis of teprotumumab versus IVMP has several methodological strengths that enhance the reliability and relevance of the findings. First, all plausible comparative approaches were thoroughly assessed as part of the feasibility assessment and statistical analysis plan, ensuring that the selected methodology was both appropriate and comprehensive. A key strength of the analysis was the pooling of IVMP studies prior to conducting the MAICs. This allowed for the inclusion of the full body of available evidence and mitigated the risk of over-reliance on any single comparator study.

The selection of studies was done with careful adherence to clinical guidelines: only studies using IVMP in cumulative doses between 4.5 g and 5.0 g were included, in accordance with EUGOGO and ATA/ETA guidelines (1, 91). This enhances the clinical applicability of the results, particularly in the European context. Moreover, the pooling of studies increased the effective sample size, thereby improving the precision of treatment effect estimates. Only RCTs were included in the base case analysis. As RCTs are widely considered the gold standard for evaluating treatment efficacy, their use strengthens the internal validity of the results. All included studies were rigorously screened to meet pre-specified PICOS criteria, further supporting the methodological robustness of the analysis. Importantly, the analysis controlled for as many relevant PFs and TEMs as the data allowed, offering a more robust and clinically aligned comparison than previously published MAICs.

However, the analysis is not without limitations. Although covariate selection was informed by prior analyses, expert opinion, and validated by three British key opinion leaders, some important biomarkers—such as FT3, FT4, and TSH receptor-related antibodies (TSI/TSHR)—could not be included due to data unavailability. Additionally, disease duration, which was identified as an important TEM, could not be matched across treatment arms because of a lack of distributional overlap between the teprotumumab and IVMP.

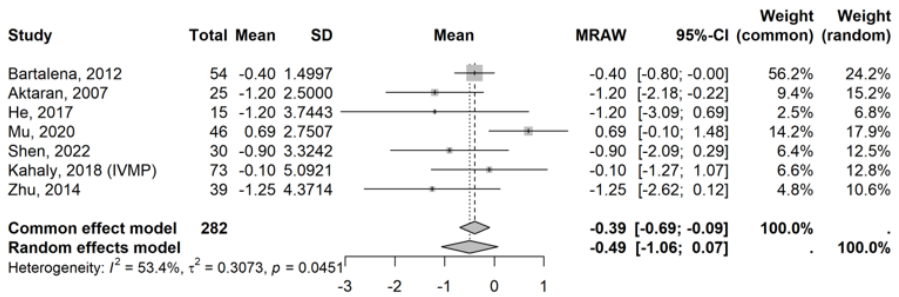
To enhance the robustness of the treatment effect estimates, a meta-analysis of the IVMP studies was conducted prior to the MAIC. While this was methodologically sound and necessary given the small sample sizes of individual studies, certain studies that lacked required baseline data were excluded from the pooling process. This introduces a risk of residual confounding bias. That said, only two studies were excluded, and the remaining seven RCTs provided a broad and representative dataset for analysis.

Finally, the comparative analysis used outcome data from different timepoints—IVMP outcomes at week 12 and teprotumumab outcomes at week 24—reflecting each treatment's expected peak efficacy. This approach was necessary to avoid underestimating teprotumumab's true effect. However, it does not capture possible residual effects—such as sustained efficacy or delayed AEs—that may occur after the 12-week IVMP treatment window, and thus some degree of uncertainty remains.

Presentation of results

The following forest plots illustrate the weighting applied to each included study per outcome, based on baseline characteristics. These visual representations aim to clarify how the study-specific attributes influenced the contribution of each study to the overall effect estimates, see Figure 8 and Figure 9. The results are presented in text in Section 7.2

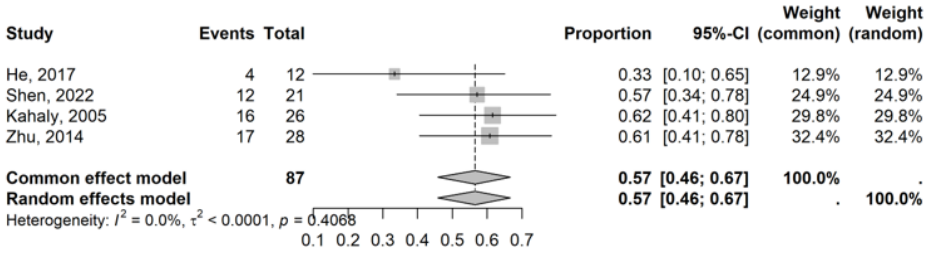
Figure 8: Forest plot for mean change from baseline proptosis - IVMP studies



Abbreviations: τ^2, heterogenetic variance; CI, confidence Interval; IVMP, intravenous methylprednisolone; I^2, higgins heterogeneity index; MRAW, untransformed mean; p value, probability value; SD, standard deviation.

Source: (57)

Figure 9: Forest plot for diplopia response rate - IVMP studies



Abbreviations: τ^2, heterogenetic variance; CI, confidence interval; IVMP, intravenous methylprednisolone; p, probability; I^2, higgins heterogeneity index.

Source: (57)

Table 84: Comparative analysis of studies comparing teprotumumab with IVMP for patients with active moderate to severe TED

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
Change from baseline proptosis, 12 weeks	Smith et al. 2017 Douglas et al. 2020 Bartalena et	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	Full description provided in section 7.1.	Yes

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
	al. 2012								
	Aktaran et al. 2007								
	He et al. 2017								
	Mu et al.								

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
	2020								
	Shen et al. 2022								
	Kahaly et al. 2018								
	Zhu et al.								

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
	2014								
Diplopia response rate, 12 weeks	Smith et al. 2017 Douglas et al. 2020 Muet	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	Full description provided in section 7.1.	Yes

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
	al. 2020								
	Shen et al. 2022								
	Kahaly et al. 2018								

To present the rescaled weights for each of the two respective outcomes, histograms were created. See

Figure 10 and

Figure 11.



Figure 10: Histogram of rescaled weights for mean change from baseline proptosis



Figure 11: Histograms of rescaled weights for the diplopia response rate MAIC

Appendix E. Extrapolation of Patient Transitions

E.1 Parametric Extrapolation Models

NA

E.1.1 **Extrapolation of [Clinical** Outcome 1]

NA

E.1.1.1 Log-Cumulative Hazard Plots and Residual Plots

NA

E.1.1.2 Internal validity

E.1.1.2.1 Assessment of Statistical and Visual Fit (AIC and BIC)

NA

E.1.1.2.2 Assessment of Smoothed Hazard Functions

NA

E.1.1.3 External Validity

NA

E.1.1.4 Other Assumptions

NA

E.1.2 **Extrapolation of [Clinical** Outcome 2]

NA

E.2 Transition Probabilities

E.2.1 Internal Validity

NA

E.2.2 External Validity

E.2.3 Other Assumptions

NA

E.2.4 Transition matrix

Teprotumumab: Cycle 1 to Cycle 2

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Teprotumumab: Cycle 2 to Cycle 3

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Teprotumumab: Cycle 3 to Cycle 4

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, NP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LP, ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP, CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IVMP: Cycle 1 to Cycle 2

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	85%	4%	7%	0%	2%	0%
LP, NP	11%	79%	1%	7%	0%	2%
SP, ID	26%	1%	66%	3%	4%	0%
LP, ID	3%	24%	8%	61%	1%	4%
SP, CD	16%	1%	8%	0%	71%	4%
LP, CD	2%	15%	1%	7%	9%	65%

IVMP: Cycle 2 to Cycle 3

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	100%	0%	0%	0%	0%	0%
LP, NP	0%	100%	0%	0%	0%	0%
SP, ID	0%	0%	100%	0%	0%	0%
LP, ID	0%	0%	0%	100%	0%	0%
SP, CD	0%	0%	0%	0%	100%	0%
LP, CD	0%	0%	0%	0%	0%	100%

IVMP: Cycle 3 to Cycle 4

Off/On	SP, NP	LP, NP	SP, ID	LP, ID	SP, CD	LP, CD
SP, NP	100%	0%	0%	0%	0%	0%
LP, NP	0%	100%	0%	0%	0%	0%

SP, ID	0%	0%	100%	0%	0%	0%
LP, ID	0%	0%	0%	100%	0%	0%
SP, CD	0%	0%	0%	0%	100%	0%
LP, CD	0%	0%	0%	0%	0%	100%

Appendix F. Serious Adverse Events

Safety data from the Phase 2 and OPTIC Phase 3 study were collected and reported according to predefined protocol specifications. Treatment-emergent adverse events (TEAEs) were defined as AE that occurred or worsened after the first administration of study drug on Day 1 through the end of the double-masked treatment period. The TEAE reporting period extended until 21 days after the final dose of study drug.

According to the International conference on Harmonisation (ICH) an AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which did not necessarily have a causal relationship with the treatment. This included any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to treatment. Pre-existing conditions that worsened during the study were reported as AEs.

In the OPTIC Phase 3 study, additional clarifications were applied. New ophthalmic findings considered related to TED and not to the investigational product were not reported as AEs. Unchanged chronic conditions were not recorded as AEs unless a clear exacerbation occurred. Disease progression attributable to TED, such as worsening proptosis, was generally not reported as an AE unless it met the criteria for a SAE or led to treatment discontinuation.

SAEs were defined as any event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, caused a congenital anomaly or birth defect, or was considered medically important by the investigator or sponsor. These definitions were consistent across Phase 2 and OPTIC Phase 3 studies, with minor protocol-specific clarifications.

F.1.1 Detailed safety results – Phase 2 study

Detailed safety results from the Phase 2 study are presented in Table 85. The table provides a complete overview of all adverse events and serious adverse events reported in the safety population.

Table 85: Adverse Events and Serious Adverse Events (Safety Population) – Phase 2

	Teprotumumab (n=43)[a]	Placebo (n=44)
AE during intervention – no. of patients (%)[b]		
Nausea	8 (18.6)	4 (9.1)
Muscle spasms	8 (18.6)	2 (4.5)

Diarrhea	6 (14.0)	2 (4.5)
Hyperglycemia	5 (11.6)	2 (4.5)
Alopecia	3 (7.0)	2 (4.5)
Dry skin	3 (7.0)	0
Dysgeusia	3 (7.0)	0
Headache	3 (7.0)	2 (4.5)
Paresthesia	3 (7.0)	0
Hearing impairment	3 (7.0)	0
Weight loss	3 (7.0)	0
Any AE during intervention	32 (74.4)	32 (72.7)
SAE – no. of patients (%)[c]		
Optic neuropathy[d]	0	1 (2.3)
Diarrhea	1 (2.3)	0
Inflammatory bowel disease	1 (2.3)	0
Escherichia sepsis	1 (2.3)	0
Hashimoto's encephalopathy	1 (2.3)	0
Urinary retention	1 (2.3)	0
Any SAE	5 (11.6)	1 (2.3)

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

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

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

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

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

Abbreviation: AE, adverse event; DON, dysthyroid optic neuropathy; SAE: serious adverse event.

Source: (7, 27)

F.1.2 Detailed safety results – OPTIC Phase 3

Detailed safety results from the OPTIC Phase 3 trial are presented in Table 86, including all adverse events and serious adverse events reported in the safety population.

Table 86: Adverse Events and Serious Adverse Events (Safety Population) – OPTIC Phase 3

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

Visual-field defect	0	1 (2.4)
Any SAE	2 (4.9)	1 (2.4)

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

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

Source: (8, 27)

F.1.3 Detailed safety results – IVMP

Bartalena et al. 2012 (56)

A formal safety profile definition was not provided.

Treatment response was categorized as improvement, no change, or deterioration. AE were classified as major or minor. Mild AE were observed in 12/52 HD patients (21%), 18/54 MD patients (30%), and 14/53 LD patients (26%), with no statistically significant differences across groups. Reported minor AE included transient flushes during infusion, mild cushingoid features (n=6), mild BP elevation not requiring treatment (n=3), mild GI symptoms controlled with omeprazole (n=1), and mild weight gain (n=2).

Major AE occurred slightly more frequently in the HD group (n=5) versus MD (n=3) and LD (n=2). The HD group included three cases of major depression or psychosis; one case of major depression occurred in the MD group. One patient in the LD group died from myocardial infarction at week 6. These findings suggest that although serious AE are more frequent at higher cumulative doses, LD regimens are not without risk.

AE associated with high-dose IV GC are a major concern, particularly acute liver injury and cardio-/cerebrovascular events. In this study, no hepatotoxicity was reported with cumulative methylprednisolone doses <8 g. No patient experienced hepatotoxicity defined as a ≥4× elevation in liver enzymes. It is noted, however, that this AE remains rare (~0.6%). Minor AE occurred frequently across all dosing groups.

The myocardial infarction fatality occurred in an LD patient with pre-existing COPD one week after the sixth infusion. Overall, no significant differences in safety scores were observed between groups.

DON developed during weeks 6–12 in six patients: 3 (6%) in the MD group and 3 (6%) in the LD group. Between weeks 12–24, DON developed in four additional patients—3 (6%) in the HD group and 1 (2%) in the MD group. All four had shown no improvement during methylprednisolone treatment. As a result, overall ophthalmic improvement at week 24 did not significantly differ across groups (HD: 43%, MD: 40%, LD: 34%).

CAS (including spontaneous retrobulbar pain, pain on eye movement, conjunctival hyperemia, eyelid erythema, chemosis, carbuncular swelling, and eyelid edema) and the Bahn & Gorman diplopia score were used to assess activity. CAS significantly declined in all groups during treatment; however, the rate of decline was significantly greater in the HD versus LD group. Use of a 7.47 g cumulative methylprednisolone dose yielded a short-term benefit over lower doses but was accompanied by slightly increased toxicity.

Aktaran et al. 2007 (55)

No dedicated safety endpoint or formal safety profile assessment was reported.

A higher proportion of favorable outcomes was observed in the IVGC group compared to the OGC group across multiple domains, including effectiveness, tolerability, side-effects, and QoL. IVGC was better tolerated, with 56% of patients reporting AE, compared to 81% in the OGC group ($p < 0.01$).

Weight gain was the most frequently reported AE in both groups, particularly among female patients. Cushingoid features were observed in two patients in the OGC group and in one patient in the IVGC group, with a higher tendency noted in the OGC group overall. GI AE were comparable between groups, likely due to pre-existing GI complaints and prophylactic use of H_2-receptor blockers.

Twelve percent of patients in the IVGC group experienced palpitations and hot flashes on treatment days.

He et al. 2017 (60)

During treatment, recurrence of ophthalmic symptoms occurred in 29.4% (5/17) of patients in the MR group and 53.3% (8/15) in the WR group ($p > 0.05$), presenting as either reappearance or worsening of original symptoms. Symptom severity was generally more pronounced in the MR group, with patients reporting particularly marked discomfort around 10 days after each pulse therapy. In the WR group, subjective worsening was typically noted shortly after IVMP doses were halved at week 7 or approximately 5 days after each pulse.

One patient underwent orbital decompression, and another developed retrobulbar pain at week 7—symptoms not previously present.

There were no significant differences in AE between the groups. One patient discontinued early due to severe gastric pain, headache, and hidrosis after the first infusion; symptoms resolved within one day of treatment cessation. No severe AE—such as hepatotoxicity defined by ≥3× elevation in liver enzymes—were observed.

Weight gain was the most frequently reported AE, with an average increase of approximately 4 kg during treatment. Abdominal pain was reported in 9.1% of MR patients and 11.1% of WR patients. Blood glucose elevation was seen in 9.1% of MR and 5.6% of WR patients. Hypokalemia occurred in one patient in each group. In total, AE were reported in 63.6% of MR patients and 50.0% of WR patients.

Both MR and WR regimens were effective and safe in the treatment of GO. Symptom improvement followed a more fluctuating course in the MR group, while progress in the WR group was slower and steadier. However, the WR group showed a higher recurrence rate and slightly lower overall efficacy compared to MR.

Zhu et al. 2014 (63)

Body weight, BP, blood glucose, blood lipids, liver function, ion concentrations, and one mineral density (BMD) were assessed to monitor treatment-associated weight gain, decreased BMD or osteoporosis, hypertension, IFG/IGT/Diabetes mellitus, hyperlipidemia, impaired liver function, hypokalemia, and hyperuricemia. BMD (g/cm^2) of the lumbar spine, femoral neck, and hip was measured using DXA (GE-Lunar Prodigy; GE Healthcare).

AE occurring at weeks 4 and 12 in patients with normal baseline values and no self-reported history were evaluated as follows:

1. Body weight gain of 0.5, 1, 2, and 3 kg at weeks 4 and 12 compared to baseline
2. BMD of L2–L4, femoral neck, and total hip assessed by T score. Osteoporosis was defined as T ≤ –2.5 in any of the three regions, and bone loss as –2.5 < T < –1.0, per WHO criteria
3. Development of:
   – IFG: fasting glucose 6.1–7.0 mmol/L and 2-h glucose <7.8 mmol/L
   – IGT: fasting glucose <7.0 mmol/L and 2-h glucose 7.8–11.1 mmol/L
   – Diabetes mellitus: fasting glucose ≥7.0 mmol/L or 2-h glucose >11.1 mmol/L
4. Development of hypertension: systolic BP >140 mmHg or diastolic BP >90 mmHg
5. Development of hypokalemia: serum potassium <3.5 mmol/L
6. Development of hyperuricemia: serum uric acid >420 µmol/L (men) or >360 µmol/L (women)
7. Development of liver function impairment: ALT or AST >40 U/L or >100 U/L (≥2.5× ULN)
8. Development of hyperlipidemia based on ATP III criteria: total cholesterol >6.22 mmol/L, triglycerides >2.26 mmol/L, LDL >4.14 mmol/L, or HDL <1.0 mmol/L

Treatment-related AE were evaluated at weeks 4, 8, and 12. Two patients on the daily protocol experienced notable AE:

- One 44-year-old female with normal viral hepatitis markers developed liver enzyme elevations >3× ULN in week 2, despite no history of liver disease.
- One 47-year-old male developed severe, persistent hiccups in week 3, interfering with daily life.

Both patients recovered after discontinuation of methylprednisolone. No other severe AE were observed. The most common AE were weight gain and hypokalemia. By the end of IV methylprednisolone therapy, 36/79 patients (46.1%) had gained >0.5 kg, and 14/78 patients (17.9%) had gained >3 kg. There were no statistically significant differences between the two groups.

Kahaly et al. 2005 (62)

IV glucocorticoids were generally well tolerated, with significant differences in AE rates between the groups. Both the total number of patients experiencing side-effects and the number of major AE (defined as depression or severe hypertension) were higher in the oral group. Fasting blood glucose, liver enzymes, and renal parameters remained within the normal range in both groups throughout steroid treatment and after therapy completion. These laboratory values also remained stable during the 6-month follow-up.

At week 12, a significant reduction in BMD of the lumbar spine was observed in the oral group (baseline: 1.10 g/cm² [range: 0.8–1.3]; week 12: 0.95 g/cm² [range: 0.6–1.2]; P < 0.05), whereas BMD in the IV group remained stable (baseline: 1.15 g/cm²; week 12: 1.12 g/cm²). No significant changes were observed in the femoral neck in either group.

<u>Six-month follow-up</u>

Following the completion of glucocorticoid therapy, additional interventions were required less frequently in the IV group. Within the 6-month follow-up period, optic neuropathy developed in 4/35 patients (11%) in the oral group compared to 0 in the IV group (P = 0.01). Orbital decompression was performed in 11 patients (32%) in the oral group versus 5 patients

(14%) in the IV group (P = 0.003). Squint surgery was required in 12 patients (35%) and 7 patients (20%) in the oral and IV groups, respectively (P = 0.02).

Major AE included 2 cases of depression in the oral group. Reported AE in this group included weight gain >3 kg (26%), GI symptoms (17%), sleeplessness (14%), myalgias, hypertension, hirsutism, depression, and palpitations.

Of note, abrupt withdrawal of IV steroids may trigger reactivation of underlying liver autoimmunity following prolonged immunosuppression, potentially leading to liver injury. Therefore, precautionary measures are recommended, including limiting the cumulative IVMP dose to 6–8 g, evaluating liver morphology, viral markers, and autoantibodies prior to treatment, and excluding high-risk patients. Monitoring of liver function and morphology is advised before, during, and after IV therapy.

Overall, IV steroids were deemed safe, with significantly different AE profiles between the two groups (P < 0.001).

Kahaly et al. 2018 (52)

This study assessed safety in all patients who received at least one dose of study drug. AE were documented and coded according to MedDRA, as recommended by ICH guidelines. Each AE was evaluated for alternative causes to determine its relatedness to mycophenolate exposure; events were classified as side-effects if a relation was established.

AE were followed until a stable outcome was observed or until the patient was lost to follow-up. Seriousness was assessed using the ICH E6 GCP criteria. Patients who discontinued due to AE, side-effects, or worsening of TED were retained in the primary analysis. WBC count, liver enzymes, serum thyroid-related hormones, and TSHR-Ab (measured by CLIA; Abbott, Wiesbaden, Germany; cutoff: 1.8 IU/L) were assessed at weeks 0, 6, 12, 24, and 36.

A total of 201 AE were reported in 79/164 patients (48%). No SUSAR were observed. The most frequently reported AE were eye surgery (12 patients, 7%) and insomnia (11 patients, 7%).

Twenty-four SAE occurred in 23 patients (14%), including thyroidectomy, orbital decompression for DON, and inpatient treatment for unspecific symptoms. Of these, 11 SAE occurred in 10 patients in the methylprednisolone group and 13 in the methylprednisolone + mycophenolate group. In total, 68 drug-related side-effects were reported in 37 patients (23%).

Side-effects occurred in 16/81 patients (20%) in the monotherapy group and in 21/83 patients (25%) in the combination group (p=0.48). In the monotherapy group, 29 side-effects were reported (19 grade 1, 10 grade 2), and in the combination group, 39 events were observed (31 grade 1, 8 grade 2) (see Table 2). No patients required dose adjustments or discontinued due to drug toxicity. No major treatment-related AE or premature dropouts occurred due to SAE.

These findings are consistent with results from the large European multicenter transplant trial investigating MMF in combination with ciclosporin and corticosteroids, which demonstrated that treatment-related AE are dose dependent. The present trial also supports the findings of the first prospective longitudinal study evaluating the tolerability and toxicity of mycophenolate in TED using standardized definitions.

At the post-hoc 24-week timepoint, the response rate was significantly higher in the methylprednisolone + mycophenolate group, without an increase in drug-induced AE. Overall, the safety profile indicated acceptable tolerability of both methylprednisolone and mycophenolate, with no SAE and no treatment discontinuations due to AE.

Shen et al. 2022 (15)

All patients underwent ophthalmic, endocrine, and safety assessments at baseline, week 6, and week 12. To monitor treatment-associated adverse events, the following parameters were evaluated: complete blood count, body weight, blood pressure, blood glucose, blood lipids, liver function tests, electrolytes, urea, urinalysis, and BMD. These assessments were aimed at detecting potential agranulocytosis, weight gain, bone loss or osteoporosis, hypertension, diabetes, hyperlipidemia, hepatic impairment, hypokalemia, hyperuricemia, and urinary tract infections. Any self-reported medical events were also recorded. AEs were graded according to the CTCAE, version 5.0.

BMD was measured by dual-energy X-ray absorptiometry (GE-Lunar Prodigy; GE Healthcare) in the lumbar spine, femoral neck, and total hip at baseline and week 12.

AEs occurring at weeks 6 and 12 were evaluated as follows:

1. **Weight gain**: An increase of more than 2.5% and 5% compared to baseline at week 12. Only a ≥5% increase (approximately 3 kg in this cohort) was counted as an AE, as this corresponds to grade 1 in CTCAE.
2. **New-onset diabetes mellitus**: Defined as fasting plasma glucose ≥7 mmol/L, 2-hour post-OGTT glucose ≥11.1 mmol/L, or HbA1c ≥6.5%, with normal glycemic markers at baseline (fasting glucose <5.6 mmol/L, 2-h glucose <7.8 mmol/L, HbA1c <5.7%).
3. **New-onset hypertension**: Defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg in patients with normal baseline BP.
4. **Hypokalemia**: Serum potassium <3.5 mmol/L with normal potassium at baseline.
5. **Hyperuricemia**: Serum uric acid >420 μmol/L (men) or >360 μmol/L (women) with normal values at baseline.
6. **Hepatic impairment**: ALT or AST above the upper normal limit in patients with normal baseline values.
7. **Hyperlipidemia**: Evaluated and classified according to CTCAE criteria.
8. **Neutropenia**: Defined as neutrophil count $<2 \times 10^9$/L and graded according to CTCAE.
9. **BMD**: BMD of L1–L4, femoral neck, and total hip reported as T-scores.
10. **Osteoporosis**: Defined as a T-score ≤−2.5 in any of the three measured sites.
11. **Bone loss**: Defined as a T-score between −1.0 and −2.5, according to WHO criteria (1994).

All AEs were classified as mild to moderate in severity, and no patients discontinued treatment. The group receiving reduced-dose methylprednisolone plus MTX experienced significantly fewer AEs (21 in group 2) compared with the other groups (41 in group 1 and 38 in group 3, $P = 0.017$). The most frequently reported AE was new-onset dyslipidemia, observed in 50% of patients in groups 1 and 3, though without statistically significant differences among groups.

Compared to standard methylprednisolone monotherapy, group 2 exhibited a significantly lower incidence of new-onset hypokalemia at week 6 ($P = 0.02$) and less weight gain at week 12 ($P = 0.04$). New-onset hypertension occurred more frequently in group 1 than in group 3

at both week 6 (*P* = 0.047) and week 12 (*P* = 0.02). MTX-related AEs such as neutropenia were observed in one patient in group 2 (grade 2) and three patients in group 3 (grade 1).

Patients with known risk factors for severe AEs, including pre-existing liver or renal impairment, a history of hepatitis or tuberculosis, or malignancy, were excluded from the study. AEs were closely monitored at six-week intervals. Neutropenia was observed in four patients (1/30 in the reduced methylprednisolone + MTX group and 3/30 in the methylprednisolone + MTX group), and all cases resolved with leucogen treatment.

These findings suggest that, with appropriate pretreatment screening and close monitoring, the reduced methylprednisolone plus MTX regimen is associated with a lower incidence of AEs compared to methylprednisolone monotherapy. As most AEs appeared to be dose-dependent, the study supports that reduced-dose methylprednisolone combined with MTX can offer similar efficacy with improved safety.

Mu et al. 2020 (61)

To assess treatment-associated side effects, body weight, blood pressure, routine biochemical parameters, and electrocardiogram (ECG) were measured at baseline and at the 12-week follow-up visit. These assessments were also performed if the patient reported discomfort during the treatment period.

Major AEs were defined as life-threatening liver failure and cardio- or cerebrovascular complications. Minor AEs included weight gain (defined as an increase of ≥2 kg at the 12-week follow-up compared to baseline), hyperglycemia (fasting blood glucose ≥7 mmol/L or 2-hour postprandial glucose ≥11.1 mmol/L), hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), renal dysfunction (eGFR <60 ml/min/1.73 m²), hepatic dysfunction (ALT or AST ≥2.5 times the upper limit of normal), GI discomfort, sleeplessness, and infections.

IV glucocorticoid treatment was generally well tolerated in both regimens, with no SAEs, including severe liver dysfunction (liver enzymes ≥2.5× ULN) or cardiovascular events. The total number of patients experiencing minor side effects was higher in the daily regimen group (P<0.01) compared to the WR (P<0.05). The most frequently reported AEs in the DR were sleeplessness, GI discomfort, and hyperglycemia, whereas weight gain was relatively common in the WR. BP, as well as liver and renal function parameters, remained within the normal range in both treatment groups.

No major AEs were recorded in either regimen. Worsening of eye symptoms (reported in two patients) occurred only in the WR. A larger number of minor AEs were observed among patients receiving the DR.

The present results indicate that in patients with active, moderate-to-severe TAO, the DR of IV glucocorticoids was associated with a higher response rate compared to the weekly protocol. However, both regimens showed distinct safety profiles in terms of AEs.

F.1.4 Adverse events and the health economic model

A clinical and RWE SLR was conducted to identify common AEs associated with IVMP, as included in the model. As AEs reported in literature are treatment-emergent and not treatment-related adverse events, it is necessary to include a minimum incidence rate to avoid rare AEs from introducing bias to the result.

In the base case, the AE probabilities for IVMP were sourced from Salvi et al. (2015) because this was the only study reporting grade ≥3 AEs that occurred in more than 5% of

patients (92). Three alternative publications were explored that reported all AEs (irrespective of severity) occurring in more than 5% of patients (55, 93, 94).

For each AE source, the duration over which each reported probability was measured differed. To transform the probabilities to a time frame relevant for the CEM (i.e., six weeks, corresponding to the model cycle length), the method described in Appendix K was used.

The probabilities of AEs for teprotumumab were sourced from the Phase 2 and OPTIC Phase 3 trial. No grade ≥3 AEs occurred in ≥5% of patients, hence no AEs were included for teprotumumab in the base case analysis, although this can be changed in the health economic model. Only three types of grade ≥3 AE occurred in ≥5% of the IVMP treatment arm of Salvi et al. (2015); hyperglycemia, 10-fold increase of aminotransferases and 5-fold increase of gamma-glutamyl transferase (92). Based on the transformed probabilities from the study by Salvi et al. (2015), each of these three AEs was included in the model with a frequency of 1.6% per cycle for IVMP. AEs were only included in the model during the cycles in which patients received treatment.

Table 87: Adverse events used in the health economic model

Adverse events	Teprotumumab	IVMP		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Hyperglycemia	0.0%	1.6%	Salvi et al. 2015 (92)	Only grade ≥3 AEs that occurred in more than 5% of patients
10-fold increase of aminotransferases	0.0%	1.6%	Salvi et al. 2015 (92)	Grade ≥3 AEs that occurred in more than 5% of patients
5-fold increase of gamma-glutamyl transferase	0.0%	1.6%	Salvi et al. 2015 (92)	Grade ≥3 AEs that occurred in more than 5% of patients

Abbreviations: AE, adverse event; IVMP, intravenous methylprednisolone.

F.1.5 Transformation of AE probabilities

To transform the probabilities of AEs to a time frame relevant for the CEM (i.e., six weeks, corresponding to the model cycle length), they were first converted from a probability to a rate using the following equation:

Equation 1

$$r = \frac{-[\ln(1-p)]}{t/6} \quad (95)$$

Where r is the rate (which is assumed constant over time) and p is the probability over the time period t, in weeks. The denominator is divided by six to scale the rate to a six-weekly rate.

The rate is then converted back to a probability using the following equation:

Equation 2

$$p = 1 - e^{-rt} \quad (95)$$

Appendix G. Health-Related Quality of Life

G.1 Data Collection – Overview of Responses

NA

G.2 Reporting of Domains

NA

G.3 Mapping

No mapping algorithm was applied, as no validated mapping from GO-QoL to EQ-5D exists and utility values were derived using a de novo TTO study.

G.4 Calculation of Utility Values

Health-state utility values were not collected in the pivotal Phase 2 and OPTIC Phase 3 clinical trials, as EQ-5D was considered insufficiently sensitive to detect relevant changes in health-related quality of life (HRQoL) in patients with active moderate to severe thyroid eye disease (TED). Patient-reported HRQoL in the clinical trials was instead assessed using the GO-QoL instrument. However, no validated mapping algorithm exists to translate GO-QoL outcomes to EQ-5D utilities.

Consequently, a targeted literature review was conducted to identify published studies reporting utility values or other HRQoL estimates relevant to patients with TED. Several studies were identified; however, none provided utility values aligned with the health-state definitions used in the health economic model. A study by Beauchamp et al. (2005) reported utility values by different grades of diplopia in patients with strabismus who had surgery planned or were managed non-surgically. However, baseline patient characteristics were not reported, and it was therefore unclear to what extent the study population included patients with active TED. As such, the applicability of the reported utility decrements to the TED population was considered uncertain. Furthermore, diplopia represented only one component of the health-state definitions applied in the economic model.

Additional evidence was identified from Gerding et al. (1997) and Choi et al. (2012). Neither study reported directly elicited utility values but instead provided partial estimates of quality of life. The study by Gerding et al. (1997) included a comparison with ulcerative colitis, for which utility estimates are available in the literature; however, the TED data were sparse and more than 20 years old. The estimates reported by Choi et al.

(2012) were more recent but were derived from a Korean population and were therefore not considered appropriate for use in the present model context. A targeted literature search was also conducted to identify utility values for surgery in relevant disease proxies; however, no suitable data sources were identified.

Due to the limitations of the existing literature, a de novo utility study was conducted using a vignette-based time trade-off (TTO) approach. Utilities were elicited from a demographically representative sample of the general US population without TED, recruited through a proprietary panel. In total, 111 participants completed the TTO interviews, including 10 participants in a pilot study and 101 participants in the main study. The majority of participants were aged 55–64 years, and approximately two-thirds were female. Although these characteristics do not fully reflect the general population, they were considered appropriate in representing the population affected by moderate to severe TED.

General population interviews were conducted to minimize bias associated with personal experience of TED or interest in treatment outcomes. Prior to the TTO interviews, visual analogue scale (VAS) exercises were conducted to familiarize participants with the health-state descriptions and the concept of valuing health states. The VAS was also used to assess the participants' own health status at the time of the interview.

The TTO study applied a finite 10-year time horizon and utilities were anchored at 1 for full health and 0 for death. Participants were presented with vignette-based health-state descriptions reflecting the proptosis and diplopia health states included in the economic model and were asked to trade off years lived in these health states against a shorter duration in full health. Utility values were calculated directly from respondents' TTO valuations. As utility values were directly elicited for each health state, no regression-based estimation or mapping was applied.

Mean utility values across health states decreased with increasing severity of disease, as expected. A smaller reduction in utility was observed when the severity of proptosis remained constant, and only minimal changes were observed between lower diplopia states. Pairwise comparisons using Wilcoxon rank sum tests indicated statistically significant differences in utility values for 9 out of 15 health-state comparisons. The remaining six comparisons did not show statistically significant differences and were between neighboring health states with only small incremental differences in disease severity.

The mean health score measured using the VAS in the study population was 77.64, while the mean VAS score reported for the US general population was 80.4 (95% CI: 74.59–80.69), indicating that the study sample was broadly comparable to the general population in terms of overall health status.

Although the TTO study was conducted in a US population, all utility values were reviewed and validated by a Danish clinical expert, who considered them reflective of the HRQoL of patients with moderate to severe TED in Denmark. These utility values were therefore applied as base-case utilities for the active phase of disease.

For patients entering the chronic phase of TED, no published utility values aligned with the model health-state definitions were identified. Evidence from the literature indicates that disease activity, particularly inflammatory symptoms, is an important determinant of HRQoL in TED. In particular, Wang et al. (2021) demonstrated a clear association between clinical activity score (CAS) and patient-reported quality of life, with lower disease activity associated with improved quality of life.

Based on this evidence, utility values applied in the chronic phase were derived by adjusting the TTO-based utility values reported by Smith et al. (2023). The adjustments reflect improvements in underlying quality of life associated with reduced inflammation and pain following transition to the chronic phase, while maintaining similar levels of proptosis and diplopia. The direction and relative magnitude of these adjustments were supported by clinical expert input. Chronic utility values were applied from cycle 26 onwards, with patients assumed to remain in the same proptosis and diplopia health states, with the only change being the utility values applied.

G.5 Adverse Event Disutilities

Although only disutilities associated with three types of AEs were included in the base case as described in section 9.2, all disutilities which are available for inclusion in the model are listed below.

Table 88: Adverse Events, Disutilities and Average Durations

Adverse event	Disutility	Average duration (days)	Sources and assumptions
Muscle spasms	0.04	63	Sourced from Matza *et al.* 2019 and Douglas *et al.* 2022. (68, 96)
Alopecia	0.04	168	For AEs ongoing, assumed AE occurred over the treatment course; Sourced from Hall *et al.* 2019 and Douglas *et al.* 2022. (68, 97)
Nausea	0.06	2	Sourced from Hagiwara *et al.* 2018 and Douglas *et al.* 2022. (68, 98)
Sleepiness/fatigue	0.03	32	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Diarrhea	0.05	3	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Dry skin	0.00	75	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)

Dysgeusia	0.03	23	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Headache	0.03	23	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Amenorrhea	0.06	168	Disutility for hormone dysfunction assumed same as cushingoid habitus and for AEs ongoing, assumed AE occurred over the treatment course; Sourced from Douglas *et al.* 2022. (68)
Dizziness	0.03	9	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Stomatitis	0.14	114	Sourced from Paracha *et al.* 2018 and Douglas *et al.* 2022. (68, 99)
Abdominal pain	0.05	11	Sourced from NICE TA804 and Douglas *et al.* 2022. (68, 100)
Cough	0.01	75	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 100)
Influenza	0.01	59	Sourced from Sullivan *et al.* 2011 and Douglas *et al.* 2022. (68, 99)
Cushingoid habitus	0.06	105	Assuming AE occurred over the course of treatment; sourced from NICE HST14, Roy *et al.* 2015 and Marcocci *et al.* 2001. (93, 94, 101)
Weight gain	0.01	98	Assuming AE occurred over the course of treatment; sourced from Smith-Palmer *et al.* 2016, Roy *et al.* 2015 and Aktaran *et al.* 2007. (55, 93, 102)
Hypertension	0.05	112	Assuming AE occurred over the course of treatment; sourced from Sullivan *et al.* 2011 and Roy *et al.* 2015. (93, 99)
Depression	0.08	10	Sourced from Kolovos *et al.* 2017 and Matza *et al.* 2019. (96, 103)
Myalgias	0.09	3	Sourced from Sullivan *et al.* 2011. (99)

Glucose intolerance	0.00	98	Disutility assumed to be 0 and assuming AE occurred over the course of treatment; sourced from Marcocci *et al.* 2001. (94)
Gastritis	0.05	3	Sourced from NICE TA804 and Douglas *et al.* 2022. (68, 100)
Urinary tract infection	0.10	14	Sourced from NICE TA127. (104)
Palpitation	0.04	1	Sourced from Sullivan *et al.* 2011 and Aktaran *et al.* 2007. (55, 99)
Hyperglycemia	0.01	84	Assuming AE occurred over the course of treatment; sourced from Drummond *et al.* 2018 and Aktaran *et al.* 2007. (55, 79)
10-fold increase of aminotransferases	0.00	168	Disutility assumed to be 0 and assuming AE occurred over the course of treatment; sourced from Salvi *et al.* 2015. (92)
5-fold increase of gamma-glutamyl transferase	0.00	168	Disutility assumed to be 0 and assuming AE occurred over the course of treatment; sourced from Salvi *et al.* 2015. (92)
Rash	0.00	75	Assumed same as dry skin.
Hearing impairment	0.01	168	Sourced from Salomon et al. 2015 and assuming AE occurred over the course of treatment. (105)

Abbreviations: AE, adverse event.

G.6 OPTIC-J Baseline Characteristics

Table 1. Demographic and clinical characteristics at the baseline visit (intent-to-treat set).

	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)
Thyrotropin, mIU/L	0.43 (0.01–2.81)	0.77 (0.04–2.82)
Proptosis in study eye, mm	21.07 (2.46)	20.39 (2.42)
CAS in 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)

Appendix H. Literature Searches for the Clinical Assessment

H.1 Effect and Safety of the Intervention and Comparators

A global systematic literature review (SLR) was carried out to identify evidence on the efficacy and safety of teprotumumab and other treatments, as identified in randomized controlled trials (RCTs) and other clinical studies.

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

Database searches via the Ovid platform were conducted in EMBASE, MEDLINE, MEDLINE In-Process, and the Cochrane Database of Systematic Reviews (CDSR) for full-text publications and conference abstracts. The Database of Abstract of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trial (CENTRAL) were also searched.

The bibliographic databases presented in Table 89 were used to conduct the SLR. The database searches were originally conducted on 9 June 2023 and then updated on 11 September 2024, and 17 December 2025.

Table 89: Bibliographic databases included in the literature search

Database	Platform/Website	Search period	Date of search
EMBASE	Ovid	1974 to 17 December 2025	09.06.2023, 11.09.2024 and 17.12.2025
MEDLINE	Ovid	1946 to 17 December 2025	09.06.2023, 11.09.2024 and 17.12.2025
CDSR	Ovid	2005 to 17 December 2025	09.06.2023, 11.09.2024 and 17.12.2025
DARE*	University of York Centre for Reviews and Dissemination	N/A	09.06.2023, 11.09.2024 and 17.12.2025

CENTRAL	Cochrane Library	N/A	09.06.2023, 11.09.2024 and 17.12.2025

*DARE was discontinued in 2015 and only the archived version is available.

Abbreviations: CDSR, Cochrane database of systematic review; CENTRAL, Cochrane central register of controlled trials; DARE, database of abstract of reviews of effects; EBM, evidence-based medicine; MEDLINE, medical literature analysis and retrieval system online.

The databases searched are in accordance with the list of databases suggested by the HTA organizations of interest, such as the NICE, Institute for Clinical and Economic Review (ICER), CADTH, the Pharmaceutical Benefits Advisory Committee (PBAC), and the Scottish Medicines Consortium (SMC).

Conference proceedings

Proceedings from selected conferences and congresses were manually reviewed to retrieve the latest abstracts and results not yet published in journals as full-text articles, or to supplement results of previously published studies. The list of key conferences is provided in Table 90.

Table 90: Conference proceedings in the literature search

Conferences	Website	Years searched	Date of search
American Academy of Ophthalmology (AAO)	Manual Search: https://www.aao.org/annual-meeting/meeting-information	2020, 2021, 2022, 2023, 2024, 2025	09.06.2023, 11.09.2024 and 17.12.2025
American Ophthalmological Society (AOS)	Manual Search: https://www.aosonline.org/	2021, 2022, 2023, 2024, 2025	09.06.2023, 11.09.2024 and 17.12.2025
Annual Meeting of the Endocrine Society (ENDO)	Manual Search: https://academic.oup.com/jes/supplements/volume	2020, 2021, 2022, 2023, 2024, 2025	09.06.2023, 11.09.2024 and 17.12.2025
European Society of Ophthalmic Plastic and	Manual Search: https://www.esoprs.eu/about-esoprs/annual-meetings/	2021, 2022, 2023,	09.06.2023, 11.09.2024

Reconstruction Surgery (ESOPRS)	2024, 2025	and 17.12.2025

Registry search

Key clinical trial registries were searched to identify ongoing trials in TED. Information from clinical trial registries were used as a quality assurance tool to ensure all relevant studies are identified in the SLR, as well as to supplement information on study and treatment characteristics where needed. No baseline characteristics or results were extracted from clinical trial registries. The search terms “thyroid eye disease”, “Graves' ophthalmopathy”, “Graves' orbitopathy”, and “thyroid-associated ophthalmopathy” were used to identify relevant trials. Registry websites searched are presented in Table 91.

Table 91: Registry review

Registry	Website	Date of search
ClinicalTrials.gov	Manual Search: https://clinicaltrials.gov/	09.06.2023, 11.09.2024 and 17.12.2025
Health Canada Clinical Trials Database	Manual Search: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html	09.06.2023, 11.09.2024 and 17.12.2025
EU Clinical Trials Register	Manual Search: https://www.clinicaltrialsregister.eu/ctr-search/search	09.06.2023, 11.09.2024 and 17.12.2025
World Health Organization International Clinical Trials Registry Platform	Manual Search: https://trialsearch.who.int/Default.aspx	09.06.2023, 11.09.2024 and 17.12.2025

Abbreviations: EU, European Union.

HTA submission searches

The HTA submissions review was conducted on 17 December 2025. Search terms used to identify relevant submissions included the following: “thyroid eye disease”, “TED”, “Graves' ophthalmopathy”, “Graves' orbitopathy”, and “thyroid-associated

ophthalmopathy." No time restrictions were applied. The websites of HTA bodies searched are presented in Table 92.

Table 92: HTA sources included in the literature review

HTA body	Website	Date of search
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/	09.06.2023, 11.09.2024 and 17.12.2025
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/health-technology-review	09.06.2023, 11.09.2024 and 17.12.2025
Danish Medicines Council – Medicinradet	https://medicinraadet.dk/om-os/in-english	09.06.2023, 11.09.2024 and 17.12.2025
European network for Health Technology Assessment (EUnetHTA)	https://www.eunethta.eu/	09.06.2023, 11.09.2024 and 17.12.2025
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://oys.fi/fincchta/	09.06.2023, 11.09.2024 and 17.12.2025
Germany's Joint Federal Committee (Gemeinsamer Bundesausschuss [G-BA])	https://www.g-ba.de/english/	09.06.2023, 11.09.2024 and 17.12.2025
Haute Autorité de Santé (HAS)	https://www.has-sante.fr/	09.06.2023, 11.09.2024

		and 17.12.2025
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	https://www.iqwig.de/en/	09.06.2023, 11.09.2024 and 17.12.2025
Institut National d'Excellence en Santé et en Services Sociaux (INESSS)	https://www.inesss.qc.ca/en/index.html	09.06.2023, 11.09.2024 and 17.12.2025
National Committee for Health Technology Incorporation (CONITEC)	https://www.gov.br/conitec/pt-br	09.06.2023, 11.09.2024 and 17.12.2025
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	09.06.2023, 11.09.2024 and 17.12.2025
Norwegian Medicines Agency	https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm	09.06.2023, 11.09.2024 and 17.12.2025
Norwegian Knowledge Centre for Health Services	https://legemiddelverket.no/English	09.06.2023, 11.09.2024 and 17.12.2025
Pharmaceutical Benefits Advisory Committee (PBAC)	https://www.pbs.gov.au/info/industry/listing/participants/pbac	09.06.2023, 11.09.2024 and 17.12.2025
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	09.06.2023, 11.09.2024

		and 17.12.2025
Swedish Dental and Pharmaceutical Benefits Agency (TLV)	https://www.tlv.se/in-english.html	09.06.2023, 11.09.2024 and 17.12.2025

H.1.1 Search strategies

MEDLINE, EMBASE, and Cochrane searches were conducted on December 17, 2025, using the Ovid platform. Database searches were performed from inception.

The search strategies for each database are presented in Table 93, Table 94, Table 95, Table 96 and Table 97.

Table 93: Search Strategy in MEDLINE (2025 update)

#	Search terms	Hits
1	graves ophthalmopathy/	3,758
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6,756
3	or/1-2	6,756
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	374,796
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or	61,624

	pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab,kw,kf,rn.	
6	exp meprednisone/ or (prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or detla cortene beta or "deltisone b" or "deltisona b" or "sch 4358" or sch4358).ti,ab,kw,kf,rn.	110,042
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw,kf,rn.	19,017
8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	326,605
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	815,774
10	orbital radiotherapy.ti,ab,kw,kf,rn.	290
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halpryza or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw,kf,rn.	36,314

12	(toclizumab or actemra or atlizumab or "bat 1806" or bat1806 or lusinex or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw,kf,rn.	154
13	(teprotumumab or "hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza).ti,ab,kw,kf,rn.	393
14	(batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	32
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw,kf,rn.	2
16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw,kf,rn.	1
17	(VB-421 or "VB 421" or VB421).ti,ab,kw,kf,rn.	0
18	(aflibercept or "abp 938" or abp938 or "alt l9" or altl9 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or "bay 865321" or bay865321 or "chs 2020" or chs2020 or eylea or "fyb 203" or fyb203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw,kf,rn.	4,527
19	(secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw,kf,rn.	3,160
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapammune or rapamune or rapmycin or "sila 9268a" or sila9268a or tarzifxy or "tavt 18" or tav18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw,kf,rn.	28,265
21	rapamycin.ti,ab,kw,kf,rn.	41,857
22	exp betamethasone/ or (betamethason* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsopart or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or methasone or "nsc 39470" or nsc39480 or opthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw,kf,rn.	10,368
23	(((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or	1,720

	immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin*2).ti,ab,kw,kf,rn.	
24	(vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw,kf,rn.	14
25	(linstinib or "osi 906" or soi906 or osi906aa).ti,ab,kw,kf,rn.	99
26	(bimotoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw,kf,rn.	140
27	exp decompression, surgical/ or ((orbital or opthalm*) adj (operation or decompression or surgery or surgical procedure*)).ti,ab,kw,kf,rn. or (decompression adj2 surgery).ti,ab,kw,kf. or (strabismus adj2 (operation or surgery)).ti,ab,kw,kf,kw.	45,645
28	((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw,kf,rn.	1,427
29	exp atorvastatin/ or (astator or ator or atorab or atoris or atorlip or atorvadivid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or Lipitor or liprimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw,kf,rn.	12,927
30	exp doxycycline/ or (adoxa or amermycin or apprilon or atrax or azudoxat or bactidox or banndoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoin or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doinmycin or dosil or dotur or doxaciclin or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxicycline or doxilin or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxycen or doxychel or doxycin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdoxin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxyne or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramycina or tenutan or tolexine or "tolexine ge" or torymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or	23,285

	vibramycin? or vibraveineuse or vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw,kf,rn.	
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw,kf,rn.	13,159
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or cyltezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulio or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulinno or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw,kf,rn.	13,404
33	exp etanercept/ or (avent or benepali or brenzys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatocept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw,kf,rn.	10,691
34	("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw,kf,rn.	311
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw,kf,rn.	45,709
36	(K1-70 or K170 or "K1 70").ti,ab,kw,kf,rn.	64
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw,kf,rn.	4
38	or/4-37	1,730,407
39	3 and 38	2,610

40	exp Randomized Controlled Trial/ or exp Random Allocation/	747,444
41	exp Double-Blind Method/ or exp Single-Blind Method/	222,463
42	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	1,042,598
43	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	93,217
44	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/	418,381
45	exp Multicenter Study/	387,709
46	exp placebos/	40,921
47	exp Cross-Over Studies/	60,753
48	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	295,612
49	randomized controlled trial.pt.	653,925
50	controlled clinical trial.pt.	95,784
51	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	1,717,403
52	(random* adj2 allocat*).tw.	51,318
53	blind*.ti,ab,kw.	392,544
54	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1,167,802
55	prospective studies/	736,594
56	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	546,999
57	trial.ti.	355,184
58	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	187,394

59	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	64,799
60	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	303,326
61	(single arm or single group).ti,ab,hw,kf.	25,506
62	(basket adj2 trial*).ti,ab,hw,kf.	504
63	observational study/	189,305
64	observational studies as topic/	11,749
65	clinical studies as topic/	894
66	controlled before-after studies/	796
67	cross-sectional studies/	570,145
68	historically controlled study/	242
69	interrupted time series analysis/	2,707
70	cohort studies/	366,640
71	longitudinal studies/	192,577
72	prospective studies/	736,594
73	retrospective studies/	1,342,124
74	follow-up studies/	723,413
75	case-control studies/	355,642
76	single-case studies as topic/	185
77	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	294,509
78	cohort*.ti,ab,kf.	1,126,346
79	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	633,087

80	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	199,023
81	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	428,628
82	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	889,828
83	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	184,104
84	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	649
85	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	277,309
86	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	142,641
87	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	6,619
88	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	583,217
89	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	4,288
90	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	27,830
91	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2,003
92	((uncontrolled or non randomi#ed or nonrandomi#ed or pragmatic) adj1 (study or studies)).ti,ab,kf.	15,938
93	or/40-92	7,952,315
94	39 and 93	1,348
95	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative	5,522,010

	or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	
96	case reports/	2,523,612
97	(animal* not human*).sh,hw.	5,361,968
98	95 or 96 or 97	10,738,346
99	94 not 98	1,241
100	limit 99 to english language	1,140
101	limit 100 to yr="2024 -Current"	207

Table 94: Search Strategy in EMBASE (2025 update)

#	Search terms	Hits
1	endocrine ophthalmopathy/	8,550
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	8,107
3	or/1-2	10,384
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw,kf,rn.	1,144,594
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab,kw,kf,rn.	232,288

6	exp meprednisone/ or (prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or detla cortene beta or "deltisone b" or "deltisona b" or "sch 4358" or sch4358).ti,ab,kw,kf,rn.	393,667
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw,kf,rn.	107,588
8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw,kf,rn.	591,648
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.	1,131,407
10	orbital radiotherapy.ti,ab,kw,kf,rn.	361
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halpryza or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw,kf,rn.	137,322
12	exp tocilizumab/ or (toclizumab or actemra or atlizumab or "bat 1806" or bat1806 or lusinex or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw,kf,rn.	35,080
13	exp teprotumumab/ or ("hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza or teprotumumab).ti,ab,kw,kf,rn.	762
14	exp batoclimab/ or (batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw,kf,rn.	126
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw,kf,rn.	37

16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw,kf,rn.	5
17	(VB-421 or "VB 421" or VB421).ti,ab,kw,kf,rn.	1
18	exp aflibercept/ or (aflibercept or "abp 938" or abp938 or "alt l9" or altl9 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or "bay 865321" or bay865321 or "chs 2020" or chs2020 or eylea or "fyb 203" or fyb203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw,kf,rn.	12,475
19	exp secukinumab/ or (secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw,kf,rn.	10,782
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapammune or rapamune or rapmycin or "sila 9268a" or sila9268a or tarzifxy or "tavt 18" or tav18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw,kf,rn.	74,776
21	rapamycin.ti,ab,kw,kf,rn.	86,006
22	exp betamethasone/ or (betamethason* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsopart or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or methasone or "nsc 39470" or nsc39480 or opthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw,kf,rn.	30,402
23	exp thymocyte antibody/ or (((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin* 2).ti,ab,kw,kf,rn.	41,048
24	exp vunakizumab/ or (vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw,kf,rn.	69
25	exp linstinib/ or (linstinib or "osi 906" or soi906 or osi906aa).ti,ab,kw,kf,rn.	227
26	exp bimotoprost/ or (bimotoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw,kf,rn.	343
27	exp strabismus surgery/ or exp decompression surgery/ or ((orbital or opthalm*) adj (operation or decompression or surgery or surgical procedure*)).ti,ab,kw,kf,rn. or (decompression adj2 surgery).ti,ab,kw,kf. or (strabismus adj2 (operation or surgery)).ti,ab,kw,kf,kw.	82,660
28	exp eyelid reconstruction/ or ((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw,kf,rn.	8,097

29	exp atorvastatin/ or (astator or ator or atorab or atoris or atorlip or atorvadivid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or Lipitor or liprimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw,kf,rn.	54,921
30	exp doxycycline/ or (adoxa or amermycin or apprilon or atrax or azudoxat or bactidox or banndoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoin or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doinmycin or dosil or dotur or doxaciclin or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxicycline or doxilin or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxycen or doxychel or doxycin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdoxin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxyne or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramycina or tenutan or tolexine or "tolexine ge" or torymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or vibramycin? or vibraveineuse or vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw,kf,rn.	83,033
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179" or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw,kf,rn.	72,608
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or cyltezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulio or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulinno or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw,kf,rn.	56,541
33	exp etanercept/ or (avent or benepali or brenzys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatocept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw,kf,rn.	43,361

34	exp efgartigimod alfa/ or ("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw,kf,rn.	816
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw,kf,rn.	66,489
36	(K1-70 or K170 or "K1 70").ti,ab,kw,kf,rn.	107
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw,kf,rn.	7
38	or/4-37	3,165,891
39	3 and 38	4,839
40	exp Randomized Controlled Trial/ or exp randomization/	1,205,272
41	exp double blind procedure/ or exp single blind procedure/	394,163
42	exp clinical trial/ or exp controlled clinical trial/ or exp phase 4 clinical trial/ or exp phase 3 clinical trial/ or exp phase 2 clinical trial/	2,642,077
43	exp Multicenter Study/	528,991
44	exp placebo/	509,954
45	exp crossover procedure/	106,401
46	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or dumm* or mask*)).tw,ti,ab,hw,kf.	509,981
47	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	506,198
48	random*.ti,ab,kw. or randomi?ed controlled trial*.tw. or rct.tw.	2,568,699
49	(random* adj2 allocat*).tw.	71,894
50	blind*.ti,ab,kw.	657,996
51	(placebo* or assign* or allocat* or volunteer* or sham).ti,ab,kw.	1,717,446
52	prospective study/	1,023,150
53	(parallel* or factorial* or crossover* or cross over*).ti,ab,kw.	713,750
54	trial.ti.	575,541
55	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	502,728

56	(nonrandom* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	92,151
57	('double-blind' or 'double-blinded').tw,af. or (open label or open-label).af.	580,639
58	(single arm or single group).ti,ab,hw,kf.	65,371
59	(basket adj2 trial*).ti,ab,hw,kf.	1,248
60	observational study/	505,640
61	cross-sectional study/	790,718
62	cohort analysis/	1,509,353
63	longitudinal study/	265,662
64	prospective study/	1,023,150
65	retrospective study/	1,962,775
66	follow up/	2,577,122
67	exp case control study/	265,364
68	quasi experimental study/	16,064
69	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	482,536
70	cohort*.ti,ab,kf.	1,913,939
71	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	1,028,205
72	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	335,745
73	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	619,034
74	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	1,477,124
75	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	247,321
76	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	719
77	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	436,369

78	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	218,133
79	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	7,613
80	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	757,974
81	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	4,612
82	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	34,799
83	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2,757
84	((uncontrolled or non randomi#ed or nonrandomi#ed or pragmatic) adj1 (study or studies)).ti,ab,kf.	22,292
85	or/40-84	12,177,142
86	39 and 85	2,462
87	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	4,110,012
88	case report/	3,196,519
89	(animal* not human*).sh,hw.	5,211,830
90	87 or 88 or 89	12,053,148
91	86 not 90	2,055
92	limit 91 to english language	1,919
93	limit 92 to yr="2024 -Current"	372

Table 95: Search Strategy in Cochrane Central Register of Controlled Trials (2025 update)

#	Search terms	Hits
1	graves ophthalmopathy/	209
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	541
3	or/1-2	541
4	exp glucocorticoid/ or (glucocorticoid* or glucocorticoidsteroid* or glucocorticosteroid* or glycocorticoid* or glycocorticosteroid* or corticosteroid* or corticoid*).ti,ab,kw.	50,985
5	prednisone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or "de cortisyl" or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten? or deltacortisone or deltacortone or deltasone or deltison? or "di adreson" or diadreson or drazone or encorton? or enkorton or fernisone or hostacortin or insone or "liquid pred" or lodotra or me-korti or meprison or metacortandracin or Meticorten or meticortine or nisona or "nsc 10023" or nsc10023 or Orasone or "orb 101" or orb101 or orisane or panafcort or paracort or pehacort or precort or precortal or "prednicen-m" or prednicorm or prednicot or prednidib or prednisone? or prednitone or pronison? or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab,kw.	11,062
6	(prednisone or prednisolone or methylprednisone or betalone or betpar or betapred or detla cortene beta or "deltisone b" or "deltisona b" or "sch 4358" or sch4358).ti,ab,kw.	15,457
7	exp mycophenolic acid/ or (mycophenolate* or "erl 080" or erl 080a or erl080 or erl080a or melbex* or mycophenolic acid* or myfortic* or nsc 129185 or nsc129185).ti,ab,kw.	4,845
8	exp cyclosporine/ or (cyclosporin* or adi 628 or adi628 or cequa* or cgc 1072 or cgc1072 or ciclomulsion* or cicloral* or consupren* or cyclasol* or cyclokat* or "de 076" or de076 or deximune* or equoral* or gengraf* of ikervis* or iminoral* or implanta* or imusporin* or lx 201 or lx201 or "mc2 03" or mc203 or mtd 202 or mtd202 or neoplanta* or neoral* or neurostat* or "nm 0133" or nm0133 or nm133 or nm 133 or nova 22007 or nova22007 or ol 27400 or ol27400 or "opph 088" or opph088 or opsisporin* or opimmune* ot otx 101 or otx101 or p 3072 or p3072 or padciclo* or papilock* or pulminiq* or restasis* or restaysis* or sanciclo* or sandimmun* or sandimun* or sang 35 or sang35 or sangcya* or seciera* or sp 14019 or sp14019 or "sti 0529" or sti0529 t 1580 or t1580 or vekacia* or verkazia* or zinograf*).ti,ab,kw.	32,990
9	exp Azathioprine/ or (arathioprin*2 or aza-q or azafalk or azahexal or azamedac or azamun*2 or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or e or azathiprim or azathioprin*2 or azathiprim or azathiopurine or azthropsin or azatioprina or aztox or azatrilem or azopi or azoran or azothioprin or azothioprine or colinsan or immuran or immurel or immuthera or imunen or imuprin or imuran or imurane or imurek or	52,500

	imurel or imuren or jayempi or oraprine or thioazeprine or thioprine or transimune or zytrim).ti,ab,kw.	
10	orbital radiotherapy.ti,ab,kw.	28
11	exp rituximab/ or (rituximab or "abp 798" or apb798 or blitzima or "ct p10" or ctp10 or "gp 2013" or gp2013 or halpryza or "hlx 01" or hlx01 or "ibi 301" or ibi301 or "idec 102" or "idec c2b8" or idec102 or idecc2b8 or mabthera or "mk 8808" or mk8808 or "pf 05280586" or "pf 5280586" or pf05280586 or pf5280586 or "r 105" or r105 or reditux or "rg 105" or rg105 or riabni or ritemvia or ritucad or ritumax or rituxan or rituxin or rituzena or rixathon or riximyo or "ro 452294" or ro452294 or "rtxm 83" or rtxm83 or ruxience or truxima or tuxella).ti,ab,kw.	6,636
12	(toclizumab or actemra or atlizumab or "bat 1806" or bat1806 or lusinex or "msb 11456" or msb11456 or "r 1569" or r1569 or "rg 1569" or rg1569 or "ro 4877533" or ro4877533 or roactemra).ti,ab,kw.	236
13	(teprotumumab or "hzn 001" or hzn001 or rg 1507 or rg1507 or ro 4858696 or ro4858696 or "rv 001" or rv001 or tepezza).ti,ab,kw.	76
14	(batoclimab or "hbm 9161" or hbm9161 or "hl 161" or "hl 161 kkn" or "hl 161bkn" or "hl 61" or hl161 or "hl161 bkn" or hl61 or hl161bkn or "imvt 1401" or imvt1401 or "rvt 1401" or rvt1401).ti,ab,kw.	39
15	(VRDN-001 or "VRDN 001" or VRDN001).ti,ab,kw.	25
16	(VRDN-002 or "VRDN 002" or VRDN002).ti,ab,kw.	1
17	(VB-421 or "VB 421" or VB421).ti,ab,kw.	0
18	(aflibercept or "abp 938" or abp938 or "alt l9" or altl9 or "ave 0005" or "ave 005" or ave0005 or ave005 or "bay 86 5321" or "bay 865321" or bay865321 or "chs 2020" or chs2020 or eylea or "fyb 203" or fyb203 or "gbs 012" or gbs012 or "myl 1701p" or myl1701p or "sb 15" or sb15 or "sbc 420" or scb420 or vasculotropin trap or VEGF trap or zaltrap).ti,ab,kw.	1,386
19	(secukinumab or "ain 457" or ain457 or "bat 2306" or bat2306 or cosentyx or "kb 03303a" or kb03303a or scapho or "ts 1808" or ts1808).ti,ab,kw.	1,251
20	exp sirolimus/ or (sirolimus or "abi 009" or abi009 or "ay 22989" or ay22989 or "de 109" or de109 or "drgt18 2" or drgt182 or fyarro or hyftor or nab-rapamycin or nab-sirolimus or "npc 12" or npc12 or opsiria or pascomer or perceiva or "ptx 001" or ptx001 or rapalimus or rapammune or rapamune or rapmycin or "sila 9268a" or sila9268a or tarzifxy or "tavt 18" or tav18 or "tamb 002" or tmb002 or "wy 090217" or wy090217).ti,ab,kw.	5,133
21	rapamycin.ti,ab,kw.	1,121
22	exp betamethasone/ or (betamethason* or adbeon or becasone or beprogel or "beta methason" or "beta methasone" or betacortril or betadexamethasone or betamethasolone or betamethazone or betason or betnasol or betnelan or betnovate or betsolan or betsopart or celestan or celestene or celeston* or cidoten or dermabet or deprolen or flubenisolone or	3,301

	methasone or "nsc 39470" or nsc39480 or opthamesone or "rg 833" or rg833 or rinderon or "sch 4831" or sch4831 or walcort).ti,ab,kw.	
23	(((anti thymocyt* or antithymocyt*2 or antithymus or anti thymus or thymocyte or thymus) adj2 (antiserum or globulin serum or antibody or immunoglobulin)) or atgamm or grafalon or "pf 06462700" or pf6462700 or thymoglobulin*2).ti,ab,kw.	585
24	(vunakizumab or shr-1314 or shr1314 or "shr 1314").ti,ab,kw.	34
25	(linstinib or "osi 906" or soi906 or osi906aa).ti,ab,kw.	18
26	(bimotoprost or "agn 024" or agn024 or agn192024 or amiriox or bimi or durysta or "glash vista" or glashvista or latisse or lumigan or "t 4032" or t4032 or vistitan or visuplain or vizibim).ti,ab,kw.	77
27	exp decompression, surgical/ or ((orbital or opthalm*) adj (operation or decompression or surgery or surgical procedure*)).ti,ab,kw. or (decompression adj2 surgery).ti,ab,kw. or (strabismus adj2 (operation or surgery)).ti,ab,kw.	3,073
28	((blepharoplasty or "eyelid correction" or "palpebral reconstruction" or palpebroplasty or reconstruction) adj2 eyelid).ti,ab,kw.	137
29	exp atorvastatin/ or (astator or ator or atorab or atoris or atorlip or atorvadivid or atorvastatin? or atostin or atovans or atovarol or cardyl or "ci 981" or ci981 or glustar or lipibec or Lipitor or liprimar or liptonorm or lowlipen or obradon or orbeos or prevencor or sortis or statorva or storvas or tahor or torvast or totalip or xarator or "ym 548" or ym548 or zarator).ti,ab,kw.	6,229
30	exp doxycycline/ or (adoxa or amermycin or apprilon or atrax or azudoxat or bactidox or banndoclin or basedillin or bassado or biocolyn or biodoxi or bronmycin or "calcium doxycycline" or cloran or "col 101" or col101 or cyclidox or dentistar or deoxycycline or "deoxymycin dispersal" or deoxymykoin or deoxyoxytetracycline or "desoxy oxytetracycline" or desoxycycline or "dfd 09" or dfd09 or doinmycin or dosil or dotur or doxaciclin or doxacycline or doxat or doxatet or doxi-sergo or doxibiotic or doxicycline or doxilin or doximed or doximycin or doxin? or doxocycline or doxsig or doxy or "doxy-1" or doxy-caps or doxybiocin or doxycen or doxychel or doxycin or doxycycline or doxycydine or doxylag or doxylin or doxymycin or doxypuren or doxytec or doxytrim or dumoxin or duracycline or efracea or esdoxin or etidoxina or "fdx 104" or fdx104 or gewacyclin or "gs 3065" or ibralene or idocyclin or idocyklin or interdoxin or investin or longamycin or lydox or magdrin or medomycin or mespafin or mildox or miraclin or monodox or nanodox or nordox or "nsc 56228" or oracea or oraycea or paldomycin or "pernox gel" or radox or remycin or respidox or roximycin or serodoxy or servidoxine or servidoxyne or siadocin or siclidon or sigadoxin or spanor or supracyclin or supramycina or tenutan or tolexine or "tolexine ge" or torymycin or tsurupioxin or unidox or veemycin or viadoxin or "vibra s" or vibrabiotic or vibracina or vibradox or vibramicina or vibramycin? or vibraveineuse or vibravenos or "vibravenos sf" or vibravet or viradoxyl-n or wanmycin or xyrosa or zadorin or zenavod).ti,ab,kw.	2,624
31	exp infliximab/ or ("abp 710" or abp710 or avakine or avsola or "bcd 055" or bcd055 or "bow 015" or bow015 or "cmab 008" or cmab008 or "ct p13" or ctp13 or flixabi or "gb 242" or gb242 or "gp 1111" or gp1111 or inflectra or infliximabixifi or "pf 06438179" or "pf 6438179"	1,384

	or pf06438179 or pf6438179 or remicade or remsima or renflexis or revellex or "sti 002" or sti002 or "ta 650" or ta650 or essly).ti,ab,kw.	
32	exp adalimumab/ or ("abp 501" or abp501 or abrilada or "abt d2e7" or abtd2e7 or adalimumab or adaly or amgevita or amjevita or amsparity or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bcd 057" or bcd057 or "bi 695501" or bi695501 or "bxt 2922" or bxt2922 or "chs 1420" or chs1420 or cinnora or "ct p17" or ctp17 or cyltezo or "da 3113" or da3113 or dmb 3113 or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hukyndra or hulio or humira or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or "jy 026" or jy026 or kromeya or libmyris or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pbp 1502" or pbp1502 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or qletli or raheara or "sb 5" or sb5 or solymbic or sulinno or trudexa or yuflyma or yusimry or "zrc 3197" or zrc3197).ti,ab,kw.	4,197
33	exp etanercept/ or (avent or benepali or brenzys or "chs 0214" or chs0214 or "dwp 422" or dwp422 or embrel or enbrel or enerceptan or "enia 11" or enia11 or erelzi or etacept or etanar or etanercept or eticovo or "gp 2015" or "gp 2015c" or gp2015 or gp2015c or "hd 203" or hd203 or infinitam or "lbec 0101" or lbec0101 or lifmior or nepexto or opinercept or reumatocept or "sb 4" or sb4 or "tnr 001" or tnr001 or tunex or yisaipu or ylb 113 or ylb113).ti,ab,kw.	2,437
34	("argx 113" or argx113 or efgartigimod or vyvgart).ti,ab,kw.	222
35	exp selenium/ or (selenium or 80Se or selenicum or radioselenium).ti,ab,kw.	2,414
36	(K1-70 or K170 or "K1 70").ti,ab,kw.	2
37	(ATX-GD-59 or "ATX GD 59").ti,ab,kw.	0
38	or/4-37	169,638
39	3 and 38	363
40	animals/ not (humans/ and animals/)	1,299
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	6,579
42	40 or 41	7,875
43	39 not 42	360
44	limit 43 to english language	342
45	limit 44 to yr="2024 -Current"	60

Table 96: Search Strategy in Cochrane Database of Systematic Reviews (2025 update)

#	Search terms	Hits
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	11

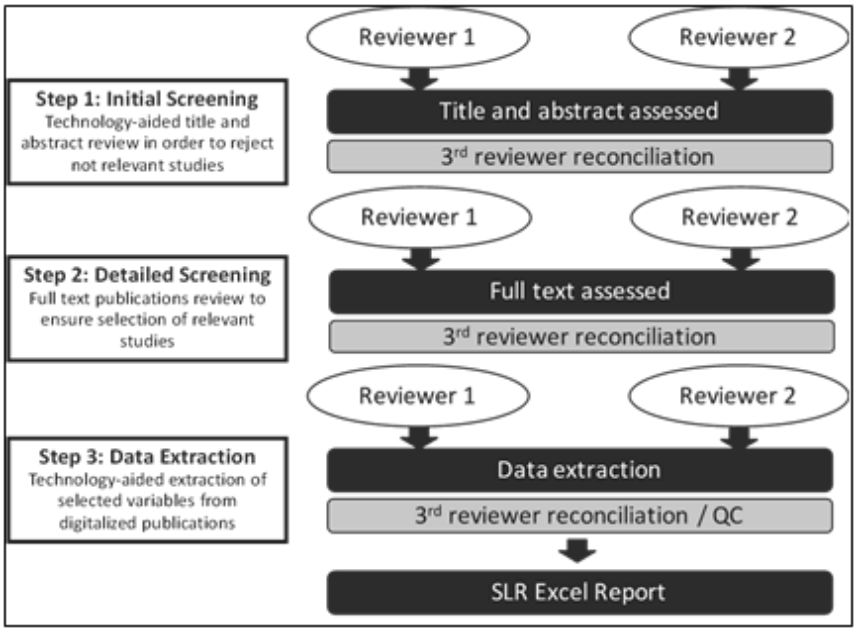
Table 97: Search Strategy in DARE (2025 update)

#	Search terms	Hits
1	(Graves ophthalmopath or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*).mp. [mp=title, full text, keywords]	2

H.2 Systematic Selection of Studies and References

Study eligibility was defined in terms of the population, intervention, comparators, outcomes, and study design (PICOS) criteria. The inclusion/exclusion criteria used to guide SLR study selection are presented in Table 98**.** During full-text screening, top-level information on the trial/study name, trial number registration, data source, study design, geographic location, TED population, sample size, and outcomes were recorded. This information was used to map out publications reporting on the same study population and to detect duplicate publications. This exercise ensured that any potential data overlap was avoided during data extraction.

Publications identified through the SLR were evaluated by two reviewers in a two-step process to assess whether they should be included for data extraction (Figure 12). The inclusion/exclusion criteria used against the publications were developed using the PICOS format. This procedure complies with stringent HTA guidelines surrounding the methodology of systematic reviews.



Technology-aided: Macros and word-finding tools were used as aids in the review to highlight keywords and elements for extraction. The reviews and extractions included two human reviewers, in compliance with HTA requirements.

Abbreviation: QC, quality control; SLR, systematic literature review.

Figure 12: Technology-Aided Data Review and Extraction

Step 1: Abstract Review

All publications were reviewed, based on their titles and abstracts, against the inclusion/exclusion criteria by two independent reviewers; disagreements were resolved by a third, independent reviewer. All papers included by the reviewers at the end of this stage were retained for Step 2.

Step 2: Full-Text Review

Publications included after abstract review (from Step 1) were obtained for a full review of the text. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion, which was reported in table format in the Excel Report, as per NICE guidance. Two independent reviewers screened all citations and full-text articles, and any discrepancies in their decisions were resolved by a third, independent reviewer. To assist the data-collection phase of the review, details for the inclusion/exclusion criteria were consulted throughout this step. This ensured that all decisions regarding the inclusion and exclusion of studies are consistent throughout the review process. Specific exclusion reasons, as per the PICOS criteria, were recorded at the full-text screening stage. The study selection process was reported in PRISMA flow diagrams .

Figure 13.

Step 3: Data Extraction

Data from studies that passed both levels of review were extracted into a pre-defined Excel-based template to ensure that data were extracted uniformly and that the extracted data were comparable across studies. Data extraction was performed by two independent reviewers and independently checked by a third, senior reviewer to align with CRD guidance for undertaking reviews in healthcare. In the event of inconsistency, a consensus-based discussion or a third reviewer was consulted to make the final decision.

Table 98: Inclusion and exclusion criteria used for assessment of studies

PICOS	Inclusion criteria	Exclusion criteria	Modification, local adaption
Population	● Patients with moderate-to-severe active TED ● Patients with chronic or acute TED	● Disease other than TED ● Non-human ● Healthy volunteers	All criteria applied

	• Patients with active or inactive TED • Patients with inflammatory or non-inflammatory TED • Patients with CON or DON		
Interventions	<u>Approved</u> • Teprotumumab <u>Recommended in guidelines/off-label use</u> *Immunomodulators*: • Glucocorticoids (oral or IV, alone or in combination) • Betamethasone • Doxycycline • Methylprednisone *Conventional DMARDs*: • Mycophenolate • Cyclosporin • Azathioprine *Other – surgery/radiotherapy*: • Orbital radiotherapy • Orbital surgery (decompression [including 2-wall vs 3-wall vs 4-wall vs fat decompression], strabismus, eyelid surgery [blepharoplasty]) • Orbital surgery with pharmacological interventions *Monoclonal antibodies*: • Tocilizumab • Rituximab	Studies not including at least one of the interventions listed in the inclusion criteria	All criteria applied

	Investigational *Monoclonal antibodies:* Batoclimab Secukinumab Vunakizumab (SHR-1314) Infliximab Adalimumab VRDN-002 Efgartigimod Veligrotug (VRDN-001) VB421 K1-70 *Other – pharmacologic:* ● Atorvastatin ● Bimatoprost ● Sirolimus (Rapamycin) ● Selenium *Immunomodulators:* ● Antithymocyte globulin ● ATX-GD-59 *T-cell co-stimulatory treatments:* ● Aflibercept ● Etanercept *Kinase inhibitors:* ● Linstinib		
Comparator	● Any included intervention ● Any non-included intervention	None	All criteria applied
Outcomes	*Efficacy:* ● Overall response ● Proptosis response	No restrictions	All criteria applied

	• CAS response • Change from baseline in proptosis • Diplopia response • Strabismus • Extraocular motility • Flare • Recurrent disease • Other clinical outcomes *Safety:* • Treatment-related grade 3 or 4 AEs • Any grade 3 or 4 AEs • SAEs • Other safety outcomes *HRQoL and PROs:* • Disease-related HRQoL outcomes (GO-QoL, TED-QoL)		
Study design	• RCTs, single-arm, non-RCTs • Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	• Non-human, pre-clinical studies • Reviews, Editorials, Notes, Comments, Letters • Case reports/case series	• All criteria applied
Language	English language	Full-text articles not published in English	All criteria applied
Timeframe	2013 to present	Published prior to 2013	All criteria applied

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

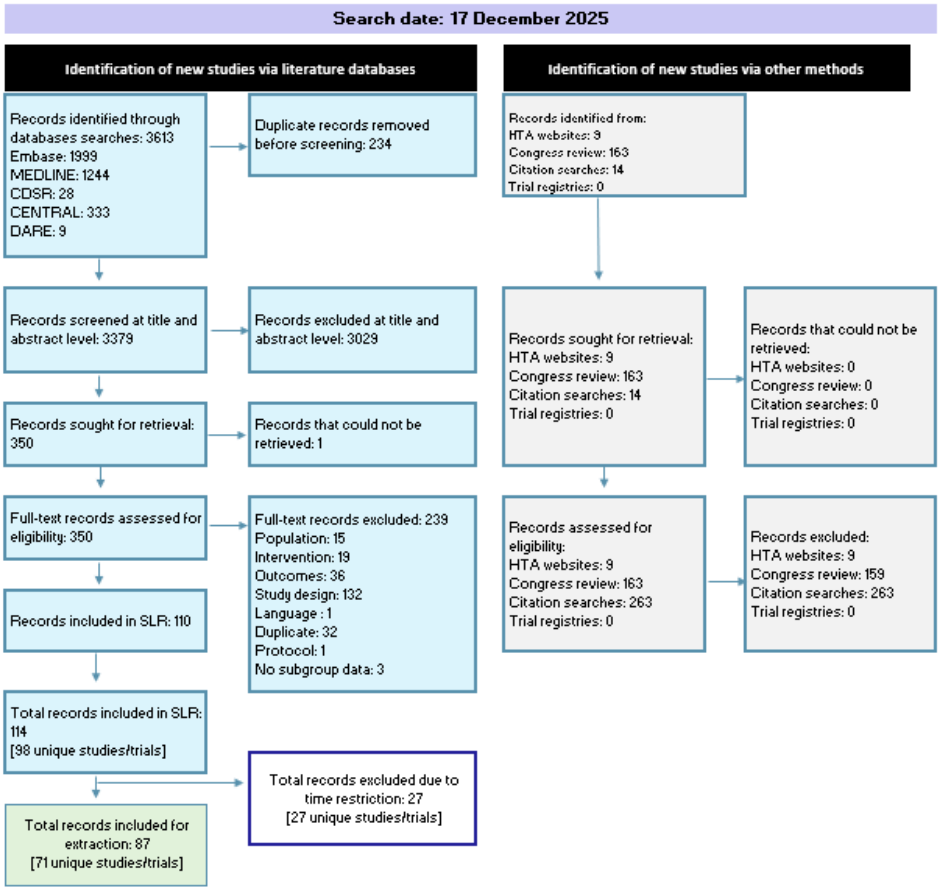
The database searches returned a total of 3,379 records (2,573 [original SLR] + 388 [first SLR update in 2024] + 418 [second SLR update in 2025]), which were screened at the title and abstract level. Of these 350 (235 [original] + 33 [first update] + 82 [second update]) were included for full-text screening. After full-text screening, 110 (77 [original] + 15 [first update] + 18 [second update]) reports from database searches met the review inclusion criteria. 163 (81 [original] + 82 [first update]) reports were identified through congress searches, 14 (13 [original] +1 [first update]) through bibliographic searches, and 9 (7 [original] + 2 [first update]) reports through HTA sources. After assessing the records against the PICOS criteria, four records (zero from both SLR updates) from methods other than database searches were deemed eligible.

In total, 114 (81 [original]+ 15 [first update] + 18 [second update]) reports from 98 unique studies were included in the SLR. Following the addition of date restrictions to include studies

published after 2013, 87 reports from 71 unique studies were included. The literature selection process is shown in .

Figure 13.

Figure 13: PRISMA Diagram - Clinical efficacy SLR



*Records with duplicated information were not extracted.X***Abbreviations**: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstract of Reviews of Effects; HTA, Health Technology Assessment; MEDLINE, Medical Literature Analysis and Retrieval System Online; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

Relevance to Danish clinical practice:

To support this submission, it was essential to identify evidence specifically relevant to Danish clinical practice and the treatment regimen for patients suffering from active moderate to severe TED. As a result, 49 records were excluded from the SLR due to a lack of relevance to this context and the Danish treatment context. To include other relevant evidence not collected from the SLR and to reflect records with relevance excluded in the SLR due to time restriction, an additional search was carried out in connection with the feasibility assessment for the MAIC. Here, three studies were

identified and included; two were identified in the SLR but previously excluded due to time restrictions (Kahaly et al., (2005) and Aktaran et al., (2007)), and one study was included from the additional search (Mu et al., (2020)). Following this refinement, a total of 10 records were identified and included as final evidence.

H.2.1 Summary of included studies

A list of all records selected for inclusion in the SLR is provided in Table 99, and a list of all records excluded at the full-text stage with reasons for exclusion is provided in Table 100. Additionally, a list of all records excluded following the assessment of relevance to the Danish treatment context is provided in Table 101.

Table 99: Overview of studies included in the analysis

Study/ID	References
Phase 2 NCT01868997	Smith TJ et al., Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med. 2017 May 4;376(18):1748-1761.
OPTIC Phase 3 NCT03298867	Douglas RS et al., Teprotumumab for the Treatment of Active Thyroid Eye Disease. N Engl J Med. 2020 Jan 23;382(4):341-352.
Bartalena et al. (2012)	Bartalena L et al., Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012 Dec;97(12):4454-63.

Aktaran et al. (2007)	Aktaran S et al. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. Int J Clin Pract. 2007 Jan;61(1):45-51.
He et al. (2017) ChiCTR-IPR-15006848	He et al. Comparison of two different regimens of intravenous methylprednisolone for patients with moderate to severe and active Graves' ophthalmopathy: a prospective, randomized controlled trial. Endocr J. 2017 Feb 27;64(2):141-149.
Zhu et al. (2014) NCT01969019	Zhu et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with Graves' ophthalmopathy. J Clin Endocrinol Metab. 2014 Jun;99(6):1999–2007.
Kahaly et al. (2005)	Kahaly et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab. 2005 Sep;90(9):5234-40.

Kahaly et al. (2018) MINGO trial EudraCT number: 2008-002123-93	Kahaly et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018;6(4):287–98.
Shen et al. (2022) ChiCTR1800015912	Shen L et al. Methotrexate plus reduced or full-dose glucocorticoids for the treatment of active, moderate-to-severe Graves' orbitopathy. Euro Thyroid J. 2022;11(5):e220017.
Mu et al. (2020)	Mu et al. Comparison of two regimens for patients with thyroid-associated ophthalmopathy receiving intravenous methyl prednisolone: A single center prospective randomized trial. Exp Ther Med. 2020;20(3):153.

H.2.2 Excluded full-text references

Publications included after the abstract review were obtained for a full review of the text. A record was kept of papers excluded at this stage, along with a clear justification for their exclusion, which was reported in table format in the Excel Report, as per NICE guidance. A list of excluded studies in the SLR, including the reason for exclusion, is provided in Table 100.

Table 100: Excluded studies/references

#	Reference	Reason for exclusion
1	Agarwal A, Kumar S, Goel R, et al. Comparative evaluation of peribulbar triamcinolone acetonide and intravenous methylprednisolone in thyroid eye disease. Clinical and	DUPLICATE CID #C2

	Experimental Ophthalmology. Conference: 52nd Annual Scientific Congress of the Royal Australian and New Zealand College of Ophthalmologists. Brisbane, QLD Australia. 49(8) (pp 819), 2022. Date of Publication: February 2022.	
2	Marcocci C, Bartalena L, Bogazzi F, et al. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. Journal of endocrinological investigation. Vol.14(10):853-860p, 1991.	DUPLICATE CID# 1374
3	Marcocci C, Bartalena L, Bogazzi F,et al. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. Journal of Endocrinological Investigation. 14(10):853-60, 1991 Nov.	DUPLICATE CID# 1374
4	Marcocci C, Bartalena L, Bogazzi F, et al. Radioiodine treatment of Graves' hyperthyroidism and progression of ophthalmopathy: protective effect of systemic corticosteroids. Acta endocrinologica, supplement. Vol.121(2):145-148p, 1989. Denmark	DUPLICATE CID# 1381
5	Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. New England journal of medicine. Vol.321(20):1353-1359p, 1989.	DUPLICATE CID# 1382
6	Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. New England Journal of Medicine. 321(20):1353-9, 1989 Nov 16.	DUPLICATE CID# 1382
7	Kahaly GJ, Douglas RS, Holt RJ, et al. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. The lancet. Diabetes & endocrinology. Vol.9(6):360-372p, 2021. United Kingdom Lancet Publishing Group	DUPLICATE CID# 1558
8	Leite C.D.A., Pereira T.D.S., Chiang J., et al. Ocular motility changes after inferomedial wall and balanced medial plus lateral wall orbital decompression in Graves' orbitopathy: A randomized prospective comparative study. Clinics. 76 (no pagination), 2021. Article Number: e2592. Date of Publication: 2021.	DUPLICATE CID# 1561
9	Kose S., Uretmen O., Emre S., et al. Recession of the inferior rectus muscle under topical anesthesia in thyroid ophthalmopathy. Journal of Pediatric Ophthalmology and Strabismus. 39(6) (pp 331-335), 2002. Date of Publication: November/December 2002.	DUPLICATE CID# 1738

10	Kahaly GJ., Riedl M., Koumig J., et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. The lancet. Diabetes & endocrinology. Vol.6(4):287-298p, 2018. United Kingdom Lancet Publishing Group (E-mail: cususerv@lancet.com)	DUPLICATE CID# 1740
11	Rajendram R., Taylor PN., Wilson VJ., et al. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2X2 factorial, double-blind, randomised controlled trial. The lancet. Diabetes & endocrinology. Vol.6(4):299-309p, 2018.	DUPLICATE CID# 1741
12	Alkawas AA., Hussein AM., Shahien EA,. Et al.Orbital steroid injection versus oral steroid therapy in management of thyroid-related ophthalmopathy. Clinical & experimental ophthalmology. Vol.38(7):692-697p, 2010.	DUPLICATE CID# 2030
13	Gorman CA. Radiotherapy for Graves' ophthalmopathy: results at one year. Thyroid. Vol.12(3):251-255p, 2002.	DUPLICATE CID# 2186
14	Gorman C.A. Radiotherapy for Graves' ophthalmopathy: Results at one year. Thyroid. 12(3) (pp 251-255), 2002. Date of Publication: 2002.	DUPLICATE CID# 2186
15	Marcocci C., Bartalena L., Tanda ML.,et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. Journal of clinical endocrinology and metabolism. Vol.86(8):3562-3567p, 2001.	DUPLICATE CID# 2195
16	Marcocci C., Bartalena L., Tanda M.L., et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: Results of a prospective, single-blind, randomized study. Journal of Clinical Endocrinology and Metabolism. 86(8) (pp 3562-3567), 2001. Date of Publication: 2001.	DUPLICATE CID# 2195
17	Kahaly G., Pitz S., Muumlller-Forell W., et al. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. Clinical and experimental immunology. Vol.106(2):197-202p, 1996.	DUPLICATE CID# 2243
18	Kahaly G., Pitz S., Muller-Forell W., et al. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. Clinical and Experimental Immunology. 106(2) (pp 197-202), 1996. Date of Publication: 1996.	DUPLICATE CID# 2243

19	Kahaly GJ,. Douglas R., Holt RJ., et al. 48-week follow-up of a multicenter, randomized, double-masked, placebo-controlled treatment trial of teprotumumab in thyroid-associated ophthalmopathy. Thyroid. Vol.28, pp.A1, 2018-10-03 to 2018-10-07. 88th Annual Meeting of the American Thyroid Association. Washington, DC. United States. Netherlands Mary Ann Liebert Inc.	DUPLICATE CID# 2306
20	Taylor P., Rajendram R., Lee R., et al.,Factors predicting long-term outcome and the need for surgery in graves orbitopathy extended follow-up from the cirted trial. Thyroid. Vol.31(SUPPL 1):A100p, 2021-09-30 to 2021-10-03. 90th Annual Meeting of the American Thyroid Association. Virtual. Netherlands Mary Ann Liebert Inc.	DUPLICATE CID# 353
21	Kahaly G, Riedl M, Koenig J, et al. Combined mycophenolate with intravenous methylprednisolone therapy is more effective than intravenous methyl-prednisolone alone in active and moderate-to-severe graves' orbitopathy-A randomized, observer blind, multicenter trial. Thyroid. Vol.27, pp.A2, 2017-10-18 to 2017-10-22. 87th Annual Meeting of the American Thyroid Association. Victoria, BC. Canada. Netherlands Mary Ann Liebert Inc.	DUPLICATE CID# 641
22	Vannucchi G., Campi I., Covelli D., et al. The effect of rituximab (RTX) and intravenous methylprednisolone (IVMP) on TSH-receptor antibodies (TRAb) and the CXCL-10 chemokine in patients with active graves' orbitopathy (GO). European thyroid journal. Vol.3, pp.93, 2014-09-06 to 2014-09-10. 38th Annual Meeting of the European Thyroid Association, ETA 2014. Spain. S. Karger AG	DUPLICATE CID# 879
23	Ugradar S., Wang Y., Mester T., et al. Improvement of asymmetric thyroid eye disease with teprotumumab. British Journal of Ophthalmology. 106(6):755-759, 2022 06.	DUPLICATE CID# 185
24	Wang L, Chen L, Xing J.99 Tc-MDP combined with methylprednisolone sodium succinate in treatment of thyroid-associated ophthalmopathy: an analysis of clinical efficacy. Academic journal of second military medical university. Vol.33(7):808-809p, 2012. China Editorial Department of Acad J Sec Mil Med Univ (800 Xiangyin Road, Shanghai 200433, China)	FULL TEXT NOT ACCESSED No FT access
25	Khataminia G., Ostadian F., Noroozzadeh M., et al. Acetazolamide and Thyroid-Associated Ophthalmopathy; a Preliminary Tested Hypothesis in a TertiaryReferral Center. Medical Hypothesis Discovery & Innovation in Ophthalmology. 2(4):109-12, 2013 Winter.	INTERVENTION Acetazolamide
26	Goncalves A.C.P., Nogueira T., Goncalves A.C.A., et al. A Comparative Study of Full-Thickness Blepharotomy Versus Transconjunctival Eyelid Lengthening in the Correction of Upper Eyelid Retraction in Graves' Orbitopathy. Aesthetic plastic	INTERVENTION Blepharotomy,

	surgery. 42(1) (pp 215-223), 2018. Date of Publication: 01 Feb 2018.	Transconjunctival Eyelid Lengthening
27	Stamato FJ., Maciel RM., Manso PG., et al. Colchicine in the treatment of the inflammatory phase of Graves' ophthalmopathy: a prospective and randomized trial with prednisone. Arquivos Brasileiros de Oftalmologia. 69(6):811-6, 2006 Nov-Dec.	INTERVENTION Colchicine
28	Altiparmak UE., Acar DE., Ozer PA., et al. Topical cyclosporine A for the dry eye findings of thyroid orbitopathy patients. Eye. 24(6):1044-50, 2010 Jun.	INTERVENTION CsA eyedrops
29	Lauer SA., Silkiss RZ., McCormick SA. Oral montelukast and cetirizine for thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 24(4):257-61, 2008 Jul-Aug.	INTERVENTION Montelukast and cetirizine
30	Bordaberry M., Marques DL., Pereira-Lima JC., et al. Repeated peribulbar injections of triamcinolone acetonide: a successful and safe treatment for moderate to severe Graves' ophthalmopathy. Acta Opthalmologica. 87(1):58-64, 2009 Feb.	INTERVENTION Peribulbar triamcinolone injection
31	Prummel MF., Wiersinga WM., Oosting H., et al. The effect of long-term prednisone treatment on growth hormone and insulin-like growth factor-1. Journal of Endocrinological Investigation. 19(9):620-3, 1996 Oct.	INTERVENTION Prednisone vs Retrobulbar irradiation
32	Watanabe N., Noh JY., Kozaki A., et al. Radioiodine-Associated Exacerbation of Graves' Orbitopathy in the Japanese Population: Randomized Prospective Study. Journal of Clinical Endocrinology & Metabolism. 100(7):2700-8, 2015 Jul.	INTERVENTION Prophylactic corticosteroid
33	Kung AW., Michon J., Tai KS., et al. The effect of somatostatin versus corticosteroid in the treatment of Graves' ophthalmopathy. Thyroid. 6(5):381-4, 1996 Oct.	INTERVENTION Somatostatin analogue octreotide vs Prednisone
34	Jarhult J, Rudberg C, Larsson E, et al. Graves' disease with moderate-severe endocrine ophthalmopathy-long term results of a prospective, randomized study of total or subtotal thyroid resection. Thyroid. 15(10):1157-64, 2005 Oct.	INTERVENTION Thyroidectomy
35	Moleti M, Violi MA, Montanini D, et al. Radioiodine ablation of postsurgical thyroid remnants after treatment with recombinant human TSH (rhTSH) in patients with moderate-to-severe graves' orbitopathy (GO): a prospective, randomized, single-blind clinical trial. Journal of Clinical Endocrinology & Metabolism. 99(5):1783-9, 2014 May.	INTERVENTION Thyroidectomy

36	Bouzas E, Karadimas P, Kotsiras I, et al. Topical Cyclosporin 0.05% Ophthalmic Emulsion in Patients With Dysthyroid Ophthalmopathy. IOVS. Vol.46, pp.ARVO E-abstract, 2005.	INTERVENTION Topical cyclosoporin
37	Erdotan M.F, Demir O, Ersoy R.U, et al. Comparison of early total thyroidectomy with antithyroid treatment in patients with moderate to severely active graves' orbitopathy, a randomized prospective trial. European Thyroid Journal. Conference: 35th Annual Meeting of the European Thyroid Association. Krakow Poland. Conference Publication: (var.pagings). (pp 88), 2011. Date of Publication: September 2011.	INTERVENTION Total thyroidectomy vs medical antithyroid treatment
38	Ebner R, Devoto MH, Weil D, et al. Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone. British Journal of Ophthalmology. 88(11):1380-6, 2004 Nov.	INTERVENTION Triamcinolone vs no treatment
39	de-Pablo-Gomez-de-Liano L., Fernandez-Vigo J.I., Troyano-Rivas J., et al. Evaluacion del grosor de los musculos extraoculares y la quemosis tras tocilizumab en oftalmopatia de Graves mediante tomografia de coherencia optica, Response to tocilizumab treatment in Graves' ophthalmopathy by measuring rectus muscle thickness and chemosis using optical coherence tomography. Archivos de la Sociedad Espanola de Oftalmologia. 93(8) (pp 386-391), 2018. Date of Publication: 01 Aug 2018.	LANGUAGE FT in Spanish
40	Menconi F, Marino M, Pinchera A, et al. Effects of total thyroid ablation versus near-total thyroidectomy alone on mild to moderate Graves' orbitopathy treated with intravenous glucocorticoids. Journal of Clinical Endocrinology & Metabolism. 92(5):1653-8, 2007 May.	NO SUBGROUP DATA No subgroup on moderate TED
41	Kauppinen-Makelin R, Karma A, Leinonen E, et al. High dose intravenous methylprednisolone pulse therapy versus oral prednisone for thyroid-associated ophthalmopathy. Acta Ophthalmologica Scandinavica. 80(3):316-21, 2002 Jun.	NO SUBGROUP DATA No subgroup on moderate TED
42	Watanabe N, Noh J.Y, Kozaki A, et al. Radioiodine-associated exacerbation of graves' orbitopathy in the Japanese population: Randomized prospective study. Journal of Clinical Endocrinology and Metabolism. 100(7) (pp 2700-2708), 2015. Date of Publication: 01 Jul 2015.	NO SUBGROUP DATA Mixed population - No TED subgroup data reported
43	Zhao R, Wang J, Deng J, et al. Efficacy of (99m)Tc-EDDA/HYNIC-TOC SPECT/CT scintigraphy in Graves' ophthalmopathy. American Journal of Nuclear Medicine and Molecular Imaging. 2(2):242-7, 2012.	OUTCOMES No outcomes of interest

44	Ugradar S, Katz B, O'Shaughnessy D, et al. VRDN-001, A NOVEL SELECTIVE INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) ANTAGONIST ANTIBODY FOR THYROID EYE DISEASE (TED): PHASE 1/ 2 PROOF OF CONCEPT IN PATIENTS WITH TED. Thyroid. Conference: 91st Annual Meeting of the American Thyroid Association, ATA 2022. Montreal, QC Canada. 32(Supplement 1) (pp A154), 2022. Date of Publication: October 2022.	OUTCOMES Initial Phase 1/2 results
45	Wichary H, Gasinska T. Methylprednisolone and hepatotoxicity in Graves' ophthalmopathy. Thyroid. 22(1):64-9, 2012 Jan.	OUTCOMES Lab results
46	Mysliwiec J, Kretowski A, Topolska J, et al. Serum Th1 and Th2 profile cytokine level changes in patients with Graves' ophthalmopathy treated with corticosteroids. Hormone & Metabolic Research. 33(12):739-43, 2001 Dec.	OUTCOMES Laboratory outcome: Serum cytokine change
47	Mysliwiec J, Kretowski A, Szelachowska M, et al. Serum L-selectin and ICAM-1 in patients with Graves' ophthalmopathy during treatment with corticosteroids. Immunology Letters. 78(3):123-6, 2001 Oct 01.	OUTCOMES Laboratory outcomes: Serum L-selectin and ICAM-1 change
48	Mysliwiec J, Kretowski A, Stepien A, et al. Serum levels of soluble TNFalpha receptors (sTNFR1 and sTNFR2) during corticosteroid treatment in patients with Graves' ophthalmopathy. Immunological Investigations. 33(1):61-8, 2004 Feb.	OUTCOMES Laboratory outcomes: Serum sTNFR1 and sTNFR2
49	Nogueira T.M, Goncalves A.P, Goncalves A.C.A, et al. A comparative study of pre-and postoperative quantification of upper eyelid retraction in graves orbitopathy using margin reflex distance and digital eyelid image processing methods. Endocrine Reviews. Conference: 96th Annual Meeting and Expo of the Endocrine Society, ENDO 2014. Chicago, IL United States. Conference Publication: (var.pagings). 35(SUPPL. 3) (no pagination), 2014. Date of Publication: 2014.	OUTCOMES No outcomes of interest
50	Li B, Feng L, Tang H, et al. A new radiological measurement method used to evaluate the modified transconjunctival orbital fat decompression surgery. BMC Ophthalmology. 21(1):176, 2021 Apr 13.	OUTCOMES No outcomes of interest
51	Chang TC, Hsiao YL, Liao SL. Application of digital infrared thermal imaging in determining inflammatory state and follow-up effect of methylprednisolone pulse therapy in patients with Graves' ophthalmopathy. Graefes Archive for Clinical & Experimental Ophthalmology. 246(1):45-9, 2008 Jan.	OUTCOMES No outcomes of interest
52	Perros P, Weightman DR, Crombie AL, et al. Azathioprine in the treatment of thyroid-associated ophthalmopathy. Acta Endocrinologica. 122(1):8-12, 1990 Jan.	OUTCOMES No outcomes of interest

53	Censi S, Manso J, Pandolfo G, et al. Bone turnover markers, BMD and TBS after short-term, high-dose glucocorticoid therapy in patients with Graves' orbitopathy: a small prospective pilot study. Journal of Endocrinological Investigation. 42(7):859-865, 2019 Jul.	OUTCOMES No outcomes of interest
54	Takahashi Y, Vaidya A, Kakizaki H. Changes in Eyelid Pressure and Dry Eye Status after Orbital Decompression in Thyroid Eye Disease. Journal of Clinical Medicine. 10(16), 2021 Aug 20.	OUTCOMES No outcomes of interest
55	Nguyen VT, Park DJ, Levin L, et al. Correction of restricted extraocular muscle motility in surgical management of strabismus in graves' ophthalmopathy. Ophthalmology. 109(2):384-8, 2002 Feb.	OUTCOMES No outcomes of interest
56	Gasinska T, Borowska A, Wichary H, et al. Effect of methylprednisolone pulse therapy with and without alendronate on biochemical markers of bone turnover in patients with Graves' ophthalmopathy. Polskie Archiwum Medycyny Wewnetrznej. 122(7-8):341-7, 2012.	OUTCOMES No outcomes of interest
57	Ohtsuka K, Sato A, Kawaguchi S, et al. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. American Journal of Ophthalmology. 135(3):285-90, 2003 Mar.	OUTCOMES No outcomes of interest
58	Seo Y, Shin WB, Bae HW, et al. Effects of Orbital Decompression on Lamina Cribrosa Depth in Patients with Graves' Orbitopathy. Korean Journal of Ophthalmology. 33(5):436-445, 2019 Oct.	OUTCOMES No outcomes of interest
59	Legler UF. Enhanced prednisolone elimination: a possible cause for failure of glucocorticoid therapy in Graves' ophthalmopathy. Hormone & Metabolic Research. 19(4):168-70, 1987 Apr.	OUTCOMES No outcomes of interest
60	Pinas D.S, De Keizer R.O.B, Wubbels R.J, et al. Factors influencing the outcome of upper eyelid lengthening in Graves Orbitopathy. Acta Ophthalmologica. Conference: Annual Congress of the Netherlands Ophthalmological Society, NOG 2018. Groningen Netherlands. 96(Supplement 260) (pp 44), 2018. Date of Publication: March 2018.	OUTCOMES No outcomes of interest
61	Larsen SD, Heegaard S, Toft PB. Histological and clinical evaluation of the hard palate mucous membrane graft for treatment of lower eyelid retraction. Acta Opthalmologica. 95(3):295-298, 2017 May.	OUTCOMES No outcomes of interest
62	Marcocci C, Bartalena L, Bogazzi F, et al. Radioiodine treatment of Graves' hyperthyroidism and progression of ophthalmopathy: Protective effect of systemic corticosteroids. Acta	OUTCOMES No outcomes of interest

	Endocrinologica, Supplement. 121(2) (pp 145-148), 1989. Date of Publication: 1989.	
63	Vannucchi G, Campi I, Bonomi M, et al. Rituximab treatment in patients with active Graves' orbitopathy: effects on proinflammatory and humoral immune reactions. Clinical & Experimental Immunology. 161(3):436-43, 2010 Sep.	OUTCOMES No outcomes of interest
64	Mysliwiec J, Palyga I, Nikolajuk A, et al. Serum interleukin-16 and RANTES during treatment of Graves' orbitopathy with corticosteroids and teleradiotherapy. Endokrynologia Polska. 63(2):92-6, 2012.	OUTCOMES No outcomes of interest
65	Mysliwiec J, Waligorski D, Nikolajuk A, et al. Soluble CD40 and its ligand CD154 in patients with Graves' ophthalmopathy during combined therapy with corticosteroids and teleradiotherapy. Advances in Medical Sciences. 52:104-8, 2007.	OUTCOMES No outcomes of interest
66	Ito G, Kozaki A, Mizuno K, et al. Steroid therapy combined intravenous administration and retrobulbar injection for thyroid eye disease with hepatitis B core antibody positive. Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. Orlando, FL United States. 55(13) (pp 4103), 2014. Date of Publication: April 2014.	OUTCOMES No outcomes of interest
67	Nowak M, Wielkoszynski T, Kos-Kudla B, et al. The blood concentration of intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) in patients with active thyroid-associated orbitopathy before and after methylprednisolone treatment. Endokrynologia Polska. 58(6):487-91, 2007 Nov-Dec.	OUTCOMES No outcomes of interest
68	Vannucchi G, Campi I, Bonomi M, et al. Treatment of patients with Graves' orbitopathy (GO) with rituximab: Effects on humoral immunity. Endocrine Abstracts. Conference: 11th European Congress of Endocrinology, ECE 2009. Istanbul Turkey. Conference Publication: (var.pagings). 20 (pp P68), 2010. Date of Publication: 2010.	OUTCOMES No outcomes of interest
69	Mysliwiec J, Kretowski A, Szelachowska M, et al. Serum pro- and anti-inflammatory cytokines in patients with Graves' disease with ophthalmopathy during treatment with glucocorticoids. Roczniki Akademii Medycznej W Bialymstoku. 44:160-9, 1999.	OUTCOMES No outcomes of interest - lab results
70	Laban-Guceva N, Antova M, Bogoev M. No changes in serum concentrations of interleukin 10 (IL-10) and interferon gamma (IF-gamma) before and after treatment of the thyroid eye disease (TED). Bosnian Journal of Basic Medical Sciences. 7(4):358-62, 2007 Nov.	OUTCOMES Serum concentrations of interleukin 10 (IL-10) and interferon gamma (IF-gamma)

71	Kim KW, Byun JS, Lee JK. Surgical effects of various orbital decompression methods in thyroid-associated orbitopathy: computed tomography-based comparative analysis. Journal of Cranio-Maxillo-Facial Surgery. 42(7):1286-91, 2014 Oct.	OUTCOMES Analysis of surgical techniques
72	Azizi F, Abdi H, Mehran L, et al. Long-Term Follow-up of Graves Orbitopathy After Treatment With Short- or Long-Term Methimazole or Radioactive Iodine. Endocrine Practice. 29(4) (pp 240-246), 2023. Date of Publication: April 2023.	POPULATION Graves disease
73	Kahaly GJ, Riedl M, Konig J, et al. Double-Blind, Placebo-Controlled, Randomized Trial of Selenium in Graves Hyperthyroidism. Journal of Clinical Endocrinology & Metabolism. 102(11):4333-4341, 2017 11 01.	POPULATION Graves' disease
74	Michon J, Tso M, Kung A, et al. The effects of somatostatin versus corticosteroiods in graves' ophthalmopathy. IOVS. Vol.39, pp.ARVO Abstract 434, 1998.	POPULATION Graves' disease
75	Bartalena L, Marcocci C, Tanda ML, et al. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Annals of Internal Medicine. 129(8):632-5, 1998 Oct 15.	POPULATION Mild ophthalmopathy for RCT (study 1) severe ophthalmopathy for retrospective (study 2)
76	Bartalena L, Marcocci C, ogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. New England Journal of Medicine. 338(2):73-8, 1998 Jan 08.	POPULATION Mild or none ophthalmopathy
77	Almanza-Monterrubio M, Garnica-Hayashi L, Davila-Camargo A, et al. Oral selenium improved the disease activity in patients with mild Graves' orbitopathy. Journal Francais d Opthalmologie. 44(5):643-651, 2021 May.	POPULATION Mild TED
78	Marcocci C, Altea M.A, Kahaly G, et al. Selenium and pentoxifylline in patients with mild Graves' orbitopathy: Results of a randomized placebo-controlled double-blind clinical trial. Endocrine Abstracts. Conference: 12th European Congress of Endocrinology 2010, ECE 2010. Prague Czechia. Conference Publication: (var.pagings). 22 (pp P866), 2010. Date of Publication: 2010.	POPULATION Mild TED
79	Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. New England Journal of Medicine. 364(20):1920-31, 2011 May 19.	POPULATION Mild TED
80	Czarnywojtek A, Zgorzalewicz-Stachowiak M, Budny B, et al. The influence of radioiodine therapy on ocular changes and their relation to urine cotinine level in patients with Graves'	POPULATION Mild TED

	Ophthalmopathy. Neuroendocrinology Letters. 34(3):241-8, 2013.	
81	Bouzas E, Karadimas P, astorakos G, et al. Use of the somatostatin analogue lanreotide to prevent aggravation of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. IOVS. Vol.45, pp.ARVO E-abstract 5022, 2004.	POPULATION Mild TED
82	Gorman CA, Garrity JA, Fatourechi V, et al. A Prospective, Randomized, Double-blind, Placebo-controlled Study of Orbital Radiotherapy for Graves' Ophthalmopathy. Ophthalmology. 127(4S):S160-S171, 2020 04.	POPULATION Mild to moderate TED
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84	Bartalena L, Marcocci C, Bogazzi F, et al. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. New England Journal of Medicine. 321(20):1349-52, 1989 Nov 16.	POPULATION Non-moderate-to-severe
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86	A Randomized Clinical Trial to Evaluate the Effects of Atorvastatin on Graves' Orbitopathy (GO): the STAGO-2 Study. 2021. [No additional source data available.]	PROTOCOL Protocol
87	Pereira TS, Leite CA, Kuniyoshi CH, et al. A randomized comparative study of inferomedial vs. balanced orbital decompression. Analysis of changes in orbital volume, eyelid parameters, and eyeball position. Eye. 36(3):547-554, 2022 03.	STUDY DESIGN RWE
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94	Chang TC, Huang KM, Hsiao YL, et al. Relationships of orbital computed tomographic findings and activity scores to the prognosis of corticosteroid therapy in patients with Graves' ophthalmopathy. Acta Ophthalmologica Scandinavica. 75(3):301-4, 1997 Jun.	STUDY DESIGN Case series
95	Kvetny J, Frandsen NE, Johnsen T, et al. Treatment of Graves' ophthalmopathy with cyclosporin A. Acta Medica Scandinavica. 220(2):189-91, 1986.	STUDY DESIGN Case series
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97	Fatourechi V. Medical management of extrathyroidal manifestation of graves disease. Endocrine Practice. 20(12):1333-44, 2014 Dec.	STUDY DESIGN Narrative review
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115	Bednarczuk T, Schomburg L. Challenges and perspectives of selenium supplementation in Graves' disease and orbitopathy. Hormones. 19(1):31-39, 2020 Mar.	STUDY DESIGN Narrative review
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134	Zhao LQ, Yu DY, Cheng JW. Intravenous glucocorticoids therapy in the treatment of Graves' ophthalmopathy: a systematic review and Meta-analysis. International Journal of Ophthalmology. 12(7):1177-1186, 2019.	STUDY DESIGN SLR for cross-checking
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160	Zhu, H., Zou, M., Wu, D. *et al.* Quantitative assessment of extraocular muscles in Graves' ophthalmopathy using T1 mapping. *Eur Radiol* **33**, 9074–9083 (2023). https://doi.org/10.1007/s00330-023-09931-3	OUTCOMES No outcomes of interest
161	Bridging and Validation of the Specific Graves Ophthalmopathy Quality of Life Questionnaire With Health State Utility Values Smith, Terry J. et al. Endocrine Practice , Volume 30, Issue 5, 470 - 475	OUTCOMES No outcomes of interest
162	Manso, J., Censi, S., Clausi, C., Piva, I., Zhu, Y. H., Mondin, A., Pedron, M. C., Barollo, S., Bertazza, L., Midena, G., Parrozzani, R., & Mian, C. (2023). Circulating miR-146a predicts glucocorticoid response in thyroid eye disease. *European Thyroid Journal*, *12*(5), e230083.	OUTCOMES No outcomes of interest
163	C. Li, Y. Gao, Z. Zhang, X. Lv, Y. Bao, Y. Ma, et al. Surgical Outcomes of Standardized Endoscopical Deep Medial Orbital Decompression in Dysthyroid Optic Neuropathy Ophthalmic research 2024 Vol. 67 Issue 1 Pages 39-50	OUTCOMES No outcomes of interest
164	M. Jamshidian Tehrani, H. Niktinat, N. Ebrahimiadib, B. Jafari, S. M. Rafizadeh and A. Kasaee Assessment of retinal and choroidal vessel density and nerve fibre layer thickness changes after orbitotomy in patients with severe non-active thyroid orbitopathy: a prospective study. International Ophthalmology 2023 Vol. 43 Issue 12 Pages 4427-4433	RELEVANCE
165	Y. Takahashi and A. Vaidya Diagnosis and Management of Dysthyroid Optic Neuropathy International ophthalmology clinics 2023 Vol. 63 Issue 3 Pages 233-248	STUDY DESIGN
166	S. Hubschman, B. Sojitra, S. Ghiam, C. Sears, N. Hwangbo, R. A. Goldberg, et al. Teprotumumab and Orbital Decompression for the Management of Proptosis in Patients With Thyroid Eye Disease Ophthalmic Plastic and Reconstructive Surgery 2024 Vol. 40 Issue 3 Pages 270-275	STUDY DESIGN
167	V. Vermot-Desroches, K. Thia-Soui-Tchong, P. Raymond, A. Filip, J. Orgiazzi, E. Jouanneau, et al. Prognostic factors for significant 6-month recovery in dysthyroid optic neuropathy in a tertiary	STUDY DESIGN

	center: A series of 69 eyes in 38 patients Annales d'endocrinologie 2023 Vol. 84 Issue 4 Pages 430-439	
168	M. Soleymanzadeh, S. M. Rafizadeh, G. Ghochani, A. R. Mafi, M. Nazari and M. T. Rajabi Biomechanical changes of the cornea after orbital decompression in thyroid-associated orbitopathy measured by corvis ST Scientific reports 2024 Vol. 14 Issue 1 Pages 16930	STUDY DESIGN
169	T. J. Smith, Q. Fu and R. J. Holt Hearing-Related Adverse Events in Teprotumumab Oncology Clinical Trials Journal of the Endocrine Society 2023 Vol. 7 Issue Supplement 1 Pages A1034-A1035	STUDY DESIGN
170	T. J. Smith, D. Cavida, K. Hsu, S. Kim, Q. Fu, G. Barbesino, et al. Glycemic Trends in Patients with Thyroid Eye Disease Treated with Teprotumumab in 3 Clinical Trials Ophthalmology 2024 Vol. 131 Issue 7 Pages 815-826	STUDY DESIGN Pooled data
171	S. M. Rafizadeh, M. Heidari, A. Aghajani, Z. Montazeriani, P. Afshar, S. Mansourian, et al. Superficial ocular vascular changes after orbital decompression in patients with thyroid ophthalmopathy measured by anterior segment OCT angiography; an observational study Scientific reports 2024 Vol. 14 Issue 1 Pages 14572	STUDY DESIGN
172	E. Parunakian, S. Ugradar, J. Tolentino, E. Malkhasyan, P. Raika, J. Ghaly, et al. Teprotumumab improves light sensitivity in patients with thyroid eye disease Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2024 Vol. 262 Issue 9 Pages 2999-3006	STUDY DESIGN
173	F. Ozer, M. Unlu, D. Gulmez Sevim, H. Sener and C. Evereklioglu Evaluation of lamina cribrosa and peripapillary vascular density in thyroid orbitopathy and effect of intravenous methylprednisolone therapy Canadian Journal of Ophthalmology 2023	STUDY DESIGN
174	C. Lee, J. W. Park, Y. D. Kim and K. I. Woo Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant thyroid eye disease: a prospective study International Ophthalmology 2024 Vol. 44 Issue 1 Pages 179	STUDY DESIGN
175	G. J. Kahaly, P. S. Subramanian, E. Conrad, R. J. Holt and T. J. Smith Long-Term Efficacy of Teprotumumab in Thyroid Eye Disease: Follow-Up Outcomes in Three Clinical Trials Thyroid 2024 Vol. 34 Issue 7 Pages 880-889	STUDY DESIGN Pooled data
176	G. J. Kahaly, P. J. Dolman, J. Wolf, B. C. Giers, H. M. Elflein, A. P. Jain, et al. Proof-of-concept and Randomized, Placebo-	STUDY DESIGN

	controlled Trials of an FcRn Inhibitor, Batoclimab, for Thyroid Eye Disease Journal of Clinical Endocrinology and Metabolism 2023 Vol. 108 Issue 12 Pages 3122-3134	
177	R. S. Douglas, E. Parunakian, J. Tolentino, E. Malkhasyan, J. Geng, M. Sherman, et al. A Prospective Study Examining Audiometry Outcomes Following Teprotumumab Treatment for Thyroid Eye Disease Thyroid : official journal of the American Thyroid Association 2024 Vol. 34 Issue 1 Pages 134-137	STUDY DESIGN
178	Abumohssin AG, Alshareef RA, Aljohani S, Alqutub A, Alqutub A. Comparative efficacy and safety of rituximab, tocilizumab, and teprotumumab in Graves' orbitopathy: a systematic review and meta-analysis. Eye (Lond). 2025 Jul;39(10):1901-1932.	STUDY DESIGN SLR for cross-checking
179	Aishwarya A, Shrivastava D, Singh AK, Agrawal R. Efficacy and safety of various Intravenous Methylprednisolone regimens in Moderate to Severe Thyroid Eye Disease: A systematic review. Indian J Ophthalmol. 2025 Aug 1;73(8):1100-1107.	STUDY DESIGN SLR for cross-checking
180	Alkmim NR, Rajão KMAB, Figueiredo ARP, Braga WRC, Silveira LFG. Predictive factors for treatment response in active thyroid eye disease. Ann Endocrinol (Paris). 2024 Dec;85(6):582-588.	STUDY DESIGN Retrospective
181	Alves Junior JM, Bernardo W, Villagelin D. Effectiveness of Different Treatment Modalities in Initial and Chronic Phases of Thyroid Eye Disease: A Systematic Review With Meta-analysis. J Clin Endocrinol Metab. 2024 Oct 15;109(11):2997-3009.	STUDY DESIGN SLR for cross-checking
182	Arnon R, Goldberg H, Ben-Simon GJ, Priel A, Zloto O, Landau-Prat D, Cukierman-Yaffe T, Agmon-Levin N, Sagiv O. Alpha-1 antagonist treatment for eyelid retraction in patients with thyroid eye disease-a prospective pilot study. Eye (Lond). 2025 Jan;39(1):175-178.	INTERVENTION Tamsulosin (alpha1-adrenoreceptor antagonist)
183	Awad RA, Abo-Ghadir AA, Hussien MS, Awad AA, Kedwany SM, Mohammad AEA. Local Betamethasone Versus Triamcinolone Injection in Management of Thyroid Eye Disease-Related Upper Eyelid Retraction With Proptosis. Ophthalmic Plast Reconstr Surg. 2025 May-Jun 01;41(3):273-279.	DUPLICATE Included in previous SLR
184	Bartalena L, Smith TJ. Treatment of Hyperthyroidism in Graves' Disease Complicated by Thyroid Eye Disease. J Clin Endocrinol Metab. 2025 Mar 17;110(4):922-930.	STUDY DESIGN SLR for cross-checking
185	Carvalho NC, Kusubara ILR, Gomes G, Machado RM, Pellegrinelli N et al. Thermographic Assessment of Thyroid Eye Disease in Response to Steroid Therapy, Investigative Ophthalmology & Visual Science June 2025, Vol.66, 1991	OUTCOMES No outcomes of interest (orbital temperature)

186	Chen K, Lelli GJ. Efficacy, Safety, and Recurrence in Older Thyroid Eye Disease Patients Undergoing Teprotumumab Treatment. Ophthalmic Plast Reconstr Surg. 2025 May-Jun 01;41(3):e98-e99.	STUDY DESIGN Case series (4 patients)
187	Chen Y, Li S, Chen J, Feng H. Clinical characteristics and therapeutic effect of myasthenia gravis coexisting with thyroid eye disease. Neurol Sci. 2024 Dec;45(12):5909-5913.	STUDY DESIGN Retrospective
188	Ciarmatori N, Quaranta Leoni F, Quaranta Leoni FM. Redefining Treatment Paradigms in Thyroid Eye Disease: Current and Future Therapeutic Strategies. J Clin Med. 2025 Aug 6;14(15):5528.	STUDY DESIGN SLR for cross-checking
189	Comi S, Sabini E, Cosentino G, Santini F, Marinò M. Sirolimus for the treatment of Graves' orbitopathy. Thyroid Res. 2025 Dec 2;18(1):55.	STUDY DESIGN SLR for cross-checking
190	Cong X, Pei L, Hu H. Teprotumumab for treating active thyroid eye disease: A meta-analysis. Medicine (Baltimore). 2025 Jun 27;104(26):e42966.	STUDY DESIGN SLR for cross-checking
191	Cruz AAV, Rocha VHS, Peres MM, Todo M, Cunha BS. Cerebral and optic nerve complications following bony orbital decompression for Graves' orbitopathy. A systematic review. Orbit. 2025 Dec;44(6):889-897.	STUDY DESIGN SLR for cross-checking
192	Cukovic L, Ugradar S, Johnson O, Holt R et al. #1706739 Efficacy of Teprotumumab in Phenotype Type I vs Type II Thyroid Eye Disease Endocrine Practice. 2024; 30 (5): S161	STUDY DESIGN Pooled analysis
193	Cyngot P et al. Dixon MRI-based quantitative parameters of orbital tissues in patients with corticosteroid-resistant thyroid eye disease treated with tocilizumab. Polish Journal of Radiology. 2025. 90(Special Issue 1):e87.	OUTCOMES MRI quantitative parameters of orbital tissues post tocilizumab
194	de Almeida Leite CA, Pereira TS, Chiang J, Moritz RB, Gonçalves ACP, Monteiro MLR. Quality of life in patients with Graves' orbitopathy submitted to orbital decompression: comparison between balanced and inferomedial techniques. Arq Bras Oftalmol. 2024 Aug 5;87(5):e20230296.	DUPLICATE Included in previous SLR
195	Douglas RS, Parunakian E, Tolentino J, Malkhasyan E, Geng J, Sherman M, Ugradar S. A Prospective Study Examining Audiometry Outcomes Following Teprotumumab Treatment for Thyroid Eye Disease. Thyroid. 2024 Jan;34(1):134-137.	STUDY DESIGN Prospective observational
196	Duarte AF, Xavier NF, Sales Sanz M, Cruz AAV. Efficiency and Safety of Tocilizumab for the Treatment of Thyroid Eye Disease:	STUDY DESIGN SLR for cross-checking

	A Systematic Review. Ophthalmic Plast Reconstr Surg. 2024 Jul-Aug 01;40(4):367-373.	
197	Flores JM, Sioson NAG, Uy-Ho JD, Suller-Pansacola AL. 6662 Effect of Selenium Supplementation on Mild Graves' Ophthalmopathy at a Tertiary Hospital - A Six-Month Open-Labelled, Assessor-Masked, Randomized-Controlled Trial. Journal of the Endocrine Society. 2024; 8 (Issue Supplement_1)	POPULATION Mild TED
198	Giannuzzi F, Carlà MM, Crincoli E, Gambini G, Hu L, Boselli F, Cuffaro G, Parrilla C, Rigante M, Pagliara MM, Rizzo S, Savino G. Thyroid-related orbitopathy: clinical overview, novel medical treatments and the role of orbital surgery. Int Ophthalmol. 2025 May 3;45(1):160.	STUDY DESIGN SLR for cross-checking
199	Guo W, Geng J, Li D. Comparative effectiveness of various orbital decompression techniques in treating thyroid-associated ophthalmopathy: a systematic review and meta-analysis. BMC Ophthalmol. 2024 Dec 18;24(1):526.	STUDY DESIGN SLR for cross-checking
200	Householder NA, Ray C. Teprotumumab's Impact on Proptosis in Long-duration Thyroid Eye Disease: A Systematic Review and Meta-analysis. touchREV Endocrinol. 2024 Oct;20(2):100-109.	STUDY DESIGN SLR for cross-checking
201	Huang W, Ou X, Lin S, Lin W, Chen G, Huang H, Wen J. Efficacy and Safety of Teprotumumab in Thyroid Eye Disease: A Systematic Review and Meta-Analysis. Endocr Pract. 2025 May;31(5):640-649.	STUDY DESIGN SLR for cross-checking
202	Huang Z, Xu M, Zhang W, Song X. Triamcinolone acetonide and botulinum toxin A for upper eyelid retraction in thyroid-associated ophthalmopathy. Sci Rep. 2025 Feb 11;15(1):5103.	INTERVENTION Periorbital triamcinolone injection
203	Hubschman S, Sojitra B, Ghiam S, Sears C, Hwangbo N, Goldberg RA, Rootman DB. Teprotumumab and Orbital Decompression for the Management of Proptosis in Patients With Thyroid Eye Disease. Ophthalmic Plast Reconstr Surg. 2024 May-Jun 01;40(3):270-275.	DUPLICATE Excluded from previous SLR on study design
204	Jinhai Y, Qassem AAM, Qi J, Chao X, Anan W, Qi X, Hongfei L, Dequan D. Bayesian network analysis of drug treatment strategies for thyroid associated ophthalmopathy. Int Ophthalmol. 2024 Aug 4;44(1):339.	STUDY DESIGN SLR for cross-checking
205	Jinhai Y, Yunxiu C, Chao X, Yaohua W, Kai Y, Hongfei L. A meta-analysis of the efficacy of two-wall orbital decompression operations for thyroid-associated ophthalmopathy. Int Ophthalmol. 2024 Feb 15;44(1):81.	STUDY DESIGN SLR for cross-checking

206	Kahaly GJ, Subramanian PS, Conrad E, Holt RJ, Smith TJ. Long-Term Efficacy of Teprotumumab in Thyroid Eye Disease: Follow-Up Outcomes in Three Clinical Trials. Thyroid. 2024 Jul;34(7):880-889.	DUPLICATE Excluded from previous SLR (pooled data)
207	Kahaly GJ, Subramanian PS, Conrad E, Holt RJ, Smith TJ. 6814 Durability of Teprotumumab for the Treatment of Thyroid Eye Disease (TED) in Clinical Trials. J Endocr Soc. 2024 Oct 5;8(Suppl 1):bvae163.1941.	STUDY DESIGN Pooled data
208	Kahaly GJ. Efficacy and Safety of Teprotumumab in Patients with Active Thyroid Eye Disease (TED): A Pooled Analysis from 3 Randomized Trials. Thyroid. 2025; 35(Supplement 1):e33.	STUDY DESIGN Pooled data
209	Kahaly GJ, Wester ST, Liu CY, Kate H, Conrad E, Holt RJ, Hiromatsu Y. 6822 Proptosis Improvement with Teprotumumab is Independent of Race, Ethnicity, Gender and Age from Three Global Randomized, Double-Masked, Placebo-Controlled Trials of Patients with Acute Thyroid Eye Disease (TED). J Endocr Soc. 2024 Oct 5;8(Suppl 1):bvae163.2047.	STUDY DESIGN Pooled data
210	Kahaly GJ, Xi A, Barretto N, Patel H, Qashqai A, Shokoohi M, Spin P, Holt RJ. Teprotumumab Improves Quality of Life in Thyroid Eye Disease: Meta-analysis and Matching-adjusted Indirect Comparison. J Endocr Soc. 2025 Apr 8;9(6):bvaf063. doi:	STUDY DESIGN SLR for cross-checking
211	Kim Y. Synergistic Therapy for Graves' Ophthalmopathy-Associated Eyelid Retraction: Steroid, 5-FU, and Botulinum Neurotoxin a Combination. Journal of Clinical Medicine. 2024; 13(10) (no pagination).	STUDY DESIGN Retrospective
212	Kumar SV, Kumar V, Mishra SK, Sati A, Kumar NV. Efficacy and safety of botulinum toxin as a non-surgical option for upper eyelid retraction in active thyroid-associated ophthalmopathy: a prospective interventional study. Int Ophthalmol. 2025 Jul 15;45(1):293.	INTERVENTION Botulinum toxin
213	Lee C, Park JW, Kim YD, Woo KI. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant thyroid eye disease: a prospective study. Int Ophthalmol. 2024 Apr 16;44(1):179.	DUPLICATE Excluded from previous SLR (study design)
214	Li C, Gao Y, Zhang Z, Lv X, Bao Y, Ma Y, Chen R, Cheng C, Li J, Liu Y, Jin L, Luo G, Shi J, Lu R. Surgical Outcomes of Standardized Endoscopical Deep Medial Orbital Decompression in Dysthyroid Optic Neuropathy. Ophthalmic Res. 2024;67(1):39-50.	DUPLICATE Excluded from previous SLR (outcome)
215	Li M, Wei B, Gao T, Gao C. The efficacy of Tripterygium Glycosides in the treatment of Chinese patients with thyroid-	STUDY DESIGN SLR for cross-checking

	associated orbitopathy: a systematic review and meta-analysis. Front Pharmacol. 2025 Jan 6;15:1433791.	
216	Li P. Serum proteomic analysis reveals insights into the mechanism of action of teprotumumab, an insulin-like growth factor-1 receptor inhibitor, in patients with chronic thyroid eye disease (TED). Thyroid. 2024; 34(Supplement 1):A39.	OUTCOMES Reports serum proteomics in TED patients.
217	Lin S, Ou X, Cai L, Huang W, Wen J. Efficacy and safety of Tocilizumab for thyroid eye disease: a systemic review and Meta-analysis. J Endocrinol Invest. 2025 Sep;48(9):1951-1965.	STUDY DESIGN SLR for cross-checking
218	Linaburg TJ, Pradeep T, Rinelli B, Chen Y, Chen Y, Ying GS, Briceño CA, Tamhankar M. Comparison of ophthalmic surgery rates in teprotumumab-treated vs. teprotumumab-untreated thyroid eye disease patients. Arq Bras Oftalmol. 2025 Jul 21;88(5):e20240319.	STUDY DESIGN Retrospective
219	Lo JE, Freitag SK, Liu CY, Barbesino G, Ma KS. Long-term Cardiovascular, Renal, and Safety Outcomes of Teprotumumab versus Systemic Glucocorticoids in Thyroid Eye Disease: A Target Trial Emulation. Ophthalmology. 2025 Oct;132(10):1142-1151.	STUDY DESIGN Retrospective
220	Malik A. Assessment Of Quality Of Life By Baseline Factors Among Patients With Thyroid Eye Disease (TED). Journal of the Endocrine Society. 2025; 9(Supplement 1):A1196-A1197.	STUDY DESIGN Pooled data
221	Mudumbai R, Leibowitz S, Michael T. Y, Cockerham K, Abrams J, Turbin RE, Nijhawan N, Zhang-Nunes S, Kossler A, Michalsky C, Narvekar A, Ciulla T. OR31-04 Efficacy and Safety of Veligrotug (VRDN-001), a Full Antagonist Monoclonal Antibody to IGF-1 Receptor, in Active Thyroid Eye Disease (TED): THRIVE Phase 3 Topline Results. J Endocr Soc. 2025 Oct 22;9(Suppl 1):bvaf149.2237.	DUPLICATE No unique data
222	Ozer F, Unlu M, Gulmez Sevim D, Sener H, Evereklioglu C. Evaluation of lamina cribrosa and peripapillary vascular density in thyroid orbitopathy and effect of intravenous methylprednisolone therapy. Can J Ophthalmol. 2024 Oct;59(5):e489-e495.	STUDY DESIGN Retrospective
223	Park J, Lee JE. The efficacy of radiotherapy for steroid-resistant thyroid eye disease: clinical outcomes in orbital inflammation and exophthalmos. Radiat Oncol J. 2025 Jun;43(2):88-98.	STUDY DESIGN Retrospective
224	Park J, Son Y, Kim J, Kim S, Choi HY. Prognostic factors for thyroid-stimulating immunoglobulin normalization in moderate-to-severe Graves' orbitopathy: a 36-month longitudinal study. BMC Ophthalmol. 2024 Aug 21;24(1):361.	STUDY DESIGN Retrospective

225	Parunakian E, Ugradar S, Tolentino J, Malkhasyan E, Raika P, Ghaly J, Bisht C, Douglas RS. Teprotumumab improves light sensitivity in patients with thyroid eye disease. Graefes Arch Clin Exp Ophthalmol. 2024 Sep;262(9):2999-3006.	STUDY DESIGN Prospective observational
226	Sharabati I, Qafesha RM, Hindawi MD, Amro S, Ayesh BM. The efficacy and safety of selenium supplementation versus placebo in the treatment of Graves' orbitopathy: A systematic review and meta-analysis of randomised controlled trials. Clin Endocrinol (Oxf). 2024 Dec;101(6):669-681.	STUDY DESIGN SLR for cross-checking
227	Smith TJ, Cavida D, Hsu K, Kim S, Fu Q, Barbesino G, Wester ST, Holt RJ, Bhattacharya RK. Glycemic Trends in Patients with Thyroid Eye Disease Treated with Teprotumumab in 3 Clinical Trials. Ophthalmology. 2024 Jul;131(7):815-826.	DUPLICATE Excluded from previous SLR (pooled data)
228	Sun A, Wang X, Qu J, Wu Y. The Efficacy and Safety of Intravenous Tocilizumab to Treat Graves' Ophthalmopathy: A Systematic Review and Single-arm Meta-analysis. J Clin Endocrinol Metab. 2025 Feb 18;110(3):e886-e896.	STUDY DESIGN SLR for cross-checking
229	Sung, S.M., Lee, D.C. Baseline selenium is associated with response to intravenous Methylprednisolone with selenium supplementation for thyroid eye disease in a selenium-sufficient area. Sci Rep 15, 45276 (2025).	STUDY DESIGN Retrospective
230	Turbin R. Veligrotug (VRDN-001), a Full Antagonist Monoclonal Antibody to IGF-1 Receptor, in Active Thyroid Eye Disease (TED): THRIVE Phase 3 Efficacy and Safety Topline Results. Investigative Ophthalmology & Visual Science. 2025, Vol.66, 4302.	DUPLICATE No unique data
231	Ugradar S. Reduced Proptosis and Muscle/Fat Volume by MRI/CT in a Proof-of-Concept Study in TED Shows Potential for Disease- Modifying Effects of VRDN-001, a Targeted TED Therapy. Thyroid. 2024; 34(Supplement 1):A6.	STUDY DESIGN Phase 1/2 study (excluded from previous SLR)
232	Ugradar S. Evaluation of Tobacco Exposure and Teprotumumab Efficacy: Pooled Results from Acute TED Clinical Trials. Journal of the Endocrine Society. 2024; 8(Supplement 1):A1023-A1024.	STUDY DESIGN Pooled data
234	Wang E, Yang Z, Xie Z, Tian D, Xu H, Li H, Chen Y. Thyroid eye disease in the biologic era: a 40-year paradigm shift in nonsurgical therapeutic strategies. Expert Rev Clin Immunol. 2025 Jun;21(6):787-802.	STUDY DESIGN SLR for cross-checking
235	Wang L, Sun Y, Zhang M, He H, Wang J, Xu H, Hao Y, Zhang W, Wang Y, Chong KKL, Guo H, Shi B, Wang Y. Negative association between serum calcium and glucocorticoid-induced hypertension in thyroid-associated ophthalmopathy patients	STUDY DESIGN Retrospective

	treated with methylprednisolone. Front Endocrinol (Lausanne). 2025 Apr 11;16:1548953.	
236	Wu B, Zhu M, Zhang F, Cao J, Xie B, Zhu Z, Xiong W. Orbital decompression improves visual function and macular blood perfusion status in patients with thyroid-related eye disease. Front Med (Lausanne). 2024 Oct 28;11:1455226.	STUDY DESIGN Retrospective
237	Xiang Q, Yang M, Luo W, Cao Y, Shuai S, Wei X, Xiong A. Combined glucocorticoids and cyclophosphamide in the treatment of Graves' ophthalmopathy: a systematic review and meta-analysis. BMC Endocr Disord. 2024 Jan 26;24(1):12.	STUDY DESIGN SLR for cross-checking
238	Xu Y, Liu R, Huang L, Qin Y, Liu W, Huang S, Zhang J. Comprehensive Comparisons of Different Treatments for Active Graves Orbitopathy: A Systematic Review and Bayesian Model-Based Network Meta-Analysis. J Clin Endocrinol Metab. 2025 May 19;110(6):1792-1801.	STUDY DESIGN SLR for cross-checking
239	Efficacy and Systemic Effects of a Single Deep Orbital Triamcinolone Injection for Thyroid Eye Disease	INTERVENTION Triamcinolone injection
240	Zhai L, Li F, Luo B, Wang Q, Wu H, Zhao Y, Yuan G, Zhang J. Fat-suppression T2 relaxation time and water fraction predict response to intravenous glucocorticoid therapy for thyroid-associated ophthalmopathy. Eur Radiol. 2025 Feb;35(2):957-967.	STUDY DESIGN Retrospective
241	Zhang H, Sun J, Li Y, Zhu L, Shan Z, Lu W, et al. IGF-1R Inhibitor IBI311 for the Treatment of Active Thyroid Eye Disease in Chinese Patients: The RESTORE-1 Randomized Clinical Trial. JAMA Ophthalmol. 2025 Nov 1;143(11):964-971.	INTERVENTION IBI311 vs placebo RCT
242	Zong AM, Giannakakos VP, Delbourgo Patton C, Barmettler A. Botulinum Toxin Treatment in Thyroid Eye Disease: A Systematic Review and Meta-analysis. Ophthalmic Plast Reconstr Surg. 2025 May-Jun 01;41(3):250-257.	STUDY DESIGN SLR for cross-checking

H.2.2.1 Further exclusions

To ensure inclusion of only relevant evidence for teprotumumab and IVMP, additional exclusion criteria were applied to studies identified through the SLR. These criteria were aligned with the predefined inclusion and exclusion parameters established for the ITC.

One study identified for teprotumumab was excluded due to a patient population characterized by low disease activity and prolonged disease duration, rendering it unsuitable for assessment of either efficacy or safety in the target population. Another

excluded study was a single-arm trial with an insufficiently defined TED population, limiting its interpretability and relevance. Furthermore, one study being an extension to OPTIC Phase 3, was excluded, since the extension was not relevant in this relation. Consequently, the studies were not considered appropriate for inclusion in the present application.

In total, eight studies were included to inform the evidence base for IVMP.

Table 101: Studies excluded from the clinical SLR following assessment of relevance for the comparative analysis of this application

No	Reference	Reason for exclusion
1	Thu Thuy Hoang, Jianfeng He. Effects of high-dose hormone therapy in patients with thyroid-associated orbitopathy and its effect on visual acuity and ocular surface. Int J Clin Exp Med 2020;13(11):8636-8643	POPULATION All TED
2	Roy A, Dutta D, Ghosh S, Mukhopadhyay P, Mukhopadhyay S, Chowdhury S. Efficacy and safety of low dose oral prednisolone as compared to pulse intravenous methylprednisolone in managing moderate severe Graves' orbitopathy: A randomized controlled trial. Indian J Endocrinol Metab. 2015;19(3):351-358.	POPULATION Not specified as active TED
3	Xu N, Cui Y, Fu D, Sun F. Tear inflammatory cytokines and ocular surface changes in patients with active thyroid eye disease treated with high-dose intravenous glucocorticoids. J Endocrinol Invest. 2020;43(7):901-910.	STUDY DESIGN
4	Detiger SE, Kremer TM, A S H Dalm V, et al. A pilot study on the use of prednisolone-encapsulated liposomes for the treatment of moderate-to-severe Graves' orbitopathy with reduced systemic steroid exposure. Acta Ophthalmol. 2021;99(7):797-804.	INTERVENTION/COMPARATOR
5	Beleslin BN, Ciric J, Zarkovic M, et al. Efficacy and safety of combined parenteral and oral steroid therapy in Graves' orbitopathy. Hormones (Athens, Greece). 2014;13(2):222-8.	STUDY DESIGN
6	Miśkiewicz P, Milczarek-Banach J, Rutkowska-Hinc B, Kondracka A, Bednarczuk T. High-dose intravenous methylprednisolone therapy in patients with Graves' orbitopathy is associated with the increased activity of factor VIII. J Endocrinol Invest. 2019;42(2):217-225.	POPULATION Patients with several risk factors
7	D. Paridaens et al. Nanocort in the medical treatment of moderate-to-severe Graves' orbitopathy: A pilot study. Volume 98, Issue S264. Special Issue: Abstracts of the Netherlands Ophthalmological Society (NOG) Annual	INTERVENTION/COMPARATOR

	Congress, 2–4 September 2020, Groningen, The Netherlands.	
8	Ye X, Zhao H, Liu J, Lu B, Shao J, Wang J. Efficacy and safety of tripterygium glycosides for active moderate to severe Graves' ophthalmopathy: a randomised, observer-masked, single-centre trial [retracted in: Eur J Endocrinol. 2021 Apr;184(4):Z1]. Eur J Endocrinol. 2021;184(2):277-287.	OUTCOME
9	Muller I. Randomized controlled trial of belimumab and methylprednisolone in active moderate severe graves' orbitopathy. ATA 2021.	PUBLICATION
10	Salvi M, Vannucchi G, Currò N, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab. 2015;100(2):422-431.	INTERVENTION/COMPARATOR
11	Savino G, Mandarà E, Gari M, Battendieri R, Corsello SM, Pontecorvi A. Intraorbital injection of rituximab versus high dose of systemic glucocorticoids in the treatment of thyroid-associated orbitopathy. Endocrine. 2015;48(1):241-247.	INTERVENTION/COMPARATOR
12	Campi I, Vannucchi G, Muller I, et al. Therapy With Different Dose Regimens of Rituximab in Patients With Active Moderate-To-Severe Graves' Orbitopathy. Front Endocrinol (Lausanne). 2022;12:790246. Published 2022 Jan 25.	INTERVENTION/COMPARATOR
13	Vannucchi G, Campi I, Covelli D, Currò N, Lazzaroni E, et al. Efficacy Profile and Safety of Very Low-Dose Rituximab in Patients with Graves' Orbitopathy. Thyroid. 2021 May;31(5):821-828. doi: 10.1089/thy.2020.0269. Epub 2021 Mar 31. Erratum in: Thyroid. 2022 May;32(5):605.	INTERVENTION/COMPARATOR
14	Janes J, Kahaly G, Liang S, Tedeschi P. ODP509 Proof-of-concept, Multicenter, Open-Label Phase 2a Study of Batoclimab in Active and Moderate-to-Severe Thyroid Eye Disease. Journal of the Endocrine Society. 2022 November; 6(Supplement_1):A778–A779.	INTERVENTION/COMPARATOR
15	Erdei A, Paragh G, Kovacs P, Karanyi Z, Berenyi E, et al. Rapid response to and long-term effectiveness of anti-CD20 antibody in conventional therapy resistant Graves' orbitopathy: A five-year follow-up study. Autoimmunity. 2014 Dec;47(8):548-55.	INTERVENTION/COMPARATOR
16	Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. Ophthalmic Plast Reconstr Surg. 2014;30(2):162-167.	INTERVENTION/COMPARATOR

17	Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. Am J Ophthalmol. 2018;195:181-190.	INTERVENTION/COMPARATOR
18	Kahaly, G et al. RF35 | PSAT269 Double-Blind, Randomized, Placebo-controlled, Multicenter, Phase 2b Study of Batoclimab in Active and Moderate-to-Severe Thyroid Eye Disease. ENDO 2022.	INTERVENTION/COMPARATOR
19	Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab. 2015;100(2):432-441.	INTERVENTION/COMPARATOR
20	Lanzolla G, Sabini E, Leo M, et al. Statins for Graves' orbitopathy (STAGO): a Phase 2, open-label, adaptive, single centre, randomised clinical trial. Lancet Diabetes Endocrinol. 2021;9(11):733-742. doi:10.1016/S2213-8587(21)00238-2	OUTCOME
21	Rajendram R, Taylor PN, Wilson VJ, et al. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2 × 2 factorial, double-blind, randomised controlled trial. Lancet Diabetes Endocrinol. 2018;6(4):299-309.	INTERVENTION/COMPARATOR
22	Nicosia L, Reverberi C, Agolli L, Marinelli L, De Sanctis V, et al. Orbital Radiotherapy Plus Concomitant Steroids in Moderate-to-Severe Graves' Ophthalmopathy: Good Results After Long-Term Follow-Up. Int J Endocrinol Metab. 2019 Jan 27;17(1):e84427.	INTERVENTION/COMPARATOR
23	Hamed-Azzam S, Mukari A, Feldman I, Saliba W, Jabaly-Habib H, Briscoe D. Fornix triamcinolone injection for thyroid orbitopathy. Graefes Arch Clin Exp Ophthalmol. 2015;253(5):811-816.	INTERVENTION/COMPARATOR
24	Li J, Xiao Z, Hu X, et al. The Efficacy of Rituximab Combined with 131I for Ophthalmic Outcomes of Graves' Ophthalmopathy Patients. Pharmacology. 2017;99(3-4):144-152. doi:10.1159/000453618	POPULATION
25	Wu Y, Tong B, Luo Y, Xie G, Xiong W. Effect of radiotherapy on moderate and severe thyroid associated ophthalmopathy: a double blind and self-controlled study. Int J Clin Exp Med. 2015 Feb 15;8(2):2086-96.	INTERVENTION/COMPARATOR
26	Wu_IJP_2016 – Article Not Applicable.	NOT APPLICABLE
27	Rajabi MT, Tabary M, Baharnoori S, Salabati M, Mahmoudzadeh R, et al. Orbital anatomical parameters	INTERVENTION/COMPARATOR

	affecting outcome of deep lateral orbital wall decompression. Eur J Ophthalmol. 2021 Jul;31(4):2069-2075.	
28	Goel R, Shah S, Gupta S, Khullar T, Singh S, et al. Alterations in retrobulbar haemodynamics in thyroid eye disease. Eye (Lond). 2023 Dec;37(17):3682-3690.	INTERVENTION/COMPARATOR
29	Doumit G, Abouhassan W, Yaremchuk MJ. Aesthetic refinements in the treatment of graves ophthalmopathy. Plast Reconstr Surg. 2014 Sep;134(3):519-526.	INTERVENTION/COMPARATOR
30	Leite CA, Pereira TS, Chiang J, Moritz RB, Gonçalves ACP, Monteiro MLR. Ocular motility changes after inferomedial wall and balanced medial plus lateral wall orbital decompression in Graves' orbitopathy: a randomized prospective comparative study. Clinics (Sao Paulo). 2021;76:e2592. Published 2021 Apr 9.	INTERVENTION/COMPARATOR
31	Sellari-Franceschini S, Rocchi R, Marinò M, et al. Rehabilitative orbital decompression for Graves' orbitopathy: results of a randomized clinical trial. J Endocrinol Invest. 2018;41(9):1037-1042.	INTERVENTION/COMPARATOR
32	Ugradar S, Shi L, Wang Y, Mester T, Yang H, Douglas RS. Teprotumumab for non-inflammatory thyroid eye disease (TED): evidence for increased IGF-1R expression. Eye (Basingstoke). 2021;35(9):2607-2612.	POPULATION
33	Douglas RS, Couch S, Wester ST, Fowler BT, Liu CY, et al. Efficacy and Safety of Teprotumumab in Patients With Thyroid Eye Disease of Long Duration and Low Disease Activity. J Clin Endocrinol Metab. 2023 Dec 21;109(1):25-35.	POPULATION
34	Awad RA, Abo-Ghadir AA, Hussien MS, Awad AA, Kedwany SM, Mohammad AEA. Peri-levator Betamethasone Versus Triamcinolone Injection in Management of Thyroid Eye Disease-related Upper Eyelid Retraction Without Proptosis. Ophthalmic Plast Reconstr Surg. 2024 Nov-Dec 01;40(6):610-616.	INTERVENTION/COMPARATOR
35	Wu Q, Zhou J, Fang W, Jiang WH, Pu XY, et al. Structural and Functional Brain Changes After Glucocorticoid Therapy in Thyroid-Associated Ophthalmopathy. J Clin Endocrinol Metab. 2024 Feb 20;109(3):649-658.	POPULATION
36	Stoynova MA, Shinkov AD, Dimitrova ID, Yankova IA, Kovatcheva RD. Comparison of the efficacy of two different glucocorticoid regimens for treatment of active moderate-to-severe Graves' orbitopathy. Int Ophthalmol. 2023 Dec;43(12):4747-4757.	STUDY DESIGN

37	Li Z, Luo Y, Huang Q, Chen Z, Song D, et al. A Randomized Clinical Trial of Intravenous Methylprednisolone With 2 Protocols in Patients With Graves Orbitopathy. J Clin Endocrinol Metab. 2023 Dec 21;109(1):36-45.	AVAILABILITY
38	Dorado Cortez O, Grivet D, Perrillat N, Gain P, Thuret G. Treatment of corticosteroid-resistant Graves' orbitopathy with tocilizumab: a single-centre prospective study. Orbit. 2023 Aug;42(4):411-417.	INTERVENTION/COMPARATOR
39	Ueland HO, Halsøy K, Rødahl E. Blepharotomy Versus Levator Recession With Adjustable Sutures for Correction of Upper Eyelid Retraction in Thyroid Eye Disease. Ophthalmic Plast Reconstr Surg. 2024 Sep-Oct 01;40(5):516-522.	INTERVENTION/COMPARATOR
40	Lv X, Gao Y, Ma Y, Li C, Ren Y, et al. Comparison of surgical effect in active and inactive Dysthyroid Optic Neuropathy after Endoscopic Transnasal Medial Orbital Decompression. Graefes Arch Clin Exp Ophthalmol. 2024 Jan;262(1):281-293002E	INTERVENTION/COMPARATOR
41	Leite CA, Pereira TS, Chiang J, Moritz RB, Gonçalves ACP, Monteiro MLR. Quality of life in patients with Graves' orbitopathy submitted to orbital decompression: comparison between balanced and inferomedial techniques. Arq Bras Oftalmol. 2024 Aug 5;87(5):e20230296.	INTERVENTION/COMPARATOR
42	Guo J, Ma R, Gan L, Li X, Xue K, Cheng J, Qian J. Changes in retinal nerve fibre layer, ganglion cell layer and visual function in eyes with thyroid eye disease of different severities with and without orbital decompression. Eye (Lond). 2023 Jun;37(8):1571-1576.	INTERVENTION/COMPARATOR
43	Stoynova MA, Shinkov AD, Novoselski MT, Petrova VV, Dimitrova ID, Yankova IA, Kovatcheva RD. Changes in therapeutic response, ocular manifestations of Graves' orbitopathy and quality of life during the first year after orbital radiotherapy. Int Ophthalmol. 2023 Nov;43(11):4305-4314.	INTERVENTION/COMPARATOR
44	Matoc I, Kasa K, Kasumović A, Prpić A, Vukojević A, et al. One Incremental Stride for Doxycycline, One Substantial Advancement for Thyroid Eye Disease. Diagnostics. 2024; 14(8):791.	INTERVENTION/COMPARATOR
45	Swaify IY, Nasr HE, El Essawy RA, Elessawy KB. Periocular methotrexate versus periocular triamcinolone injections for active thyroid-associated orbitopathy: a randomized clinical trial. Jpn J Ophthalmol. 2023 Nov;67(6):699-710.	INTERVENTION/COMPARATOR

46	Wang C, Qiao J, Liu S, Piao S, Zhou Y, et al. Selenium in the treatment of mild-to-moderate Graves' orbitopathy: a 5-year prospective controlled cohort study. Endocrine. 2024 Jun;84(3):1072-1080.	INTERVENTION/COMPARATOR
47	Potita P, Pruksakorn V, Srichomkwun P, Kingpetch K, Saonanon P. Selenium supplementation in inactive moderate to severe Graves' orbitopathy patients: a randomized controlled trial. Orbit. 2024 Jun;43(3):329-336.	INTERVENTION/COMPARATOR
48	Douglas RS, et al. Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment: OPTIC-X study. Ophthalmology. 2022 Apr;129(4):438-449.	OUTCOME

H.3 Quality assessment

This SLR had several strengths. Firstly, a robust methodology was followed in accordance with NICE and PRISMA standards. A comprehensive database search strategy capturing relevant publications was utilized, along with grey literature searches and key congress reviews. Unlike other SLRs in this indication, the searches were not restricted to one intervention or intervention class (106-109). Finally, gaps, inconsistencies, and trends in the literature were identified.

Despite these strengths, there are limitations to consider when interpreting the findings. Timeframe restrictions were applied. Additionally, there was variance in how key outcomes, such as overall response and CAS response, were defined. Among clinical studies, there were limited head-to-head trials comparing interventions of interest, and statistical or sensitivity analyses were not performed among teprotumumab and other interventions. This affects the comparability of intervention effects on outcomes of interest. Reports on TED subpopulations, such as chronic and inflammatory TED, were limited, and definitions of those populations were inconsistent, presenting a gap in understanding of intervention effects in these subpopulations. Lastly, the SLR was limited to English-language publications. While this is generally considered acceptable (most key clinical and RWE studies are published in English-language journals), there is a risk of bias and the potential exclusion of relevant studies.

H.4 Unpublished data

Any unpublished data used to present the efficacy and safety of teprotumumab have been attained from the Phase 2 and OPTIC Phase 3 clinical trials, including sources such as the clinical study report (CSR), ad hoc analyses, or longer follow-up data than what is available in published literature. There is no publication plan available for this data.

Appendix I. Literature Searches for Health-Related Quality of Life

I.1 Systematic Search

A SLR for HRQOL was conducted to support this submission. A comprehensive global SLR with searches was conducted on June 9, 2023, with an SLR update conducted on October 3, 2024 and December 17, 2025. The objective of the SLR was to identify evidence on HRQOL outcomes, patient-reported outcomes, and utilities relevant for patients with TED. Subgroups of interest included active/chronic, active/inactive, inflammatory/non-inflammatory, and compressive optic neuropathy/dysthyroid optic neuropathy TED.

The HRQOL/utilities SLR methodology followed the same approach outlined for the clinical SLR reviewed in Appendix H.

For the primary SLR, the searches via the Ovid platform were conducted in EMBASE, MEDLINE, MEDLINE In-Process, and CDSR for full-text publications and conference abstracts. DARE and CENTRAL were also searched. Additionally, the HTA database, the NHS, EED and EconLit databases were searched.

The bibliographic databases presented in Table 102 were used to conduct the HRQOL/utilities SLR.

Table 102: Electronic databases sources for HRQoL/Utilities SLR

Database	Platform/source	Search period	Date of search completion
EMBASE	Ovid	1974 to December 16 2025	09.06.2023, 03.10.2024 and 17.12.2025
MEDLINE	Ovid	1946 to December 16 2025	09.06.2023, 03.10.2024 and 17.12.2025
CDSR	Ovid	N/A	09.06.2023, 03.10.2024 and 17.12.2025
DARE*	Centre for Reviews and Dissemination	N/A	09.06.2023, 03.10.2024 and 17.12.2025
CENTRAL	Cochrane Library	N/A	09.06.2023, 03.10.2024 and 17.12.2025
International HTA Database	International Network of Agencies for Health	N/A	09.06.2023, 03.10.2024 and 17.12.2025

Database	Platform/source	Search period	Date of search completion
	Technology Assessment		
NHS EED*	Centre for Reviews and Dissemination	N/A	09.06.2023, 03.10.2024 and 17.12.2025
EconLit	American Economic Association	1886 to December 16 2025	09.06.2023, 03.10.2024 and 17.12.2025

* DARE and NHS EED were discontinued in 2015 and only the archived versions are available.
Abbreviations: CDSR, Cochrane Database of Systematic Review; CENTRAL, Cochrane Central Register of Controlled Trials; EBM, Evidence Based Medicine; HRQoL, health-related quality of life; NHS, National Health Service.

The sources listed above are in accordance with the list of databases suggested by the HTA organizations of interest, such as the NICE, CADTH, the Pharmaceutical Benefits Advisory Committee (PBAC), and the Scottish Medicines Consortium (SMC) as well as the Institute for Clinical and Economic Review (a non-profit organization).

Conference proceedings

Proceedings from the last three editions of selected conferences and congresses were manually reviewed to retrieve the latest abstracts and results not yet published in journals as full-text articles, or to supplement results of previously published studies. This congress review was conducted in May 2023 and updated in October 2024 and December 2025. The list of key conferences is provided in Table 103.

Table 103: Conference proceedings

Conferences	Years searched	Website (manual search)
American Academy of Ophthalmology (AAO)	2020, 2021, 2022, 2023, 2024, 2025	https://www.aao.org/annual-meeting/meeting-information
American Ophthalmological Society (AOS)	2021, 2022, 2023, 2024, 2025	https://www.aosonline.org/
Annual Meeting of the Endocrine Society (ENDO)	2020, 2021, 2022, 2023, 2024, 2025	https://academic.oup.com/jes/supplements/volume
European Society of Ophthalmic Plastic and Reconstruction Surgery (ESOPRS)	2021, 2022, 2023, 2024, 2025	https://www.esoprs.eu/esoprs-meetings/40th-esoprs-meeting-2022-in-nice/program

HTA submission searches

The HTA submissions review was conducted between May 24, 2023, and May 26, 2023 and updated searches were undertaken on October, 6 2024 and December 17, 2025. The websites of select HTA bodies and the Institute for Clinical and Economic Review (a non-profit organization), as listed in Table 104, were searched for relevant submissions using the following terms: "thyroid eye disease," "TED," "Graves' ophthalmopathy," "Graves' orbitopathy," and "thyroid-associated ophthalmopathy." No time restrictions were applied.

Table 104: HTA Sources

HTA Body	Website
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/
Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/health-technology-review
Danish Medicines Council – Medicinradet	https://medicinraadet.dk/om-os/in-english
European network for Health Technology Assessment (EUnetHTA)	https://www.eunethta.eu/
European Medicines Agency (EMA)	https://www.ema.europa.eu/en
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://oys.fi/fincchta/
Germany's Joint Federal Committee (Gemeinsamer Bundesausschuss [G-BA])	https://www.g-ba.de/english/
Haute Autorité de Santé (HAS)	https ://www.has-sante.fr/
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	https://www.iqwig.de/en/
Institut National d'Excellence en Santé et en Services Sociaux (INESSS)	https ://www.inesss.qc.ca/en/index.html

National Committee for Health Technology Incorporation (CONITEC)	https://www.gov.br/conitec/pt-br
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/
Norwegian Medicines Agency	https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm
Norwegian Knowledge Centre for Health Services	https://legemiddelverket.no/English
Pharmaceutical Benefits Advisory Committee (PBAC)	https://www.pbs.gov.au/info/industry/listing/participants/pbac
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/
Swedish Dental and Pharmaceutical Benefits Agency (TLV)	https://www.tlv.se/in-english.html
Non-profit organization	
Institute for Clinical and Economic Review	https://icer.org/

Registry Search

The Cost-Effectiveness Analysis (CEA) Registry was searched to identify any cost-utility analyses reporting on TED (Table 105). "Thyroid eye disease," "Graves' ophthalmopathy," "Graves' orbitopathy," and "thyroid-associated ophthalmopathy" terms were used to identify relevant analyses. The search was conducted on May 30, 2023, October 6, 2024 and December 17, 2025.

Table 105: Registry review

Registry	Website (manual search)
CEA	https://cear.tuftsmedicalcenter.org/

Bibliographic searches

The bibliographies of systematic reviews and meta-analyses identified through database searches were used to identify studies that met PICOS criteria for the HRQOL/utilities SLR. Furthermore, bibliographies from selected studies were also reviewed to identify relevant studies. This process ensured that papers and articles not captured in the initial search were included in the review.

I.1.1 Search strategies

Primary search

MEDLINE, EMBASE, Cochrane searches, and EconLit were conducted on June 9, 2023, using the Ovid platform. Database searches were performed from inception. Additionally, the HTA database and NHS EED were searched on their respective websites. The search strategies for each database are presented in Table 106, Table 107, Table 108,Table 109,Table 110,Table 111,Table 112 and Table 113.

Table 106: Search strategy table for Ovid EMBASE – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
1	endocrine ophthalmopathy/	6746
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6608
3	or/1-2	8570
4	exp "Quality of Life"/ or exp questionnaire/ or exp "quality of life assessment"/	1482270
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	139105
6	(quality adj4 life).ti,ab.	608450
7	(quality adj2 well?being).ti,ab,kw,kf.	809
8	quality adjusted life year/	35319
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	33428
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	34509
11	patient-reported outcome/	53467
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	68199
13	PRO.ti,ab,kw,kf.	384569
14	exp health survey/	267742
15	exp health status/ or health status indicator/	312030

16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	30721
17	(utilit* or disutilit*).ti,ab,kw,kf.	379214
18	disability adjusted life.ti,ab,kw,kf.	6485
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	9404
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	7029
21	Standard Gamble/ or sg.ti,ab,kw.	20449
22	willingness to pay.ti,ab,kw,kf.	13119
23	(TTO or WTP or DCE).ti,ab,kw,kf.	18405
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	67467
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	887786
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	150242
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	96623
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	1027
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	70
30	(15D or 15-D or 15 dimension).ti,ab,kw.	7677
31	european quality of life 5 dimensions questionnaire/	8337
32	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	30389
33	health utilit*.ti,ab,kw.	4647

34	(HSUV or HSUVs).ti,ab,kw.	195
35	(hui or hui1 or hui2 or hui3).tw.	3086
36	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or TED quality of life scale or GLS).ti,ab.	10758
37	or/4-36	3611849
38	3 and 37	1199
39	case report/	2911202
40	animal/ not (human/ and animal/)	1180818
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	2151235
42	or/39-41	6105617
43	38 not 42	1099
44	limit 43 to english language	1021

Table 107: Search strategy table for Ovid MEDLINE – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
1	graves ophthalmopathy/	2982
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	5599
3	or/1-2	5599
4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	1380872
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	76450
6	(quality adj4 life).ti,ab.	379596
7	(quality adj2 well?being).ti,ab,kw,kf.	490
8	Quality-Adjusted Life Years/	15665

No.	Query	Results
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	22403
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	19823
11	Patient Reported Outcome Measures/	13408
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	41619
13	PRO.ti,ab,kw,kf.	248484
14	exp health surveys/	623261
15	exp health status/ or health status indicators/	453704
16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	16615
17	(utilit* or disutilit*).ti,ab,kw,kf.	265763
18	disability adjusted life.ti,ab,kw,kf.	5258
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	7369
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	4822
21	sg.ti,ab,kw.	13441
22	willingness to pay.ti,ab,kw,kf.	8513
23	(TTO or WTP or DCE).ti,ab,kw,kf.	11842
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	43131
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	674522
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	97869
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty	63083

No.	Query	Results
	or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	613
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	39
30	(15D or 15-D or 15 dimension).ti,ab,kw.	6071
31	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	16431
32	health utilit*.ti,ab,kw.	2750
33	(HSUV or HSUVs).ti,ab,kw.	107
34	(hui or hui1 or hui2 or hui3).tw.	1945
35	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or TED quality of life scale or GLS).ti,ab.	4283
36	or/4-35	2800493
37	3 and 36	869
38	case reports/	2339517
39	animals/ not (humans/ and animals/)	5094204
40	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	652065
41	or/38-40	8034372
42	37 not 41	827
43	limit 42 to english language	769

Table 108: Search strategy table for CENTRAL – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
1	graves ophthalmopathy/	144
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	417
3	or/1-2	417
4	animals/ not (humans/ and animals/)	2672
5	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	9926
6	4 or 5	12595
7	3 not 6	412
8	limit 7 to english language	385

Table 109: Search strategy table for Ovid CDSR – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	11

Table 110: Search strategy table for DARE – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
Search DARE: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	17

Table 111: Search strategy table for the HTA database – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2

Table 112: Search strategy table for NHS EED – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 113: Search strategy table for EconLit – HRQOL/utilities SLR (June 9, 2023).

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Updated search 1

All the updated database searches were conducted on October 3, 2024. The search strategies for each database are presented in Table 114, Table 115, Table 116, Table 117, Table 118, Table 119, Table 120 and Table 121.

Table 114: Search strategy table for Ovid EMBASE – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
1	endocrine ophthalmopathy/	7,483
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	7,238
3	or/1-2	9,358
4	exp "Quality of Life"/ or exp questionnaire/ or exp "quality of life assessment"/	1,637,518
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	151,567
6	(quality adj4 life).ti,ab.	669,935
7	(quality adj2 well?being).ti,ab,kw,kf.	939
8	quality adjusted life year/	38,488

No.	Query	Results
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	36,923
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	38,113
11	patient-reported outcome/	66,254
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	79,823
13	PRO.ti,ab,kw,kf.	413,486
14	exp health survey/	291,868
15	exp health status/ or health status indicator/	346,628
16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	34,285
17	(utilit* or disutilit*).ti,ab,kw,kf.	412,060
18	disability adjusted life.ti,ab,kw,kf.	7,838
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	10,268
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	7,778
21	Standard Gamble/ or sg.ti,ab,kw.	22,807
22	willingness to pay.ti,ab,kw,kf.	14,635
23	(TTO or WTP or DCE).ti,ab,kw,kf.	20,148
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	73,118
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	948,265
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	162,996
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty	103,348

No.	Query	Results
	or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	1,074
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	73
30	(15D or 15-D or 15 dimension).ti,ab,kw.	8,057
31	european quality of life 5 dimensions questionnaire/	10,798
32	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	33,887
33	health utilit*.ti,ab,kw.	5,006
34	(HSUV or HSUVs).ti,ab,kw.	228
35	(hui or hui1 or hui2 or hui3).tw.	3,422
36	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or TED quality of life scale or GLS).ti,ab.	12,181
37	or/4-36	3,935,474
38	3 and 37	1,380
39	case report/	3,047,580
40	animal/ not (human/ and animal/)	1,231,031
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	2,270,875
42	or/39-41	6,404,785
43	38 not 42	1,263
44	limit 43 to english language	1,176
45	limit 44 to yr="2023 -Current"	202

Table 115: Search strategy table for Ovid MEDLINE – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
1	graves ophthalmopathy/	3,381
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6,127
3	or/1-2	6,127
4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	1,460,716
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	85,813
6	(quality adj4 life).ti,ab.	429,584
7	(quality adj2 well?being).ti,ab,kw,kf.	594
8	Quality-Adjusted Life Years/	16,903
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	25,541
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	22,658
11	Patient Reported Outcome Measures/	16,319
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	51,242
13	PRO.ti,ab,kw,kf.	273,708
14	exp health surveys/	639,260
15	exp health status/ or health status indicators/	511,770
16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	19,146
17	(utilit* or disutilit*).ti,ab,kw,kf.	295,754
18	disability adjusted life.ti,ab,kw,kf.	6,535
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	8,119
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	5,443

No.	Query	Results
21	sg.ti,ab,kw.	15,117
22	willingness to pay.ti,ab,kw,kf.	9,830
23	(TTO or WTP or DCE).ti,ab,kw,kf.	13,354
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	47,701
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	735,036
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	108,405
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	68,946
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	652
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	42
30	(15D or 15-D or 15 dimension).ti,ab,kw.	6,423
31	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	18,930
32	health utilit*.ti,ab,kw.	3,040
33	(HSUV or HSUVs).ti,ab,kw.	118
34	(hui or hui1 or hui2 or hui3).tw.	2,120
35	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or TED quality of life scale or GLS).ti,ab.	5,248
36	or/4-35	3,042,922
37	3 and 36	984
38	case reports/	2,437,267

No.	Query	Results
39	animals/ not (humans/ and animals/)	5,229,551
40	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	707,935
41	or/38-40	8,321,587
42	37 not 41	940
43	limit 42 to english language	882
44	limit 43 to yr="2023 -Current"	146

Table 116: Search strategy table for CENTRAL – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
#1	MeSH descriptor: [Graves Ophthalmopathy] explode all trees	199
#2	(("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thryoid associated" NEXT opthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	502
#3	#1 OR #2	502
#4	[mh animals] NOT ([mh humans] AND [mh animals])	3663
#5	(note or case report or editorial or short or short survey or survey or book or chapter):pt	1573
#6	#4 OR #5	5236
#7	#3 NOT #6	502
#8	#3 NOT #6 with Publication Year from 2023 to 2024, in Trials	82

Table 117: Search strategy table for Ovid CDSR – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
1	(("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thryoid associated" NEXT opthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	6
2	Limited to last 2 years	0

Table 118: Search strategy table for DARE – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
Search DARE: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	17
2023-2024		0

Table 119: Search strategy table for the HTA database – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2
2	2023-2024	0

Table 120: Search strategy table for NHS EED – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 121: Search strategy table for EconLit – HRQOL/utilities SLR (October 3, 2024).

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Updated search 2

All the updated database searches were conducted on December 17, 2025. The search strategies for each database are presented in Table 122, Table 123, Table 124, Table 125, Table 126, Table 127, Table 128 and Table 129.

Table 122: Search Strategy in MEDLINE: Updated search 2

No.	Query	Results
1	graves ophthalmopathy/	3,758
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6,756
3	or/1-2	6,756
4	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/	1,562,515
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	95,558
6	(quality adj4 life).ti,ab.	485,918
7	(quality adj2 well?being).ti,ab,kw,kf.	682
8	Quality-Adjusted Life Years/	18,746
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	30,413
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	27,202
11	Patient Reported Outcome Measures/	20,466
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	62,222
13	PRO.ti,ab,kw,kf.	301,756
14	exp health surveys/	665,132
15	exp health status/ or health status indicators/	548,190
16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	21,906
17	(utilit* or disutilit*).ti,ab,kw,kf.	336,233
18	disability adjusted life.ti,ab,kw,kf.	9,425
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	8,792
20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	6,108

21	sg.ti,ab,kw.	16,780
22	willingness to pay.ti,ab,kw,kf.	11,225
23	(TTO or WTP or DCE).ti,ab,kw,kf.	15,078
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	53,993
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	795,899
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	120,454
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	75,396
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	693
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	44
30	(15D or 15-D or 15 dimension).ti,ab,kw.	6,723
31	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	21,641
32	health utilit*.ti,ab,kw.	3,322
33	(HSUV or HSUVs).ti,ab,kw.	139
34	(hui or hui1 or hui2 or hui3).tw.	2,292
35	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or GO quality of life scale or GLS).ti,ab.	6,231
36	or/4-35	3,314,055
37	3 and 36	1,122
38	case reports/	2,523,612
39	animals/ not (humans/ and animals/)	5,372,532
40	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	744,017
41	or/38-40	8,585,993
42	37 not 41	1,073
43	limit 42 to english language	1,011
44	limit 43 to yr="2024 -Current"	211

Table 123: Search strategy in Embase: Updates search 2

No	Query	Results
1	endocrine ophthalmopathy/	8,550
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	8,107
3	or/1-2	10,384
4	exp "Quality of Life"/ or exp questionnaire/ or exp "quality of life assessment"/	1,909,352
5	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).ti,ab.	174,251
6	(quality adj4 life).ti,ab.	804,595
7	(quality adj2 well?being).ti,ab,kw,kf.	1,173
8	quality adjusted life year/	42,653
9	(quality adjusted life* or quality-adjusted life* or quality-adjusted-life* or disability adjusted life* or disability-adjusted life* or disability-adjusted-life*).ti,ab,kw,kf.	43,609
10	(QALY or qal* or qwb* or qald* or qale* or qtime* or daly*).ti,ab,kw,kf.	44,776
11	patient-reported outcome/	88,422
12	((patient adj2 reported adj2 outcome*) or (self adj2 reported adj2 outcome*)).ti,ab,kw,kf.	100,156
13	PRO.ti,ab,kw,kf.	460,668
14	exp health survey/	324,378
15	exp health status/ or health status indicator/	407,452
16	(euroQoL* or euro QoL* or euro-QoL* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eQoL-5d* or eQoL5D* or eQoL 5d*).ti,ab,kw,kf.	40,756
17	(utilit* or disutilit*).ti,ab,kw,kf.	471,076
18	disability adjusted life.ti,ab,kw,kf.	11,524
19	(hye* or health* year* equivalent* or hui*).ti,ab,kw,kf.	11,458

20	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	8,727
21	Standard Gamble/ or sg.ti,ab,kw.	25,171
22	willingness to pay.ti,ab,kw,kf.	16,430
23	(TTO or WTP or DCE).ti,ab,kw,kf.	22,880
24	(utility adj3 (score*1 or scoring or valu* or measur* or evaluat* or scale*1 or instrument*1 or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure*1 or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).ti,ab,kw.	83,633
25	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).ti,ab.	1,060,151
26	(VAS or visual analog* scale* or visual-analog* scale*).ti,ab,kw,kf.	190,005
27	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).ti,ab.	116,563
28	(sf8 or sf 8 or sf eight or sfeight).ti,ab,kw.	1,158
29	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	84
30	(15D or 15-D or 15 dimension).ti,ab,kw.	8,507
31	european quality of life 5 dimensions questionnaire/	16,634
32	(euro QoL or eq 5d or euro qual or euro qual5d or euro QoL5d or eq-5d or eq5-d or eq5d or euroqual or euroQoL or euroqual5d or euroQoL5d).ti,ab,kw.	40,202
33	health utilit*.ti,ab,kw.	5,489
34	(HSUV or HSUVs).ti,ab,kw.	262
35	(hui or hui1 or hui2 or hui3).tw.	3,872
36	(Thyroid Eye Disease Quality of Life Scale or TED-QOL or "TED QOL" or TEDQOL or Graves' ophthalmopathy quality of life questionnaire or GO-QOL or "GO QOL" or GOQOL or GO quality of life scale or GLS).ti,ab.	14,458
37	or/4-36	4,478,007
38	3 and 37	1,635

39	case report/	3,196,519
40	animal/ not (human/ and animal/)	1,275,063
41	(note or case report or editorial or short or short survey or survey or book or chapter).pt.	2,339,871
42	or/39-41	6,663,545
43	38 not 42	1,505
44	limit 43 to english language	1,408
45	limit 44 to yr="2024 -Current"	291

Table 124: Search Strategy in EconLit: Updated search 2

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Table 125: Search Strategy in Cochrane CENTRAL: Updated search 2

No.	Query	Results
#1	MeSH descriptor: [Graves Ophthalmopathy] explode all trees	215
#2	(("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thryoid associated" NEXT opthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	546
#3	#1 OR #2	546
#4	[mh animals] NOT ([mh humans] AND [mh animals])	1308
#5	(note or case report or editorial or short or short survey or survey or book or chapter):pt	1578
#6	#4 OR #5	2886
#7	#3 NOT #6	546
#8	#3 NOT #6 with Publication Year from 2024 to 2025, in Trials	7

Table 126: Search Strategy in CDSR: Updated search 2

No.	Query	Results
1	(("Graves" NEXT ophthalmopath*):ti,ab,kw OR ("graves" NEXT orbitopath*):ti,ab,kw OR ("thyroid-associated" NEXT ophthalmopath*):ti,ab,kw OR ("thryoid associated" NEXT opthalmopath*):ti,ab,kw OR ("graves eye" NEXT disease*):ti,ab,kw OR ("thyroid-associated eye" NEXT disease*):ti,ab,kw OR ("thyroid associated eye" NEXT disease*):ti,ab,kw OR ("thyroid eye" NEXT disease*):ti,ab,kw OR ("Dysthyroid" NEXT Ophthalmopath*):ti,ab,kw)	6
2	Limited to last 2 years	0

Table 127. Search Strategy in DARE: Updated search 2

No.	Query	Results
Search DARE: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	17
2024-2025		0

Table 128. Search Strategy in NHS EED: Updated search 2

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 129. Search Strategy in HTAs: Updated search 2

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2
2	2024-2025	0

I.1.2 Systematic selection of studies

The study eligibility followed the same approach outlined for the clinical SLR reviewed in Appendix H. The inclusion/exclusion criteria used to guide the HRQOL/utilities SLR study selection are presented in Table 130.

The study systematic review process followed the same outlined for the clinical SLR reviewed in Appendix H.

Table 130: Inclusion and exclusion criteria used for assessment of studies

PICOS	Inclusion criteria	Exclusion criteria
Population	• Patients with moderate-to-severe active TED • Patients with chronic or acute TED • Patients with active or inactive TED • Patients with inflammatory or non-inflammatory TED • Patients with CON, DON	• Disease other than TED • Non-human • Healthy volunteers
Interventions	No restriction	None
Comparator	No restriction	None
Outcomes	• HRQoL outcomes measured by general instruments (i.e., Short-Form 36 items (SF-36)) • Disease-specific HRQOL scales (i.e., Graves' ophthalmopathy – Quality of life (GO-QoL), Thyroid Eye Disease-Quality of Life (TED-QoL)) • Disease-related PROs • Health state utilities (i.e., EQ-5D, Health Utility Index (HUI-3)), Disutility for health states • Utility elicitation and valuation method • Utilities for health states or by disease states • Disease severity utility • HRQoL mapped to utilities • Standard gamble, Time Trade-Off	No restrictions
Study design	• Clinical trials reporting utility values or results from a scale that can be mapped to obtain utility values • Retrospective, prospective, and cross-	• Non-human, pre-clinical studies • Reviews, Editorials, Notes, Comments, Letters • Case reports/case series

	sectional studies assessing HRQoL/PRO • Studies reporting utility data • Utility validation or elicitation studies • Mapping studies • Economic studies reporting utilities • Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	
Language	English language	Full-text articles not published in English
Timeframe	2013 to present	Published prior to 2013

Abbreviations: CON, compressive optic neuropathy; DON, dysthyroid optic neuropathy; EQ-5D, euroQoL 5-dimension; GO-QOL, graves' ophthalmopathy – quality of life; HRQOL, health-related quality of life; HUI-3; health utility index-3; MAIC, matching-adjusted indirect comparison; PRO, patient-reported outcome; SF-36, 36-item short form health survey; TED, thyroid eye disease; TED-QOL, thyroid eye disease-quality of life.

Original search (conducted June 9, 2023)

The database searches returned 2,205 records which were screened at the title and abstract level, of which 626 were included for full-text screening. After full-text screening, 135 reports met review inclusion criteria. Prior to extraction, an additional 68 records were excluded: 40 records due to publication date (i.e., 2013) and 28 records based on clinical trial design not reporting utility values or results from a scale that can be mapped to obtain utility values; in total, 67 records were included from database sources.

Eighty-one reports were identified through congress searching, 204 through bibliographic search, and seven reports through HTA website searches, of which seven met the eligibility criteria. Prior to extraction, an additional two records were excluded due to publication date (i.e., 2013); in total, five records were included from other sources.

Seventy-two reports from 64 unique studies were included in the SLR.

Updated search 1 (conducted October 3, 2024)

The database searches returned 430 records of which 151 were duplicates so 279 were screened at the title and abstract level. Of these, 51 were included for full-text screening. After full-text screening, 22 reports met review inclusion criteria. In addition, three reports were identified through the congress search. In total, 25 reports from 24 unique studies were included in the SLR.

Updated search 2 (conducted December 17, 2025)

The database searches returned 509 records of which 169 were duplicates so 284 were screened at the title and abstract level. Of these, 56 were included for full-text screening.

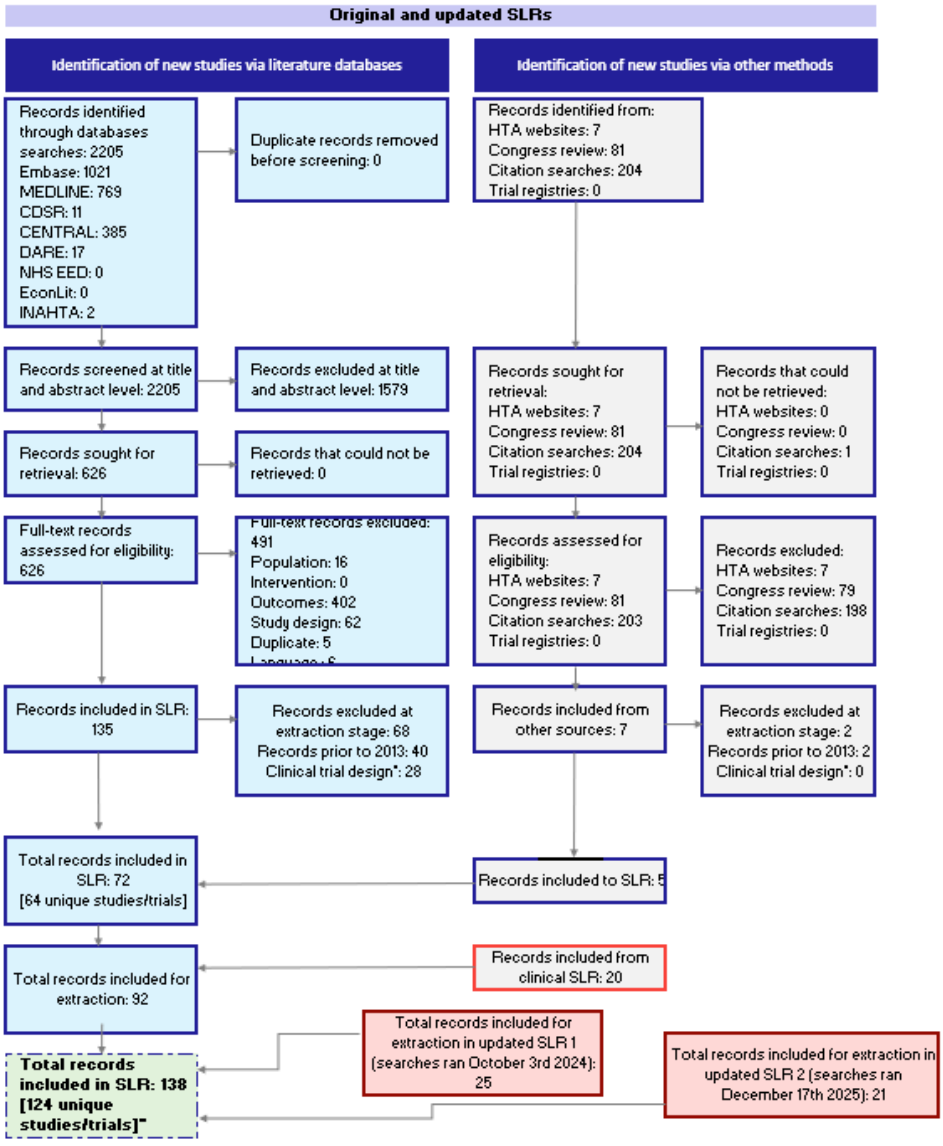
After full-text screening, 21 reports met review inclusion criteria. In total, 21 reports from 21 unique studies were included in the SLR.

The overall literature selection process is shown**Error! Reference source not found.** Figure 14.

Overall search

The study selection process for the overall search was reported in a PRISMA flow diagram and presented in Figure 14.

Figure 14: PRISMA Diagram - HRQoL/Utilities SLR (overall search)



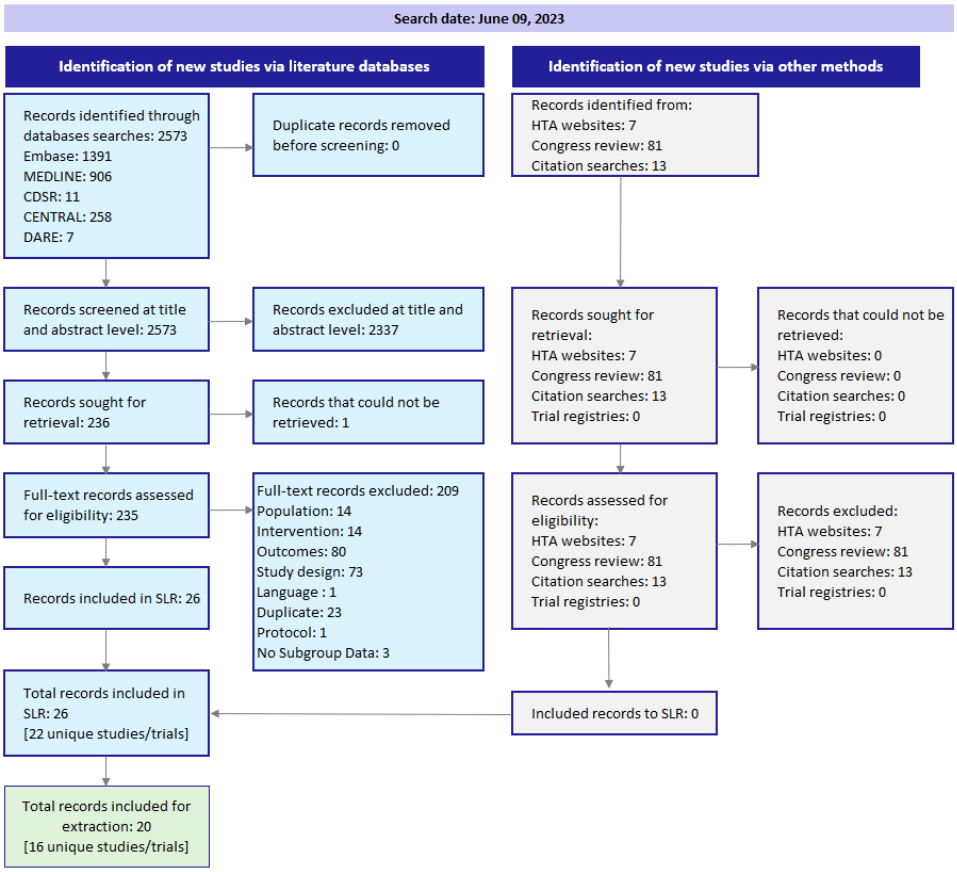
†Records with duplicated information were not extracted.

Abbreviations: CDSR, cochrane database of systematic reviews; CENTRAL, cochrane central register of controlled trials; DARE, database of abstracts of reviews of effects; EconLit, economics literature database; EMBASE, excerpta medica database; HRQOL, health-related quality of life; HTA, health technology assessment; INAHTA, international network of agencies for health technology assessment; MEDLINE, medical literature

analysis and retrieval system online; NHS EED, national health service economic evaluation database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review.

HRQOL data were also captured in the clinical SLR from a subset of studies reporting HRQOL/patient-reported outcomes (PRO). In the primary search, the database searches returned 2,573 records which were screened at the title and abstract level; 235 of these were included for full-text screening. After full-text screening, 26 reports met the review inclusion criteria and reported HRQOL/PRO outcomes. Prior to extraction, six records were excluded due to publication date (i.e., prior to 2013). Eighty-one reports were identified through congress searching, 13 through bibliographic search, and seven reports through HTA website searches, all of which did not meet the eligibility criteria. In total, 20 reports from 16 unique studies were included from the clinical SLR. The literature selection procedure is shown in Figure 15.

Figure 15: PRISMA diagram – Clinical SLR subset reporting HRQOL/PRO outcomes.



Abbreviations: CDSR, cochrane database of systematic reviews; CENTRAL, cochrane central register of controlled trials; DARE, database of abstracts of reviews of effects; EMBASE, excerpta medica database; HRQOL, health-related quality of life; HTA, health technology assessment; MEDLINE, medical literature analysis and retrieval system online; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PRO, patient reported outcome; SLR, systematic literature review.

One RCT study was captured in the HRQOL/utilities SLR for reporting results that can be mapped to obtain utility values. This study was also captured in the clinical SLR, as it also reported HRQOL data. In the updated clinical SLR, no publications were identified that included HRQOL data.

A total of 92 reports from 79 trials were included in the original SLR on HRQOL and utilities. After the updated search, a total of 117 publications reporting on 103 trials were included.

Appendix J. Literature Searches for Additional Inputs to the Health Economic Model

J.1 Systematic Search

An SLR for input to the health economic model was conducted to support this submission. A comprehensive global SLR with searches was conducted on May 22, 2023, with an SLR update conducted on October 3, 2024 and December 17, 2025. The objective of the SLR was to identify evidence on the cost burden and healthcare resource utilization (HCRU) associated with moderate to severe, active TED, and any economic evaluations of relevant comparators in TED. Subgroups of interest included acute (active)/chronic (inactive), active/inactive, inflammatory/non-inflammatory, and compressive optic neuropathy/dysthyroid optic neuropathy TED.

The SLR methodology followed the same outlined for the clinical SLR reviewed in Appendix H.

For the SLR, the searches via the Ovid platform were conducted in EMBASE, MEDLINE, and MEDLINE In-Process for full-text publications and conference abstracts. DARE and CENTRAL were also searched. Additionally, the HTA database, the NHS EED and EconLit databases were searched.

The bibliographic databases presented in Table 131 were used to conduct the primary economic/HCRU SLR.

Table 131: Bibliographic databases included in the economic/HCRU SLR (primary search)

Database	Platform/source	Relevant period for the search	Date of search completion
EMBASE	Ovid	From 1974 to Dec 16, 2025	22.05.2023, 03.10.2024 and 17.12.2025
MEDLINE	Ovid	From 1946 to Dec 26, 2025	22.05.2023, 03.10.2024 and 17.12.2025
International HTA Database	International Network of Agencies for Health Technology Assessment	NR	22.05.2023, 03.10.2024 and 17.12.2025
NHS EED*	Centre for Reviews and Dissemination	NR	22.05.2023, 03.10.2024 and 17.12.2025
EconLit	American Economic Association	From 1886 to Dec 16, 2025	22.05.2023, 03.10.2024 and 17.12.2025

*NHS EED was discontinued in 2015 and only the archived version is available.
Abbreviations: EconLit, economic literature; EED, economic evaluation database; EMBASE, excerpta medica database; HCRU, healthcare resource utilization; HTA, health technology assessment; MEDLINE, medical literature analysis and retrieval system online; NHS, national health service; NR, not reported; SLR, systematic literature review.

Conference proceedings

The conference proceedings review was the same outlined for the HRQOL/utilities SLR reviewed in Appendix I..

HTA submission searches

The HTA submission searches review was the same outlined for the HRQOL/utilities SLR reviewed in Appendix I..

Registry search

The registry searches review was the same outlined for the HRQOL/utilities SLR reviewed in Appendix I..

Bibliographic search

The bibliographies of systematic reviews and meta-analyses identified through the database searches were used to identify studies that met the PICOS criteria for the SLR. Furthermore, bibliographies from selected studies were also reviewed to identify relevant studies. This process ensured that papers and articles not captured during the initial search were included in the review.

J.1.1 Search strategies

Primary search

MEDLINE, EMBASE and EconLit searches were conducted on May 22, 2023, using the Ovid platform. Database searches were performed from inception. Additionally, the HTA database and NHS EED were searched on their respective websites. The search strategies for each database are presented in Table 132, Table 133, Table 134, Table 135 and Table 136.

Table 132: Search strategy table for Ovid EMBASE – economic/HCRU SLR (May 22, 2023)

No.	Query	Results
1	endocrine ophthalmopathy/	6725
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6584
3	or/1-2	8544
4	economics/	244409

5	cost/	62490
6	exp health economics/	1023767
7	economic aspect/	123980
8	financial management/ or health care cost/ or health care financing/ or hospital cost/	363190
9	budget/	33695
10	budget*.ti,ab,kf.	47729
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	348226
12	..nlpx "query=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2","desiredResults=10000","minHitsDivisor=7","permitHyponyms=NO","lowestVocabularySearchLevel=none","phrasesBroken=NO","speedWanted=NoHypos",Comment=Including Related Terms","elimEnable=NO",ConstraintMinTerms=1"	10012

13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	291938
14	(value adj2 (money or monetary)).ti,ab,kf.	4099
15	health care utilization/	93395
16	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.	640174
17	hospitalization cost/ or hospitalization/ or "length of stay"/ or hospital admission/ or hospitalized child/ or child hospitalization/ or hospitalized adolescent/ or hospital patient/	1108258
18	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.	1193788
19	productivity/ or absenteeism/	66511
20	(Productivit* or WPAI or work limitation*).tw.	94513
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.	20344
22	statistical model/ or economic model/	176142
23	economic model*.ab,kf.	6250

24	probability/	148931
25	markov.ti,ab,kf.	38314
26	monte carlo method/	50668
27	monte carlo.ti,ab,kf.	63508
28	decision theory/	1848
29	decision tree/	21393
30	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	51620
31	(discrete event simulation* or microsimulation*).ti,ab,kf.	4300
32	("de novo" adj1 model*).ti,ab,kf.	294
33	or/4-32	3977527
34	3 and 33	405
35	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3748316
36	case report/	2903431
37	(animal* not human*).sh,hw.	4843985

38	35 or 36 or 37	11065316
39	34 not 38	299
40	limit 39 to english language	265
41	limit 40 to yr="2012 -Current"	185

Table 133: Search strategy table for Ovid MEDLINE – economic/HCRU SLR (May 22, 2023)

No.	Query	Results
1	graves ophthalmopathy/	2974
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	5586
3	or/1-2	5586
4	Economics/	27500
5	exp Costs and Cost Analysis"/	264433

6	Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/	79862
7	budget*.ti,ab,kf.	35750
8	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	278862
9	..nlpx "query=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2","desiredResults=10000","minHitsDivisor=7","permitHyponyms=NO","lowestVocabularySearchLevel=none","phrasesBroken=NO","speedWanted=NoHypos",Comment=Including Related Terms","elimEnable=NO",ConstraintMinTerms=1"	7828
10	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	207113
11	(value adj2 (money or monetary)).ti,ab,kf.	3010
12	Drug Utilization/	21519
13	Health Resources/	14678

14	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.	433802
15	hospitalization/ or "length of stay"/ or Patient Admission/ or Child, Hospitalized/ or Adolescent, Hospitalized/	250882
16	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.	694370
17	burden*.ti,ab,kf.	316006
18	efficiency/ or absenteeism/	24466
19	(Productivit* or WPAI or work limitation*).tw.	80180
20	(work* or school* or employ*).tw.	2854752
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.	16067
22	(indirect?treatment?comparison* or indirect?comparison* or indirect treatment comparison* or indirect comparison*).ti,ab,kf.	2734
23	technology assessment, biomedical/	11003
24	(health technology assessment* or health technolog* or biomedical technology assessment* or biomedical technolog* or HTA).ti,ab,kf.	13644

25	exp models, economic/	16209
26	economic model*.ab,kf.	4170
27	markov chains/	15952
28	markov.ti,ab,kf.	28779
29	monte carlo method/	32135
30	monte carlo.ti,ab,kf.	59671
31	exp Decision Theory/	13224
32	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	37024
33	(discrete event simulation* or microsimulation*).ti,ab,kf.	2817
34	("de novo" adj1 model*).ti,ab,kf.	223
35	or/4-34	4736040
36	3 and 35	314
37	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or	5037995

	legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	
38	case reports/	2336495
39	(animal* not human*).sh,hw.	5079576
40	37 or 38 or 39	9979454
41	36 not 40	269
42	limit 41 to english language	234
43	limit 42 to yr="2012 -Current"	164

Table 134: Search strategy table for the HTA database – economic/HCRU SLR (May 22, 2023)

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2
Year limit	2012-2023	0

Table 135: Search strategy table for NHS EED – economic/HCRU SLR (May 22, 2023)

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 136: Search strategy table for EconLit – economic/HCRU SLR (May 22, 2023)

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Updated search 1

All the updated database searches were conducted on October 3, 2024. The search strategies for each database are presented in Table 137, Table 138, Table 139, Table 140 and Table 141.

Table 137: Search strategy table for Ovid EMBASE – economic/HCRU SLR (October 3, 2024)

No.	Query	Results
1	endocrine ophthalmopathy/	7,483

No.	Query	Results
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	7,238
3	or/1-2	9,358
4	economics/	246,764
5	cost/	65,054
6	exp health economics/	1,095,879
7	economic aspect/	129,206
8	financial management/ or health care cost/ or health care financing/ or hospital cost/	383,836
9	budget/	35,216
10	budget*.ti,ab,kf.	51,221
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	371,630

No.	Query	Results
12	..nlp (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	9,792
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	319,555
14	(value adj2 (money or monetary)).ti,ab,kf.	4,408
15	health care utilization/	103,353
16	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.	690,279
17	hospitalization cost/ or hospitalization/ or "length of stay"/ or hospital admission/ or hospitalized child/ or child hospitalization/ or hospitalized adolescent/ or hospital patient/	1,224,947
18	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.	1,305,091
19	productivity/ or absenteeism/	70,091
20	(Productivit* or WPAI or work limitation*).tw.	104,479

No.	Query	Results
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.	21,431
22	statistical model/ or economic model/	182,674
23	economic model*.ab,kf.	6,828
24	probability/	159,086
25	markov.ti,ab,kf.	41,477
26	monte carlo method/	55,003
27	monte carlo.ti,ab,kf.	68,255
28	decision theory/	1,890
29	decision tree/	26,020
30	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	60,212
31	(discrete event simulation* or microsimulation*).ti,ab,kf.	4,783
32	("de novo" adj1 model*).ti,ab,kf.	323
33	or/4-32	4,302,397

No.	Query	Results
34	3 and 33	493
35	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.	3,959,460
36	case report/	3,047,580
37	(animal* not human*).sh,hw.	5,017,358
38	35 or 36 or 37	11,572,918
39	34 not 38	359
40	limit 39 to english language	320
41	limit 40 to yr="2023 -Current"	66

Table 138: Search strategy table for Ovid MEDLINE – economic/HCRU SLR (October 3, 2024)

No.	Query	Results
1	graves ophthalmopathy/	3,381
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye	6,127

No.	Query	Results
	disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	
3	or/1-2	6,127
4	Economics/	27,539
5	exp Costs and Cost Analysis"/	273,490
6	Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/	80,521
7	budget*.ti,ab,kf.	38,835
8	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	302,475
9	..nlp (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	8,781

No.	Query	Results
10	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	233,211
11	(value adj2 (money or monetary)).ti,ab,kf.	3,294
12	Drug Utilization/	21,621
13	Health Resources/	14,963
14	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.	474,500
15	hospitalization/ or "length of stay"/ or Patient Admission/ or Child, Hospitalized/ or Adolescent, Hospitalized/	263,978
16	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.	769,299
17	burden*.ti,ab,kf.	367,405
18	efficiency/ or absenteeism/	25,057
19	(Productivit* or WPAI or work limitation*).tw.	91,421
20	(work* or school* or employ*).tw.	3,186,215

No.	Query	Results
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.	16,924
22	(indirect?treatment?comparison* or indirect?comparison* or indirect treatment comparison* or indirect comparison*).ti,ab,kf.	3,104
23	technology assessment, biomedical/	11,365
24	(health technology assessment* or health technolog* or biomedical technology assessment* or biomedical technolog* or HTA).ti,ab,kf.	15,894
25	exp models, economic/	16,536
26	economic model*.ab,kf.	4,564
27	markov chains/	16,478
28	markov.ti,ab,kf.	31,591
29	monte carlo method/	33,334
30	monte carlo.ti,ab,kf.	64,515
31	exp Decision Theory/	13,860
32	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	45,252

No.	Query	Results
33	(discrete event simulation* or microsimulation*).ti,ab,kf.	3,203
34	("de novo" adj1 model*).ti,ab,kf.	246
35	or/4-34	5,247,599
36	3 and 35	368
37	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	5,321,363
38	case reports/	2,437,267
39	(animal* not human*).sh,hw.	5,219,100
40	37 or 38 or 39	10,397,632
41	36 not 40	317
42	limit 41 to english language	282

No.	Query	Results
43	limit 42 to yr="2023 -Current"	66

Table 139: Search strategy table for the HTA database – economic/HCRU SLR (October 3, 2024)

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	2
Year limit	2023-2024	0

Table 140: Search strategy table for NHS EED – economic/HCRU SLR (October 3, 2024)

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 141: Search strategy table for EconLit – economic/HCRU SLR (October 3, 2024)

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	0

Updated search 2

Table 142. Search Strategy for MEDLINE: updated search 2

No.	Query	Results
1	graves ophthalmopathy/	3,758
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	6,756
3	or/1-2	6,756
4	Economics/	27,557
5	exp Costs and Cost Analysis"/	284,425
6	Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/	81,355
7	budget*.ti,ab,kf.	41,782
8	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	324,479
9	..nlp (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	9,465

10	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	265,466
11	(value adj2 (money or monetary)).ti,ab,kf.	3,585
12	Drug Utilization/	21,837
13	Health Resources/	15,436
14	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.	512,053
15	hospitalization/ or "length of stay"/ or Patient Admission/ or Child, Hospitalized/ or Adolescent, Hospitalized/	279,343
16	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.	839,694
17	burden*.ti,ab,kf.	428,883
18	efficiency/ or absenteeism/	25,655
19	(Productivit* or WPAI or work limitation*).tw.	104,300
20	(work* or school* or employ*).tw.	3,523,690
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.	17,806
22	(indirect?treatment?comparison* or indirect?comparison* or indirect treatment comparison* or indirect comparison*).ti,ab,kf.	3,518
23	technology assessment, biomedical/	11,828

24	(health technology assessment* or health technolog* or biomedical technology assessment* or biomedical technolog* or HTA).ti,ab,kf.	18,572
25	exp models, economic/	17,098
26	economic model*.ab,kf.	4,970
27	markov chains/	17,652
28	markov.ti,ab,kf.	34,529
29	monte carlo method/	35,028
30	monte carlo.ti,ab,kf.	69,489
31	exp Decision Theory/	14,746
32	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	55,459
33	(discrete event simulation* or microsimulation*).ti,ab,kf.	3,627
34	("de novo" adj1 model*).ti,ab,kf.	270
35	or/4-34	5,767,206
36	3 and 35	438
37	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case	5,522,010

	or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	
38	case reports/	2,523,612
39	(animal* not human*).sh,hw.	5,361,968
40	37 or 38 or 39	10,738,346
41	36 not 40	378
42	limit 41 to english language	341
43	limit 42 to yr="2024 -Current"	86

Table 143. Search Strategy in Embase: Updated search 2

No.	Query	Results
1	endocrine ophthalmopathy/	
2	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.	
3	or/1-2	

4	economics/
5	cost/
6	exp health economics/
7	economic aspect/
8	financial management/ or health care cost/ or health care financing/ or hospital cost/
9	budget/
10	budget*.ti,ab,kf.
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
12	..nlp (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
14	(value adj2 (money or monetary)).ti,ab,kf.
15	health care utilization/
16	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab,kf.

17	hospitalization cost/ or hospitalization/ or "length of stay"/ or hospital admission/ or hospitalized child/ or child hospitalization/ or hospitalized adolescent/ or hospital patient/
18	(hospitali* or length of stay* or length of hospital stay* or length of hospitali#ation* or ICU or inpatient or admission).tw.
19	productivity/ or absenteeism/
20	(Productivit* or WPAI or work limitation*).tw.
21	((work or working) adj1 (absen* or loss* or disabilit* or abilit* or impairment* or limitation* or incapacit* or capacit*)).tw.
22	statistical model/ or economic model/
23	economic model*.ab,kf.
24	probability/
25	markov.ti,ab,kf.
26	monte carlo method/
27	monte carlo.ti,ab,kf.
28	decision theory/
29	decision tree/
30	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.

31	(discrete event simulation* or microsimulation*).ti,ab,kf.
32	("de novo" adj1 model*).ti,ab,kf.
33	or/4-32
34	3 and 33
35	(book or chapter or conference review or editorial or erratum or letter or note or short survey or tombstone).pt.
36	case report/
37	(animal* not human*).sh,hw.
38	35 or 36 or 37
39	34 not 38
40	limit 39 to english language
41	limit 40 to yr="2023 -Current"

Table 144. Search Strategy in EconLit: Updated search 2

No.	Query	Results
1	(Graves ophthalmopath*3 or graves orbitopath*3 or thyroid-associated ophthalmopath*3 or thryoid associated opthalmopath*3 or graves eye	0

	disease*2 or thyroid-associated eye disease*2 or thyroid associated eye disease*2 or thyroid eye disease*2 or Dysthyroid Ophthalmopath*3).mp.

Table 145. Search Strategy for NHS EED: Updated search 2

No.	Query	Results
Search NHS EED: Any field	(Graves ophthalmopath* or graves orbitopath* or thyroid-associated ophthalmopath* or thryoid associated opthalmopath* or graves eye disease* or thyroid-associated eye disease* or thyroid associated eye disease* or thyroid eye disease* or Dysthyroid Ophthalmopath*)	0

Table 146. Search Strategy in HTAs: Updated search 2

No.	Query	Results
All	((graves* or thyroid or dysthyroid)) AND ((ophthalmopath* or orbitopath* or "eye disease"))	
Year limit	2023-2024	

J.1.2 Systematic selection of studies

The study eligibility followed the same outline for the clinical SLR reviewed in Appendix H. The inclusion/exclusion criteria used to guide the economic/HCRU was two-folded with one PICOS criteria being for economic evaluations and other being for HCRU and costs, with the criteria presented in Table 147 and Table 148, respectively.

Table 147: Inclusion and exclusion criteria used for assessment of studies in the economic/HCRU SLR – economic evaluations

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with moderate to severe active TED Patients with chronic or acute TED Patients with active or inactive TED Patients with inflammatory or non-inflammatory TED Patients with CON, DON	Disease other than TED Non-human Healthy volunteers	
Intervention	Approved Teprotumumab Recommended in guidelines/off-label use *Immunomodulators*: Glucocorticoids (oral or IV, alone or in combination) Betamethasone Doxycycline Methylprednisolone	Studies not including at least one of the interventions listed in the inclusion criteria	

Conventional DMARDs:

Mycophenolate

Cyclosporin

Azathioprine

Other – surgery/radiotherapy:

Orbital radiotherapy

Orbital surgery (decompression [including 2-wall vs 3-wall vs 4-wall vs fat decompression], strabismus, eyelid surgery [blepharoplasty])

Orbital surgery with pharmacological interventions

Monoclonal antibodies:

Tocilizumab

Rituximab

Investigational

Monoclonal antibodies:

Batoclimab

Secukinumab

Vunakizumab (SHR-1314)

Infliximab

Adalimumab

VRDN-002

Efgartigimod

VRDN-001

VB421

K1-70

Other – pharmacologic:

Atorvastatin

Bimatoprost

Sirolimus (Rapamycin)

Selenium

Immunomodulators:

Antithymocyte globulin

ATX-GD-59

T-cell co-stimulatory treatments:

Aflibercept

Etanercept

Kinase inhibitors:

	Linstinib	
Comparators	Any intervention*	None
Outcomes	Incremental costs Incremental health benefits QALYs, LYs, DALYs Cost-effectiveness measures (ICER, ICUR, etc.) Willingness to pay threshold Model specifications (type of model, time horizon, health states, discounting) Currency and cost year Utilities Cost inputs	No restrictions
Study design/publication type	Cost-effectiveness studies Cost-utility studies Cost-benefit analyses Cost-minimization studies Budget impact analysis Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	Non-human, pre-clinical studies Reviews, Editorials, Notes, Comments, Letters Case reports/case series

Language restrictions	English language	Full-text articles not published in English
Timeframe	2012 to present	Published prior to 2012

*This refers to any intervention listed for inclusion in the PICOS criteria. There were no restrictions for interventions. Abbreviations: CON, compressive optic neuropathy; DALY, disability-adjusted life year; DMARDs, disease-modifying antirheumatic drugs; DON, dysthyroid optic neuropathy; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; IV, intravenous; LY, life year; MAIC, matching-adjusted indirect comparison; QALY, quality-adjusted life year; SLR, systematic literature review; TED, thyroid eye disease.

Table 148: Inclusion and exclusion criteria used for assessment of studies in the economic/HCRU SLR – HCRU and costs

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with moderate to severe active TED Patients with chronic or acute TED Patients with active or inactive TED Patients with inflammatory or non-inflammatory TED Patients with CON, DON	Disease other than TED Non-human Healthy volunteers	
Intervention	No restriction	None	
Comparators	No restriction	None	
Outcomes	HCRU, including but not limited to: Outpatient visits (non-emergency) Emergency department visits Laboratory tests	No restrictions	

	Inpatient admissions, hospitalizations Length of stay Direct costs including, but not limited to: Medication costs Treatment-related costs Outpatient care costs Inpatient care costs, routine testing costs Emergency department costs Follow-up visit costs Management of AEs Out-of-pocket costs for patients, including travel Indirect costs including, but not limited to: Productivity costs Absenteeism Presenteeism	
Study design/publication type	Resource use studies Cost/economic burden of illness studies Cost analysis Piggyback RCTs	Non-human, pre-clinical studies Reviews, Editorials, Notes, Comments, Letters Case reports/case series

	Systematic reviews, meta-analyses, pooled analyses, and MAICs (for cross-checking only)	
Language restrictions	English language	Full-text articles not published in English
Timeframe	2012 to present	Published prior to 2012

Abbreviations: AE, adverse event, CON, compressive optic neuropathy; DON, dysthyroid optic neuropathy; HCRU, healthcare resource utilization; MAIC, matching-adjusted indirect comparison; RCT, randomized controlled trial; SLR, systematic literature review; TED, thyroid eye disease.

Primary search

The database searches returned 349 records which were screened at the title and abstract level, of which 108 were included for full-text screening. After full-text screening, four reports met review inclusion criteria. In addition, eighty-one reports were identified through congress searching, 13 through the bibliographic search, and seven reports through HTA sources. After assessing the records against the PICOS criteria, five records were deemed eligible. In total, nine reports from nine unique studies were included in the SLR.

Updated search 1

The database searches returned 132 records of which 20 were duplicates so 112 were screened at the title and abstract level. Of these, 15 were included for full-text screening. After full-text screening, three reports met review inclusion criteria. In addition, one report was identified through the congress search. In total, four reports from four unique studies were included in the SLR.

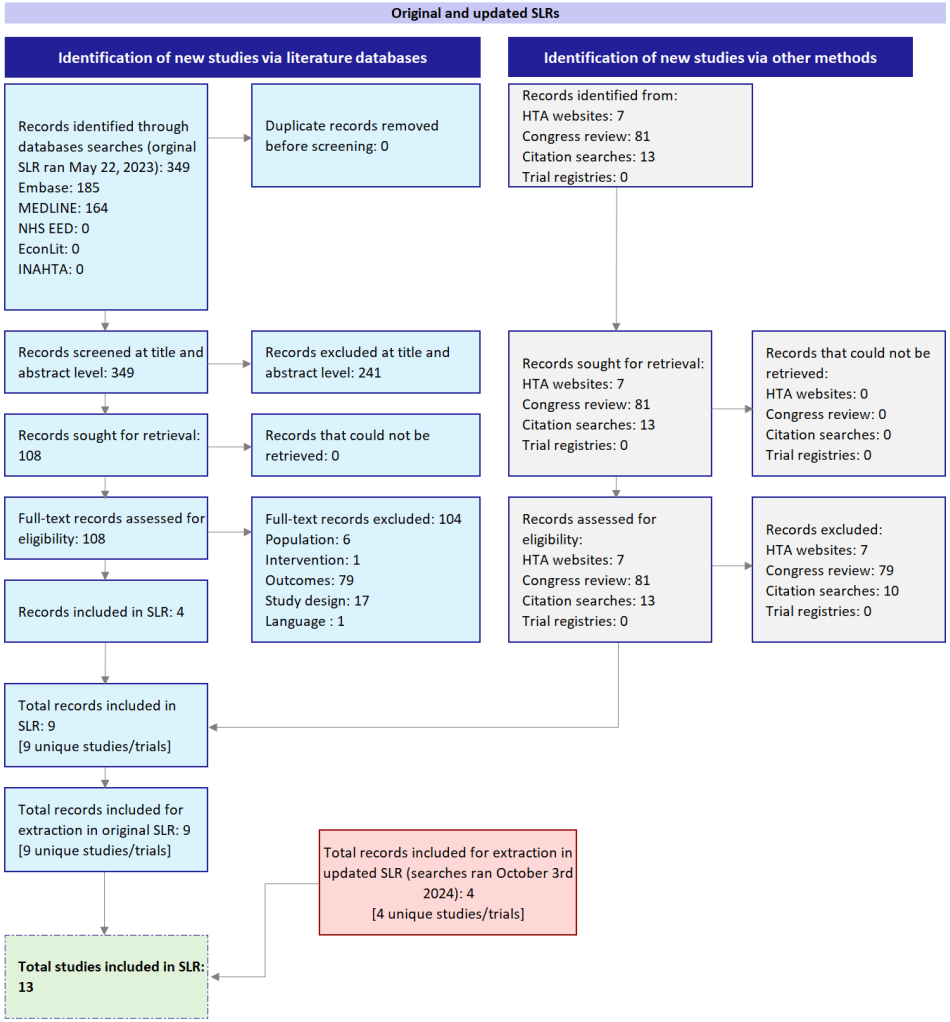
Updated search 2

The database searches returned 171 records of which 30 were duplicates so 141 were screened at the title and abstract level. Of these, 15 were included for full-text screening. After full-text screening, six reports met review inclusion criteria. In addition, one report was identified through the HRQOL electronic search.

Overall search

Overall, following the SLR updates a total of 20 publications were included in the Economic/HCRU SLR. The overall literature selection process is shown in Figure 16.

Figure 16: PRISMA Diagram – Economic/HCRU SLR (overall search)


Original and updated SLRs
Identification of new studies via literature databases
Identification of new studies via other methods
Records identified through databases searches (orginal SLR ran May 22, 2023): 349
Embase: 185
MEDLINE: 164
NHS EED: 0
EconLit: 0
INAHTA: 0
Duplicate records removed before screening: 0
Records identified from:
HTA websites: 7
Congress review: 81
Citation searches: 13
Trial registries: 0
Records screened at title and abstract level: 349
Records excluded at title and abstract level: 241
Records sought for retrieval: 108
Records that could not be retrieved: 0
Records sought for retrieval:
HTA websites: 7
Congress review: 81
Citation searches: 13
Trial registries: 0
Records that could not be retrieved:
HTA websites: 0
Congress review: 0
Citation searches: 0
Trial registries: 0
Full-text records assessed for eligibility: 108
Full-text records excluded: 104
Population: 6
Intervention: 1
Outcomes: 79
Study design: 17
Language : 1
Records assessed for eligibility:
HTA websites: 7
Congress review: 81
Citation searches: 13
Trial registries: 0
Records excluded:
HTA websites: 7
Congress review: 79
Citation searches: 10
Trial registries: 0
Records included in SLR: 4
Total records included in SLR: 9
[9 unique studies/trials]
Total records included for extraction in original SLR: 9
[9 unique studies/trials]
Total records included for extraction in updated SLR (searches ran October 3rd 2024): 4
[4 unique studies/trials]
Total studies included in SLR: 13

Abbreviations: CDSR, cochrane database of systematic reviews; CENTRAL, cochrane central register of controlled trials; DARE, database of abstract of reviews of effects; HCRU, healthcare resource utilization; HTA, health technology assessment; INAHTA, international network of agencies for health technology assessment; MEDLINE, medical literature analysis and retrieval system online; NHS EED, national health service economic evaluation database; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review.

J.1.3 Summary of included studies

N/A

J.1.4 Excluded full-text references

Publications included after abstract review were obtained for a full review of the text. A record was kept of papers excluded at this stage along with a clear justification for their exclusion. A list of excluded studies in the economic/HCRU SLR, including reason for exclusion, is provided in Table 149.

Table 149: Excluded full text references

Reference	Reason for exclusion	Comments
Li LF, Xue JL, Guan L, Su FF, Wang H, Zhang DF. Therapeutic outcomes of mycophenolate mofetil and glucocorticoid in thyroid-associated ophthalmopathy patients. Frontiers in Endocrinology. 2023 Mar 21;14:1140196.	OUTCOMES	Efficacy/safety, QoL of mycophenolate mofetil and glucocorticoid
Ma R, Li X, Peng Z, Guo J, Qian J, Zhang Y. Using 24-h intraocular pressure-related patterns to identify open-angle glaucoma in thyroid eye disease. Graefe's Archive for Clinical and Experimental Ophthalmology. 2023 Apr;261(4):1151-8.	OUTCOMES	Diagnostic model using 24-hour intraocular pressure
Oke I, Reshef ER, Elze T, Miller JW, Lorch AC, Hunter DG, Freitag SK, IRIS Registry Analytic Center Consortium. Smoking Is Associated With	POPULATION	Graves' disease w/o TED subgroup

a Higher Risk of Surgical Intervention for Thyroid Eye Disease in the IRIS Registry. American Journal of Ophthalmology. 2023 May 1;249:174-82.		
Mazonakis M, Tzedakis A, Lyraraki E, Damilakis J. Risk of developing radiogenic cancer following photon-beam radiotherapy for Graves' orbitopathy. Medical Physics. 2018 Oct;45(10):4775-82.	OUTCOMES	Probability for cancer development
Wu H, Luo B, Zhao Y, Yuan G, Wang Q, Liu P, Zhai L, Lv W, Zhang J. Radiomics analysis of the optic nerve for detecting dysthyroid optic neuropathy, based on water-fat imaging. Insights into Imaging. 2022 Sep 24;13(1):154.	OUTCOMES	Optic nerve-based radiomics model
Tran C, Pham CM, Simmons BA, Warner LL, Fuhrmeister LJ, Shriver EM. Echographic assessment of extraocular muscle response to teprotumumab. Ophthalmic Plastic & Reconstructive Surgery. 2022 Jul 1;38(4):336-9.	INTERVENTION	Orbital echography (ultrasound)
Luo B, Liu R, Wang S, Hu W, Li Y, Tong B, Zhang H, Qi X. Utility of isolated-check visual evoked potential technique in dysthyroid optic neuropathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2023 Jan 16:1-0.	OUTCOMES	Diagnostic value of isolated-check visual evoked potential
Angelo L, Niederer R, Hart R. Thyroid eye disease in New Zealand: Interaction between ethnicity and smoking status. The New Zealand Medical Journal (Online). 2020 Dec 4;133(1526):12-7.	OUTCOMES	TED epi
Wang Y, Sun J, Liu X, Li Y, Fan X, Zhou H. Robot-assisted orbital fat decompression surgery: First in human. Translational Vision Science & Technology. 2022 May 2;11(5):8-.	OUTCOMES	Efficacy/safety, QoL of robot-assisted orbital fat decompression surgery
Boulakh L, Nygaard B, Bek T, Faber J, Heegaard S, Toft PB, Poulsen HE, Toft-Petersen AP, Hesgaard HB, Ellervik C. Nationwide incidence of thyroid eye disease and cumulative incidence of strabismus and	OUTCOMES	TED epi, treatment pattern

surgical interventions in Denmark. JAMA ophthalmology. 2022 Jul 1;140(7):667-73.		
Marfowaa GD, Friedland DR, Adams JA, Osinski K, Poetker DM. Medial orbital wall decompression: Demographics influencing surgical follow-up and complications: Impacts on follow-up and complications. American Journal of Otolaryngology. 2022 Sep 1;43(5):103578.	OUTCOMES	Adherence, safety of medial orbital wall decompression
Hu H, Chen L, Zhang JL, Chen W, Chen HH, Liu H, Shi HB, Wu FY, Xu XQ. T2-Weighted MR Imaging-Derived Radiomics for Pretreatment Determination of Therapeutic Response to Glucocorticoid in Patients With Thyroid-Associated Ophthalmopathy: Comparison With Semiquantitative Evaluation. Journal of Magnetic Resonance Imaging. 2022 Sep;56(3):862-72.	STUDY DESIGN	Diagnostic tool performance
Wong MB, Maamari RN, Couch SM. Contralateral eyelid elevation following unilateral upper eyelid retraction repair. Orbit. 2022 Jul 4;41(4):452-6.	OUTCOMES	Effectiveness of unilateral upper eyelid retraction repair
Jia J, Dong J, Deng L. Network Meta-Analysis of Different Intravenous Glucocorticoid Regimes for the Treatment of Graves' Orbitopathy. Frontiers in Pharmacology. 2022 Apr 26;13:785757.	STUDY DESIGN	SLR for cross-check
Bartalena L, Marinò M, Marcocci C, Tanda ML. Teprotumumab for Graves' orbitopathy and ototoxicity: moving problems from eyes to ears?. Journal of Endocrinological Investigation. 2022 Jul;45(7):1455-7.	STUDY DESIGN	Review
Zou M, Wu D, Zhu H, Huang X, Zhao X, Zhao J, Fu W, Li R, Li B, Wan P, Hong S. Multiparametric quantitative MRI for the evaluation of dysthyroid optic neuropathy. European Radiology. 2022 Mar 1:1-8.	OUTCOMES	Prognostic value of quantitative MRI parameters

Acibucu F, Öztürk DD, Kizildag C, Aslan MZ, Gulumsek E, Sumbul MS, Neselioglu S, Erel O, Sen S, Bankir M, Sumbul HE. Proptosis is associated with thiol-disulfide in patients with Graves' ophthalmopathy. Archives of Endocrinology and Metabolism. 2022 Apr 1;66:191-7.	OUTCOMES	Difference in serum thiol-disulfide measurements
Meling Stokland A-E, Nedrebo BG, Carlsen S, Breivik L, Lovas K, Ueland HO, Husebye ES, Ueland G. A 25-year follow-up study of Graves' Disease: Remission rates, thyroid-eye disease and autoimmune comorbidity. Thyroid. 2022 Oct; 32(S1):A153.	OUTCOMES	TED flares
Hyman L, Ramesh S, Watson A, Sharpe J, Das AV, Moster M, Alessi K, Peskin E, Naik MN. Thyroid Eye Disease: A US (Wills Eye Hospital) and India (LV Prasad) Comparison. Investigative Ophthalmology & Visual Science. 2022 Jun 1;63(7):4003-A0345.	OUTCOMES	Demographic and clinical characteristics of TED, QoL
Vannucchi G, Campi I, Covelli D, Currò N, Lazzaroni E, Palomba A, Soranna D, Zambon A, Fugazzola L, Muller I, Guastella C. Efficacy profile and safety of very low-dose rituximab in patients with Graves' orbitopathy. Thyroid. 2021 May 1;31(5):821-8.	OUTCOMES	Efficacy/safety rituximab
Cockerham KP, Padnick-Silver L, Stuertz N, Francis-Sedlak M, Holt RJ. Quality of life in patients with chronic thyroid eye disease in the United States. Ophthalmology and Therapy. 2021 Dec;10:975-87.	OUTCOMES	QoL outcomes
Suresh R, Soparkar CN, Alford EL. Sinonasal complications associated with endoscopic orbital decompression. Laryngoscope Investigative Otolaryngology. 2021 Feb;6(1):71-6.	OUTCOMES	Safety of endoscopic endonasal orbital decompression
Qi X, Tong B, Hu W, Luo B. Comparing isolated-check visual evoked potential, pattern visual evoked potential, and standard automated perimetry in dysthyroid optic neuropathy eyes. Eye. 2021 Sep;35(9):2556-63.	OUTCOMES	Diagnostic value of isolated-check visual evoked potential, pattern visual evoked potential, and standard automated perimetry

Cevik Y, Taylan Sekeroglu H, Ozgen B, Erkan Turan K, Sanac AS. Clinical and radiological findings in patients with newly diagnosed graves' ophthalmopathy. International Journal of Endocrinology. 2021 May 3;2021.	OUTCOMES	Clinical ophthalmological and MRI findings
Ahn HY, Lee JK. Intravenous glucocorticoid treatment for Korean graves' ophthalmopathy patients. Journal of Korean Medical Science. 2020 Jun 15;35(23).	OUTCOMES	Effectiveness/safety of IV glucocorticoid
Mahomed S, Verwey VF. Burden of eye conditions at a specialised eye hospital in KwaZulu-Natal, South Africa. African Vision and Eye Health. 2020 Jan 1;79(1):1-5.	OUTCOMES	Eye diseases epi
Hoang TT, He J. Effects of high-dose hormone therapy in patients with thyroid-associated orbitopathy and its effect on visual acuity and ocular surface. INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE. 2020 Jan 1;13(11):8636-43.	OUTCOMES	Efficacy, QoL of hormone therapy
Naselli A, Moretti D, Regalbuto C, Arpi ML, Lo Giudice F, Frasca F, Belfiore A, Le Moli R. Evidence that baseline levels of low-density lipoproteins cholesterol affect the clinical response of Graves' ophthalmopathy to parenteral corticosteroids. Frontiers in Endocrinology. 2020 Dec 22;11:609895.	OUTCOMES	Effectiveness of IV glucocorticoid
Deaner JD, Giacometti JN. Rituximab in Ocular Adnexal Lymphoma and Orbital Inflammatory Disease. International Ophthalmology Clinics. 2020 Apr 1;60(2):63-75.	STUDY DESIGN	Review
Schovanek J, Cibickova L, Karhanova M, Kovarova D, Frysak Z, Karasek D. Retrospective analysis of patients with graves orbitopathy treated by pulses of methylprednisolone, with a focus on adverse events. Endocrine Practice. 2018 Jul 1;24(7):652-7.	OUTCOMES	Effectiveness/safety of methylprenisolone

Leo M, Sabini E, Ionni I, Sframeli A, Mazzi B, Menconi F, Molinaro E, Bianchi F, Brozzi F, Santini P, Elisei R. Use of low-dose radioiodine ablation for Graves' orbitopathy: results of a pilot, perspective study in a small series of patients. Journal of endocrinological investigation. 2018 Mar;41:357-61.	POPULATION	No TED subgroup
Gold KG, Scofield S, Isaacson SR, Stewart MW, Kazim M. Orbital radiotherapy combined with corticosteroid treatment for thyroid eye disease-compressive optic neuropathy. Ophthalmic Plastic & Reconstructive Surgery. 2018 Mar 1;34(2):172-7.	OUTCOMES	Effectiveness/safety of orbital radiotherapy
Kinori M, Godfrey KJ, Whipple KM, Kikkawa DO, Granet DB. Refractive changes following corrective surgery for thyroid-related orbitopathy. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2017 Feb 1;21(1):67-8.	OUTCOMES	Refractive changes of strabismus surgery with or without orbital decompression
Marino M, Leo M, Sabini E, Ionni I, Mazzi B, Menconi F, Molinaro E, Bianchi F, Brozzi F, Santini P, Elisei R, Vitti P, Marcocci C. Use of low-dose radioiodine ablation for Graves' orbitopathy (GO): Results of a prospective clinical study. European Thyroid Journal. 2017 Aug; 6(S1):60.	POPULATION	No TED subgroup
Mladenovic M, Buchberger M, Qerimi V, Puntscher S, Siebert U, Rochau U. Health state utilities in individuals with goiter, hypothyroidism, hyperthyroidism and graves' disease as an example for thyroid disorders–a systematic review. Value in Health. 2017 Oct 1;20(9):A483.	STUDY DESIGN	SLR without references
Lin TY, Li N, Yeh MW, Leung AM, Rootman DB. Prognostic indicators for the development of strabismus among patients with graves' ophthalmopathy. Journal of Clinical & Translational Endocrinology. 2017 Sep 1;9:38-40.	OUTCOMES	Strabismus predictors

Ference EH, Sindwani R, Tan BK, Chandra RK, Kern RC, Conley D, Smith SS. Open versus endoscopic medial orbital decompression: utilization, cost, and operating room time. American Journal of Rhinology & Allergy. 2016 Sep;30(5):360-6.	OUTCOMES	No TED subgroup econ data Safety of orbital decompression
Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, Ebeling PR. Risk factors for Graves' orbitopathy; the Australian thyroid-associated orbitopathy research (ATOR) study. The Journal of Clinical Endocrinology & Metabolism. 2016 Jul 1;101(7):2711-20.	OUTCOMES	TED risk factors and DON
Riedl M, Kuhn A, Krämer I, Kolbe E, Kahaly GJ. Prospective, systematically recorded mycophenolate safety data in Graves' orbitopathy. Journal of endocrinological investigation. 2016 Jun;39:687-94.	OUTCOMES	Safety of mycophenolate
Bartalena L, Veronesi G, Krassas G, Wiersinga W, Marcocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Azzolini C, Boboridis K, Mourits M, Soeters M, Lelio B, Nardi M, Curro N, Boschi A, Bernard M, Von Arx G, Perros P, Kahaly GJ. Evaluation of response during intravenous glucocorticoid (ivGC) treatment for moderate-to-severe and active graves' orbitopathy (GO): Is it a guidance to decide whether treatment should be continued or withdrawn?. European Thyroid Journal. 2016 Aug; 5(S1):71.	OUTCOMES	Efficacy, QoL of IV glucocorticoids
Ponto KA, Binder H, Diana T, Matheis N, Otto AF, Pitz S, Pfeiffer N, Kahaly GJ. Prevalence, phenotype, and psychosocial well-being in euthyroid/hypothyroid thyroid-associated orbitopathy. Thyroid. 2015 Aug 1;25(8):942-8.	OUTCOMES	Euthyroid/hypothyroid epi and phenotype, QoL
Riedl M, Kolbe E, Kampmann E, Krämer I, Kahaly GJ. Prospectively recorded and MedDRA-coded safety data of intravenous	OUTCOMES	Safety of methylprednisolone

methylprednisolone therapy in Graves' orbitopathy. Journal of endocrinological investigation. 2015 Feb;38:177-82.		
Laurberg P, Berman DC, Pedersen IB, Andersen S, Carlé A. Double vision is a major manifestation in moderate to severe graves' orbitopathy, but it correlates negatively with inflammatory signs and proptosis. The Journal of Clinical Endocrinology & Metabolism. 2015 May 1;100(5):2098-105.	OUTCOMES	Diplopia outcome
Mitchell AL, Goss L, Mathiopoulou L, Morris M, Vaidya B, Dickinson AJ, Quinn A, Dayan C, McLaren J, Hickey JL, Lazarus JH. Diagnosis of Graves' orbitopathy (DiaGO): results of a pilot study to assess the utility of an office tool for practicing endocrinologists. The Journal of Clinical Endocrinology & Metabolism. 2015 Mar 1;100(3):E458-62.	OUTCOMES	Utility of DiaGO assessment tool
Bloise W, Mimura LY, Moura JP. Quick vision improvement of severe graves' ophthalmopathy with a parenteral ppar-gamma antagonist and COX-2 inhibitor-sodium diclofenac. Thyroid. 2015; 25(S1):A189.	OUTCOMES	Effectiveness of diclofenac
Laurberg P, Berman D, Bulow Pedersen I, Andersen S, Malling S, Carle A. Triple therapy (glucocorticoid + ciclosporin + orbital irradiation) for diplopia (DIP) of moderate-to-severe graves' orbitopathy (MSGO). A prospective follow-up study. Thyroid. 2015; 25(S1):A12.	OUTCOMES	Effectiveness/safety of glucocorticoid+ciyclosporine+orbital irradiation
Beleslin BN, Ciric J, Zarkovic M, Stojkovic M, Savic S, Knezevic M, Stankovic B, Trbojevic B. Efficacy and safety of combined parenteral and oral steroid therapy in Graves' orbitopathy. Hormones. 2014 Apr;13:222-8.	OUTCOMES	Effectiveness/safety of glucocorticoid
Ponto KA, Zwiener I, Al-Nawas B, Kahaly GJ, Otto AF, Karbach J, Pfeiffer N, Pitz S. Piezosurgery for orbital decompression surgery in	OUTCOMES	Effectiveness orbital decompression

thyroid associated orbitopathy. Journal of Cranio-Maxillofacial Surgery. 2014 Dec 1;42(8):1813-20.		
Dharmasena A, Keenan TD, Goldacre MJ. Orbital decompression for thyroid-associated orbitopathy in England: trends over time and geographical variation. Orbit. 2014 Apr 1;33(2):109-14.	OUTCOMES	Oribital decompression admission trend
Nexo MA, Watt T, Pedersen J, Bonnema SJ, Hegedüs L, Rasmussen AK, Feldt-Rasmussen U, Bjorner JB. Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study. The Journal of Clinical Endocrinology & Metabolism. 2014 Sep 1;99(9):3184-92.	OUTCOMES	Risk of work disability, probability work transition
Di Maria C, Allen J, Dickinson J, Neoh C, Perros P. Novel thermal imaging analysis technique for detecting inflammation in thyroid eye disease. The Journal of Clinical Endocrinology & Metabolism. 2014 Dec 1;99(12):4600-6.	OUTCOMES	Clinical value of a thermal imaging analysis
Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2014 Sep 1;30(5):415-9.	OUTCOMES	Effectiveness/safety, QoL (subjective improvement) of adalimumab
Nexø MA, Watt T, Bonnema SJ, Hegedüs L, Rasmussen ÅK, Feldt-Rasmussen U, Bjørner JB. Self-reported work ability varies according to type of thyroid disease. In38th Annual Meeting of the European Thyroid Association 2014 2014.	POPULATION	No TED subgroup
Liao WL, Wan L, Wang TY, Chen CC, Tse SS, Lu CH, Tsai FJ. Association of TLR7 and TSHR copy number variation with Graves' disease and Graves' ophthalmopathy in Chinese population in Taiwan. BMC ophthalmology. 2014 Dec;14(1):1-5.	OUTCOMES	Association between CNV in the TSHR and TLR7 genes

Chang SH, Papageorgiou KI, Ang M, King AJ, Goldberg RA. High-resolution ultrasound as an effective and practical tool to analyze eyebrow profile expansion in thyroid-associated periorbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2013 Sep 1;29(5):382-5.	OUTCOMES	Clinical value of high-resolution ultrasonography
Yoo SH, Pineles SL, Goldberg RA, Velez FG. Rectus muscle resection in Graves' ophthalmopathy. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2013 Feb 1;17(1):9-15.	OUTCOMES	Effectiveness of strabismus surgery
De Bellis A, Conzo G, Cennamo G, Pane E, Bellastella G, Colella C, Iacovo AD, Paglionico VA, Sinisi AA, Wall JR, Bizzarro A. Time course of Graves' ophthalmopathy after total thyroidectomy alone or followed by radioiodine therapy: a 2-year longitudinal study. Endocrine. 2012 Apr;41:320-6.	OUTCOMES	Effectiveness of total thyroidectomy
Jiang H, Wang Z, Xian J, Li J, Chen Q, Ai L. Evaluation of rectus extraocular muscles using dynamic contrast-enhanced MR imaging in patients with Graves' ophthalmopathy for assessment of disease activity. Acta Radiologica. 2012 Feb;53(1):87-94.	OUTCOMES	Clinical value of DCE-MRI
Vokurka Topljak S, Galiot Delić M, Mandić K, Perić S, Baretić M, Juri Mandić J. Nonsurgical treatment for upper eyelid retraction in patients with inactive Graves' orbitopathy. International Ophthalmology. 2023 Jan 1:1-9.	OUTCOMES	Effectiveness, QoL (subjective complaint) of incobotulinumtoxinA
Dorado Cortez O, Grivet D, Perrillat N, Gain P, Thuret G. Treatment of corticosteroid-resistant Graves' orbitopathy with tocilizumab: a single-centre prospective study. Orbit. 2023 Jul 4;42(4):411-7.	OUTCOMES	Effectiveness/safety of tocilizumab
To JK, Wang JN, Vu AN, Ediriwickrema LS, Browne AW. Optimization of a Novel Automated, Low Cost, Three-Dimensional Photogrammetry System (PHACE). medRxiv. 2023:2023-04.	POPULATION	Healthy adults

Shao J, Huang X, Gao T, Cao J, Wang Y, Zhang Q, Lou L, Ye J. Deep learning-based image analysis of eyelid morphology in thyroid-associated ophthalmopathy. Quantitative Imaging in Medicine and Surgery. 2023 Mar 3;13(3):1592.	OUTCOMES	Deep learning-based approach to measure eyelid morphology
Wang M, Zhang H, Dong L, Li Y, Hou Z, Li D. Using the Random Forest Algorithm to Detect the Activity of Graves Orbitopathy. Journal of Craniofacial Surgery. 2023 Mar 27;34(2):e167-71.	STUDY DESIGN	Random Forest Algorithm
Cheng S, Ming Y, Hu M, Zhang Y, Jiang F, Wang X, Xiao Z. Risk prediction of dysthyroid optic neuropathy based on CT imaging features combined the bony orbit with the soft tissue structures. Frontiers in Medicine. 2022 Aug 24;9:936819.	OUTCOMES	Computed tomographic imaging features
Huang X, Ju L, Li J, He L, Tong F, Liu S, Li P, Zhang Y, Wang X, Yang Z, Xiong J. An intelligent diagnostic system for thyroid-associated ophthalmopathy based on facial images. Frontiers in Medicine. 2022 Jun 10;9:920716.	OUTCOMES	Diagnostic system based on facial images
Wen Z, Wan X, Qi CX, Huang X. Local-to-Remote brain functional connectivity in patients with thyroid-associated ophthalmopathy and assessment of its predictive value using machine learning. International Journal of General Medicine. 2022 Apr 21:4273-83.	OUTCOMES	Local-to-remote brain functional connectivity
Chen J, Xu N, Sun H, Chen G. Efficacy and Safety of Different Intravenous Glucocorticoid Regimens in the Treatment of Graves' Ophthalmopathy: A Meta-Analysis. Journal of Ophthalmology. 2021 Jul 12;2021.	STUDY DESIGN	SLR for cross-check
Kang S, Azzam SH, Minakaran N, Ezra DG. Rituximab for thyroid-associated ophthalmopathy. Cochrane Database of Systematic Reviews. 2022(6).	STUDY DESIGN	SLR for cross-check

Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, Qadeer RA, Cameron C. Proptosis and diplopia response with teprotumumab and placebo vs the recommended treatment regimen with intravenous methylprednisolone in moderate to severe thyroid eye disease: a meta-analysis and matching-adjusted indirect comparison. JAMA ophthalmology. 2022 Apr 1;140(4):328-35.	STUDY DESIGN	MAIC for cross-check
Liu W, Zhang L, Dai G, Zhang X, Li G, Yi Z. Deep neural network with structural similarity difference and orientation-based loss for position error classification in the radiotherapy of graves' ophthalmopathy patients. IEEE Journal of Biomedical and Health Informatics. 2021 Dec 23;26(6):2606-14.	OUTCOMES	Deep neural network model
Schatz MJ, McGeehan BC, Maguire MG, Briceño CA. Tobacco counseling in the setting of thyroid eye disease. Arquivos Brasileiros de Oftalmologia. 2021 Sep 10;85:13-8.	OUTCOMES	Rate and efficacy of tobacco counseling
Carreira AR, Rodrigues-Barros S, Moraes F, Loureiro T, Machado I, Campos P, Cardoso JN, Campos N. Impact of graves disease on ocular surface and corneal epithelial thickness in patients with and without graves orbitopathy. Cornea. 2022 Apr 1;41(4):443-9.	OUTCOMES	No outcomes of interest
Li B, Feng L, Tang H, Zeng L, Lin W. A new radiological measurement method used to evaluate the modified transconjunctival orbital fat decompression surgery. BMC ophthalmology. 2021 Dec;21(1):1-8.	OUTCOMES	Effectiveness of transconjunctival orbital fat decompression surgery
Chen J, Chen G, Sun H. Intravenous rituximab therapy for active Graves' ophthalmopathy: a meta-analysis. Hormones. 2021 Jun;20:279-86.	STUDY DESIGN	SLR for cross-check
Equiterio BS, Garcia DM, Cruz AA, Rootman DB, Goldberg RA, Sales-Sanz M, Galindo-Ferreiro A, Diniz S. Lid Flare measurement with	OUTCOMES	Clinical value of lateral midpupil lid distances

lateral midpupil distances. Current Eye Research. 2021 Sep 2;46(9):1309-13.		
Cruz AA, Equiterio BS, Cunha BS, Caetano FB, Souza RL. Deep lateral orbital decompression for Graves orbitopathy: a systematic review. International Ophthalmology. 2021 May;41:1929-47.	STUDY DESIGN	SLR for cross-check
Ramamurthy LB, Rangarajan V, Srirao N, Malini B, Bansal R, Yuvarajan K. Severity of thyroid eye disease and type-2 diabetes mellitus: Is there a correlation?. Indian Journal of Ophthalmology. 2020 Jun;68(6):1127.	OUTCOMES	Correlation with T2D
Lee V, Avari P, Williams B, Perros P, Dayan C, British Oculoplastic Surgery Society (BOPSS) and TEAMeD. A survey of current practices by the British Oculoplastic Surgery Society (BOPSS) and recommendations for delivering a sustainable multidisciplinary approach to thyroid eye disease in the United Kingdom. Eye. 2020 Sep;34(9):1662-71.	OUTCOMES	Oculoplastic surgeons current practices
Jefferis JM, Raoof N, Burke JP. Prioritising downgaze alignment in the management of vertical strabismus for thyroid eye disease: principles and outcomes. Eye. 2020 May;34(5):906-14.	OUTCOMES	Effectiveness of strabismus surgery
Schwob N, Palmowski-Wolfe A. Objective measurement of visual acuity by optokinetic nystagmus suppression in children and adult patients. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2019 Oct 1;23(5):272-e1.	OUTCOMES	Visual acuity by optokinetic nystagmus suppression
Garcia DM, Cruz AA, Espirito Santo RO, Milbratz GH, Ribeiro SF. Lower eyelid contour in graves Orbitopathy. Current Eye Research. 2019 Nov 2;44(11):1216-9.	OUTCOMES	Lower eyelid contour geometry
Naik MN, Vasanthapuram VH, Joseph J, Murthy SI. Microbial keratitis in thyroid eye disease: clinical features, microbiological profile, and	OUTCOMES	Incidence, clinical features, microbiologic profile, and risk indicators in the development of microbial keratitis

treatment outcome. Ophthalmic Plastic & Reconstructive Surgery. 2019 Nov 1;35(6):543-8.		
Ito M, Takahashi Y, Katsuda E, Oshima Y, Takeuchi A, Mori T, Abe S, Mori Y, Kakizaki H, Suzuki K. Predictive factors of prognosis after radiation and steroid pulse therapy in thyroid eye disease. Scientific Reports. 2019 Feb 14;9(1):2027.	OUTCOMES	Effectiveness of radiotherapy
Yong KL, Chng CL, Sie NM, Lang S, Yang M, Looi A, Choo CT, Shen S, Seah LL. Methotrexate as an adjuvant in severe thyroid eye disease: does it really work as a steroid-sparing agent?. Ophthalmic Plastic & Reconstructive Surgery. 2019 Jul 1;35(4):369-73.	OUTCOMES	Effectiveness/safety of IV methylprednisolone +/- methotrexate
Tu X, Dong Y, Zhang H, Su Q. Corticosteroids for graves' ophthalmopathy: systematic review and meta-analysis, BioMed Research International, vol. 2018, 2018. DOI: https://doi.org/10.1155/2018/4845894.	STUDY DESIGN	SLR for cross-check
de-Pablo-Gómez-de-Liaño L, Fernández-Vigo JI, Troyano-Rivas J, Niño-Rueda C, Romo-López Á, Gómez-de-Liaño R. Response to tocilizumab treatment in Graves' ophthalmopathy by measuring rectus muscle thickness and chemosis using optical coherence tomography. Archivos de la Sociedad Española de Oftalmología (English Edition). 2018 Aug 1;93(8):386-91.	LANGUAGE	Spanish
Margolin E, Lam CT. Approach to a Patient with Diplopia in the Emergency Department. The Journal of Emergency Medicine. 2018 Jun 1;54(6):799-806.	STUDY DESIGN	Review
Mueller SK, Miyake MM, Lefebvre DR, Freitag SK, Bleier BS. Long-term impact of endoscopic orbital decompression on sinonasal-specific quality of life. The Laryngoscope. 2018 Apr;128(4):785-8.	OUTCOMES	Safety, QoL of orbital decompression

Eckstein A. Combination therapy of intravenous steroids and orbital irradiation is more effective than intravenous steroids alone in patients with Graves' orbitopathy. Hormone and Metabolic Research. 2017 Sep 18;49(10):739-47.	OUTCOMES	Effectiveness/safety of IV glucocorticoids +/- orbital radiotherapy
Chatzistefanou KI, Samara C, Asproudis I, Brouzas D, Moschos MM, Tsianta E, Piaditis G. Subconjunctival orbital fat prolapse and thyroid associated orbitopathy: a clinical association. Clinical Interventions in Aging. 2017 Feb 13:359-66.	STUDY DESIGN	Case series
Xu N, Cui Y, Xie T, Zheng M. Comparative efficacy of medical treatments for thyroid eye disease: a network meta-analysis. Journal of Ophthalmology. 2018 Dec 12;2018.	STUDY DESIGN	SLR for cross-check
Yao X, Chaganti S, Nabar KP, Nelson K, Plassard A, Harrigan RL, Mawn LA, Landman BA. Structural-functional relationships between eye orbital imaging biomarkers and clinical visual assessments. InMedical Imaging 2017: Image Processing 2017 Feb 24 (Vol. 10133, pp. 413-419). SPIE.	POPULATION	No TED subgroup
Zu Horste MM, Pateronis K, Walz MK, Alesina P, Mann K, Schott M, Esser J, Eckstein AK. The effect of early thyroidectomy on the course of active Graves' orbitopathy (GO): a retrospective case study. Hormone and Metabolic Research. 2016 Jul;48(07):433-9.	OUTCOMES	Effectiveness of early thyroidectomy
Kajdaniuk D, Marek B, Niedziołka-Zielonka D, Foltyn W, Nowak M, Siemińska L, Borgiel-Marek H, Głogowska-Szeląg J, Ostrowska Z, Drożdż L, Kos-Kudła B. Transforming Growth Factor β1 (TGFβ1) and Vascular Endothelial Growth Factor (VEGF) in the blood of healthy people and patients with Graves' orbitopathy—a new mechanism of glucocorticoids action?. Endokrynologia Polska. 2014;65(5):348-56.	OUTCOMES	PK data

Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. Thyroid. 2014 Oct 1;24(10):1515-23.	STUDY DESIGN	SLR for cross-check
Kang S, Azzam SH, Minakaran N, Ezra DG. Rituximab for thyroid-associated ophthalmopathy. Cochrane Database of Systematic Reviews. 2022(6).	STUDY DESIGN	SLR for cross-check
Czarnywojtek A, Zgorzalewicz-Stachowiak M, Budny B, Wasko R, Florek E, Szczepanek E, Komar-Rychlicka K, Waligórska-Stachura J, Kurdybacha P, Miechowicz I, Ruchala M. The influence of radioiodine therapy on ocular changes and their relation to urine cotinine level in patients with Graves' Ophthalmopathy. Neuroendocrinology Letters. 2013;34(3).	OUTCOMES	Effectiveness of radioiodine therapy
Ismailova DS, Fedorov AA, Grusha YO. Ocular surface changes in thyroid eye disease. Orbit. 2013 Apr 1;32(2):87-90.	OUTCOMES	Clinical outcomes w/o intervention
Achtsidis V, Tentolouris N, Theodoropoulou S, Panagiotidis D, Vaikoussis E, Saldana M, Gouws P, Theodossiadis PG. Dry eye in Graves' ophthalmopathy: correlation with corneal hypoesthesia. European journal of ophthalmology. 2013 Jul;23(4):473-9.	OUTCOMES	Dry eye disease and corneal sensitivity
Rivera-Grana E, Lin P, Suhler EB, Rosenbaum JT. Methotrexate as a corticosteroid-sparing agent for thyroid eye disease. Journal of clinical & experimental ophthalmology. 2015 Apr;6(2).	OUTCOMES	Effectiveness/safety of methotrexate
Panda S, Asman AJ, DeLisi MP, Mawn LA, Galloway RL, Landman BA. Robust optic nerve segmentation on clinically acquired CT. InMedical Imaging 2014: Image Processing 2014 Mar 21 (Vol. 9034, pp. 362-371). SPIE.	OUTCOMES	Segmenting the optic nerve structure algorithm

Gonçalves AC, Silva LN, Gebrim EM, Matayoshi S, Monteiro ML. Predicting dysthyroid optic neuropathy using computed tomography volumetric analyses of orbital structures. Clinics. 2012;67:891-6.	OUTCOMES	Diagnostic value of orbital apex crowding volume measurements
Eing F, Abbud CM, e Cruz AA. Cosmetic orbital inferomedial decompression: quantifying the risk of diplopia associated with extraocular muscle dimensions. Ophthalmic Plastic & Reconstructive Surgery. 2012 May 1;28(3):204-7.	OUTCOMES	Effectiveness of transconjunctival inferomedial bony orbital decompression
Perros P, Chandler T, Dayan CM, Dickinson AJ, Foley P, Hickey J, MacEwen CJ, Lazarus JH, McLaren J, Rose GE, Uddin JM. Orbital decompression for Graves' orbitopathy in England. Eye. 2012 Mar;26(3):434-7.	OUTCOMES	Incidence of orbital decompression surgery
Annesi C. Limited English Proficiency and Graves' Disease at an Urban Safety Net Hospital. Journal of Surgical Research. 2024 Mar;296:56-65.	OUTCOMES	No cost data
Boutzios G. Tocilizumab improves clinical outcome in patients with active corticosteroid-resistant moderate-to-severe Graves' orbitopathy: an observational study. Frontiers in Endocrinology. 2023;14(no pagination).	OUTCOMES	No cost data
Gildea L. Evidence Gap Analysis of the Burden of Illness and Treatment of Thyroid Eye Disease. Value in Health. 2024;27(6 Supplement)	STUDY DESIGN	Review
Kim J. Cost-Effectiveness of a Digital Therapeutic for Managing Hyperthyroidism: Evaluation of Glandytm. Thyroid. 2023;33(Supplement 1)	INTERVENTION	Digital tool for diagnosis
Lu JE. Epidemiology of Orbital Inflammatory Disease: An AAO IRIS Registry Study. Ocular Immunology & Inflammation. 2024;1-4. PURPOSE: The current study queries the American Academy of	POPULATION	Patients with thyroid eye disease were excluded

Ophthalmology (AAO) Intelligent Research in Sight (IRIS) registry for data on the epidemiology, work-up, and management patterns of autoimmune orbital inflammation.		
Masaquel C. Evidence Gap Analysis of the Burden of Disease in Thyroid Eye Disease. Value in Health. 2024;27(6 Supplement)	STUDY DESIGN	Review
Perros P. Teprotumumab in thyroid eye disease: wonder drug or great divider? European Thyroid Journal. 2023;12(4) (no pagination).	STUDY DESIGN	Review
Rachmasari, K. *et al.* The Use of Medical Therapy for Thyroid Eye Disease in the Era of Teprotumumab. *Thyroid* **33(Supplement 1)**, A1 (2023).	OUTCOMES	Treatment patterns
Rachmasari KN. Impact of Teprotumumab on Clinical Practice in Thyroid Eye Disease. Endocrine Practice. 2024;30(10):937-942.	OUTCOMES	No cost data
Shemesh R. The Role of Thyroid Antibodies in Thyroid Eye Disease. International Ophthalmology Clinics. 2023;63(3):225-231.	STUDY DESIGN	Review
Vogel, M. et al. Cost of Exempting Sole Orphan Drugs from Medicare Negotiation. JAMA Internal Medicine 184(1), 63-69 (2024).	OUTCOMES	Medicare spending on Teprotumumab- US
Xi A. Disease Severity Is Associated With Poorer Quality of Life Outcomes and Higher Costs in Thyroid Eye Disease (TED): Evidence From Systematic Literature Reviews (SLRs). Value in Health. 2024;27(6 Supplement)	STUDY DESIGN	Review
Abumohssin, A. G, Comparative efficacy and safety of rituximab, tocilizumab, and teprotumumab in Graves' orbitopathy: a systematic review and meta-analysis. Eye (Basingstoke) 2025 39(10):1901-1932.	STUDY DESIGN	Review
Azzam, D. B. Nationwide orbital decompression volume, surgical approach, and subspecialty distribution patterns within the center	OUTCOMES	Treatment practice patterns

for medicare and medicaid services population in the era of teprotumumab. Orbit 2025 44(5):522-529.		
Barnett, M. J. L. Teprotumumab and sensorineural hearing loss: a propensity score-matched retrospective cohort study. Endocrine Connections 2025 14(7) (no pagination).	OUTCOMES	Incidence of sensorineural hearing loss
Chen, J. A Chinese survey of clinical practice on the management of thyroid eye disease. European Thyroid Journal 2024 13(3):e230269.	OUTCOMES	Treatment patterns
Gildea, L. Evidence Gap Analysis of the Burden of Illness and Treatment of Thyroid Eye Disease. Value in Health 2024 27(6 Supplement):S35.	DUPLICATION	Included in previous update
Masaquel, C. Evidence Gap Analysis of the Burden of Disease in Thyroid Eye Disease. Value in Health 2024 27(6 Supplement):S389.	DUPLICATION	Included in previous update
Mawn, L. Characterizing Patients With Thyroid Eye Disease Initiating Treatment With Teprotumumab: A Retrospective Cohort Study Using Linked Academy IRIS Registry And Komodo Claims Data. Journal of the Endocrine Society 2025 9(Supplement 1):A687-A688.	OUTCOMES	Baseline clinical burden
Tamhankar, M. A. The burden of illness in thyroid eye disease: current state of the evidence. Frontiers in Ophthalmology 2025 5:1565762.	STUDY DESIGN	Review
Xi, A. Disease Severity Is Associated With Poorer Quality of Life Outcomes and Higher Costs in Thyroid Eye Disease (TED): Evidence From Systematic Literature Reviews (SLRs). Value in Health 2024 27(6 Supplement):S405.	DUPLICATION	Included in previous update

J.1.5 Further exclusions

To ensure inclusion of only relevant studies for the health economic analysis, additional exclusion criteria were applied to studies identified through the SLR. A total of 13 studies met the inclusion criteria. Of these 13 studies, five studies did not report data specifically on moderate to severe TED and were excluded from the health economic model. Of the remaining eight studies reporting data specifically on moderate to severe TED, six of these reported direct or indirect costs. None of these studies were included in the final health economic analysis due to local adaptations, with DRG tariffs and costs described by the DMC being used in Denmark instead. Additionally, one study described costs and healthcare utilization regarding productivity loss in the UK, which is not relevant in a Danish context. Based on these reasons, all 13 studies were excluded from the health economic model.

Table 150: Further exclusions

No.	Reference	Reason for exclusion
1	Holt R, Taylor S, Barretto N, Hirst A, Oliver L, Brandolini G, et al. MSR67 Bridging and Validation of a Thyroid Eye Disease (TED) Specific Quality of Life (QOL) Questionnaire to Utility Values Assessed By a Time Trade-Off (TTO) Analysis. Value in Health. 2022;25(7).	OUTCOME, comparison of GO-QOL and TTO
2	Ponto KA, Merkesdal S, Hommel G, Pitz S, Pfeiffer N, Kahaly GJ. Public health relevance of Graves' orbitopathy. J Clin Endocrinol Metab. 2013;98(1):145-52.	POPULATION UK Productivity Loss without Relevance to Danish Setting
3	Singh G, Sehgal M, Mithal A, Kossler A. Abstract #1003588: Thyroid Eye Disease in the United States: Data from Emergency Department Visits and Hospitalizations. Endocrine Practice. 2021;27(6).	POPULATION ALL TED
4	Nagy P, Svider P, Sheyn A. Indications for pediatric orbital decompression: Database study utilizing the kids' inpatient database. American Academy of Otolaryngology - Head and Neck Surgery2018. p. 304.	POPULATION ALL TED

5	Bhat AM, Soler ZM, Schlosser RJ, Metson RB, Rathi VK. Orbital decompression surgery among Medicare beneficiaries in the post-teprotumumab era. International Forum of Allergy and Rhinology. 2024;14(9):1505-9.	POPULATION UNCLEAR TED
6	Shah SA, Lu T, Yu M, Hiniker S, Dosiou C, Kossler AL. Comparison of treatment cost and quality-of-life impact of thyroid eye disease therapies. Annual Meeting Association for Research in Vision and Ophthalmology, ARVO 2022; Denver, CO United States2022. p. 4002-A0344.	POPULATION UK Costs without Relevance to Danish Setting
7	Alzahrani A, Alabdulkarim H, Alrumaih A, Alayoubi A, Alharbi B, Alhumaidan A, et al. EE419 The Economic Burden of Thyroid Eye Disease in the Kingdom of Saudi Arabia. Value in Health. 2024;27(6 Supplement):S134.	POPULATION UK Costs without Relevance to Danish Setting
8	Eatamadimadi H, Elkonaissi I, Dallal SA, Shaheen R, Alharbi M, Ashoush N, et al. EE457 Economic Burden Impact of Thyroid Eye Disease in the United Arab Emirates. Value in Health. 2024;27(6 Supplement):S141.	POPULATION UK Costs without Relevance to Danish Setting
9	Nexo MA, Watt T, Pedersen J, Bonnema SJ, Hegedus L, Rasmussen AK, et al. Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study. J Clin Endocrinol Metab. 2014;99(9):3184-92.	POPULATION UNCLEAR TED
10	Cockerham K, Smith TJ, Conrad E, Holt RJ. Inactive Thyroid Eye Disease Patient Journey. Journal of the Endocrine Society. 2023;7(Supplement 1):A1032.	POPULATION ALL TED
11	Kossler A, Batten R, Cameron C, Baretto N, Taylor S, Francis-Sedlak M, et al. TED and Health Care Resource Utilization. American Acedemy of Ophthalmology2021.	POPULATION UK Healthcare Utilization without Relevance to Danish Setting

12	Campi I, Vannucchi G, Muller I, Lazzaroni E, Curro N, Dainese M, et al. Therapy With Different Dose Regimens of Rituximab in Patients With Active Moderate-To-Severe Graves' Orbitopathy. Front Endocrinol (Lausanne). 2021;12:790246.	POPULATION UK Costs without Relevance to Danish Setting
13	Singh G, MSehgal M, Mithal A, Alabiad C, Kossler A. Severe Thyroid Eye Disease in the US: A National Perspective ENDO 20212021. p. A843.	POPULATION UK Costs without Relevance to Danish Setting

J.1.1 Quality assessment

Regarding the heterogeneity, definitions confirming moderate to severe TED, and language limitations, the context was equal across the economic/HCRU SLR and the HRQOL/utilities SLR as reviewed in Appendix I.

Additionally, in the economic/HCRU SLR, there was a paucity in the evidence with only 13 studies identified, of which nine were abstracts.

J.1.1.1 Quality appraisal

Quality appraisal of included studies was conducted using validated checklist depending upon study design. Economic evaluations were assessed using Drummond checklist (110); publications reporting on cost and HCRU were assessed using the Schnitzler checklist (111).

Due to limited information in reporting, quality appraisal was conducted only on full publications and not on conference abstracts or posters.

Quality assessment was performed by a single individual for each included study and independently verified by a second individual once completed. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached. Any unresolved conflicts were decided by a third reviewer.

Table 151. Quality appraisal of all full publications included economic/HCRU SLR: Schnitzler checklist

Question	Ponto 2013	Nexo 2014	Campi 2021	Bhat 2024	Lo 2025	Stan 2025	Garrido-Hermosilla 2025
Study characteristics							
1. Is a well-defined research question or objective stated?	YES	YES	YES	YES	YES	YES	YES
2. Is the study population described?	YES	YES	YES	YES	YES	YES	YES
3a) Is (are) the chosen study perspectives stated?	YES	NO	NO	YES	NO	NO	NO
3b) If so, is (are) the chosen study perspective(s) justified?	YES	NA	NA	YES	NA	NA	NA
Methodology and cost analysis							
4. Is the epidemiological approach reported (e.g. prevalence, incidence)?	YES	YES	YES	YES	YES	YES	NO
5. Is the costing approach reported (e.g. top-down, bottom-up)?	NO	NA	NA	NO	NO	NO	NO
6. Is the data collection process reported (e.g. prospective, retrospective)?	YES	YES	NA	YES	YES	YES	YES
7a) Are all components of resource use identified that are relevant to the condition/disease, population, intervention, study objectives, and study perspective?	YES	YES	NA	UNCLEAR	NO	NO	NO

7b) If not, is a justification provided for excluding relevant components of resource use?	NA	NA	NA	UNCLEAR	NO	NO	NO
8a) Are all included components of resource use measured?	YES	YES	NA	UNCLEAR	NO	NO	NO
8b) If not, is a justification provided for not measuring certain components of resource use?	NA	NA	NA	UNCLEAR	NO	NO	NO
9a) Are all included components of resource use valued in monetary terms?	YES	NA	NA	UNCLEAR	NO	NO	NO
9b) If not, is a justification provided for not valuing certain components of resource use?	NA	NA	NA	UNCLEAR	NO	NO	NO
10a) Is the chosen time horizon specified?	YES	YES	NA	YES	YES	YES	YES
10b) If so, is the chosen time horizon justified?	YES	YES	NA	YES	NO	NO	NO
11a) Are future costs discounted?	NA	NA	NA	NO	NA	NA	NA
11b) If so, is a justification provided for the discount rate?	NA	NA	NA	NA	NA	NA	NA
12a) Are all variables whose values are uncertain subjected to sensitivity analysis?	YES	NA	NA	NO	NO	NO	NO

12b) If so, is a justification provided for which variables are subjected to sensitivity analysis?	YES	NA	NA	NA	NO	NO	NO
12c) Are analyses done on relevant subgroups?	YES	YES	NA	NA	YES	YES	YES
Results and reporting							
13. Are the study results presented transparently by cost category/sector?	YES	YES	YES	YES	NO	NO	NO
14. Do the authors discuss the generalizability of study results (e.g. comparing the results to other patient/client groups or/in other settings?	YES	YES	NO	NO	YES	YES	YES
15. Do the authors discuss important limitations?	YES	YES	NO	YES	YES	YES	YES
16. a) Do the authors discuss ethical issues?	NO	NO	NO	NO	YES	NO	YES
16. b) Do the authors discuss distributional issues?	NO	YES	NO	NO	NO	NO	NO
17. Do the authors report any potential conflicts of interest?	YES	YES	NO	YES	YES	YES	YES

J.2 Focused Search

N/A

J.2.1.1 Summary of included studies

Table 152 presents the HRQOL/utilities SLR results included in the model/analysis.

Table 152: Utilities Outcomes Reported in Included Studies in the HRQOL/Utilities SLR.

Study/ID	Population	N overall	Country	Recruitment method	Description of health states	Elicitation methods	Valuation methods

Smith et al. (2023) (59)	Moderate to severe TED, active	111	US	All patients, health care professionals, and members of the public voluntarily participated in this study following identification from a patient advisory council, an expert panel, and a general population US proprietary panel, respectively.	<u>No diplopia and small proptosis (<3 mm)</u> Mean (SD): 0.60 (0.34) Median (95% CI) [IQR]: 0.70 (0.54-0.67) [0.36-0.91] <u>No diplopia and large proptosis (≥3mm)</u> Mean (SD): 0.46 (0.32) Median (95% CI) [IQR]: 0.40 (0.40-0.52) [0.22-0.73] <u>Intermittent or inconstant diplopia and small proptosis (<3 mm)</u> Mean (SD): 0.52 (0.33) Median (95% CI) [IQR]: 0.50 (0.45-0.58) [0.28-0.81] <u>Intermittent or inconstant diplopia and large proptosis (≥3mm)</u> Mean (SD): 0.43 (0.33) Median (95% CI) [IQR]: 0.38 (0.36-0.49) [0.11-0.70]	Direct elicitation by qualitative interviews with the general population.	TTO

	Constant diplopia and small proptosis (<3 mm) Mean (SD): 0.34 (0.31) Median (95% CI) [IQR]: 0.30 (0.29-0.40) [0.03-0.53] Constant diplopia and large proptosis (≥3mm) Mean (SD): 0.30 (0.31) Median (95% CI) [IQR]: 0.23 (0.24-0.36) [0.03-0.5] Moderate to severe active TED Mean (SD): 0.44 (0.34) Median (95% CI): 0.40 (0.42-0.47)	
	No diplopia and small proptosis (<3 mm) Mean (SD): 51.71 (21.44) Median (95% CI): 50.00 (47.67-55.74) No diplopia and large proptosis (≥3mm) Mean (SD): 38.95 (17.63) Median (95% CI): 40.00 (35.64-42.27)	VAS

Intermittent or inconstant diplopia and small proptosis (<3 mm)

Mean (SD): 45.38 (17.74)

Median (95% CI): 45.00 (42.04-48.72)

Intermittent or inconstant diplopia and large proptosis (≥3mm)

Mean (SD): 36.52 (18.14)

Median (95% CI): 35.00 (33.11-39.94)

Constant diplopia and small proptosis (<3 mm)

Mean (SD): 30.56 (17.83)

Median (95% CI): 25.00 (27.20-33.91)

Constant diplopia and large proptosis (≥3mm)

Mean (SD): 27.42 (16.04)

Median (95% CI): 25.00 (24.41-30.44)

Moderate to severe active TED

Mean (SD): 38.41 (19.94)

Median (95% CI): 40.00 (36.90-39.94)

J.2.2 Excluded full-text references

Publications included after abstract review were obtained for a full review of the text. A record was kept of papers excluded at this stage, along with a clear justification for their exclusion, which was reported in table format in the Excel Report, as per NICE guidance. A list of excluded studies in the HRQOL/utilities SLR, including the reason for exclusion, is provided in Table 153.

Table 153: Studies excluded following full-text review from the HRQoL/utilities SLR.

Reference	Reason for exclusion	Comment
Karadimas P, Bouzas EA, Mastorakos G. Advice against smoking is not effective in patients with Graves' ophthalmopathy. Acta Medica Austriaca. 2003 May;30(2):59-60.	Prior to 2013	Prior to 2013
Choi YJ, Lim HT, Lee SJ, Lee SY, Yoon JS. Assessing Graves' ophthalmopathy-specific quality of life in Korean patients. Eye. 2012 Apr;26(4):544-51.	Prior to 2013	Prior to 2013
Park JJ, Sullivan TJ, Mortimer RH, Wagenaar M, Perry-Keene DA. Assessing quality of life in Australian patients with Graves' ophthalmopathy. The British Journal of Ophthalmology. 2004 Jan;88(1):75.	Prior to 2013	Prior to 2013
Lee H, Roh HS, Yoon JS, Lee SY. Assessment of quality of life and depression in Korean patients with Graves' ophthalmopathy. Korean Journal of Ophthalmology. 2010 Apr 1;24(2):65-72.	Prior to 2013	Prior to 2013
Vinogradskaya O, Fadeyev V, Lipatov D. Assessment of quality of life in Russian patients with graves' orbitopathy. European Thyroid Journal. 2011 Sept; 117.	Prior to 2013	Prior to 2013
Kashkouli MB, Heidari I, Pakdel F, Jam S, Honarbakhsh Y, Mirarmandehi B. Change in quality of life after medical and surgical treatment of Graves' ophthalmopathy. Middle East African Journal of Ophthalmology. 2011 Jan;18(1):42.	Prior to 2013	Prior to 2013
Ponto KA, Pitz S, Hommel G, Kahaly GJ. Close relationship between TSH-receptor antibodies, ocular findings, and quality of life in Graves' orbitopathy. Thyroid. 2007 Aug 1; 17(S1): S47-S48.	Prior to 2013	Prior to 2013
Gonçalves AC, Nogueira T, Gonçalves AC, Silva LD, Matayoshi S, Monteiro ML. A Comparative study of full-thickness blepharotomy versus transconjunctival eyelid lengthening in the correction of upper eyelid retraction in Graves' orbitopathy. Aesthetic plastic surgery. 2018 Feb;42:215-23.	Clinical trial design	RCT without utility
Detiger SE, Kremer TM, ASH Dalm V, de Keizer RO, Wubbels RJ, Metselaar JM, van Hagen PM, Peeters RP,	Clinical trial design	Single-arm without utility

Paridaens D. A pilot study on the use of prednisolone-encapsulated liposomes for the treatment of moderate-to-severe Graves' orbitopathy with reduced systemic steroid exposure. Acta Ophthalmologica. 2021 Nov;99(7):797-804.		
Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. British journal of ophthalmology. 1998 Jul 1;82(7):773-9.	Prior to 2013	Prior to 2013
Tehrani M, Krummenauer F, Mann WJ, Pitz S, Dick HB, Kahaly GJ. Disease-specific assessment of quality of life after decompression surgery for Graves' ophthalmopathy. European journal of ophthalmology. 2004 May;14(3):193-9.	Prior to 2013	Prior to 2013
Rajendram R, Taylor PN, Wilson VJ, Harris N, Morris OC, Tomlinson M, Yarrow S, Garrott H, Herbert HM, Dick AD, Cook A. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2× 2 factorial, double-blind, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2018 Apr 1;6(4):299-309.	Clinical trial design	RCT without utility
Wiersinga WM, Prummel MF, Terwee CB. Effects of Graves' ophthalmopathy on quality of life. Journal of endocrinological investigation. 2004 Mar;27:259-64.	Prior to 2013	Prior to 2013
Ng CM, Yuen HK, Choi KL, Chan MK, Yuen KT, Ng YW, Tiu SC. Combined orbital irradiation and systemic steroids compared with systemic steroids alone in the management of moderate-to-severe Graves' ophthalmopathy: a preliminary study. Hong Kong Medical Journal. 2005 Oct 1;11(5):322.	Prior to 2013	Prior to 2013
Jernfors M, Välimäki MJ, Setälä K, Malmberg H, Laitinen K, Pitkäranta A. Efficacy and safety of orbital decompression in treatment of thyroid-associated ophthalmopathy: long-term follow-up of 78 patients. Clinical endocrinology. 2007 Jul;67(1):101-7.	Prior to 2013	Prior to 2013
Aktaran Ş, Akarsu E, Erbağci I, Araz M, Okumuş S, Kartal M. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. International journal of clinical practice. 2007 Jan;61(1):45-51.	Prior to 2013	Prior to 2013
Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, Barbesino G, Mazzi B, Bartolomei MP, Lepri P, Cartei F. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management	Prior to 2013	Prior to 2013

of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. The Journal of Clinical Endocrinology & Metabolism. 2001 Aug 1;86(8):3562-7.		
Bartalena L, Veronesi G, Krassas GE, Wiersinga WM, Marcocci C, Marinò M, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L. Does early response to intravenous glucocorticoids predict the final outcome in patients with moderate-to-severe and active Graves' orbitopathy?. Journal of endocrinological investigation. 2017 May;40:547-53.	Clinical trial design	RCT without utility
Hoang TT, He J. Effects of high-dose hormone therapy in patients with thyroid-associated orbitopathy and its effect on visual acuity and ocular surface. INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE. 2020 Jan 1;13(11):8636-43.	Clinical trial design	RCT without utility
Bartalena L, Krassas GE, Wiersinga WM, Marcocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Veronesi G, Azzolini C. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. The Journal of Clinical Endocrinology & Metabolism. 2012 Dec 1;97(12):4454-63.	Prior to 2013	Prior to 2013
Bartalena L, Krassas GE, Wiersinga WM, Marcocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Veronesi G, Azzolini C. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. The Journal of Clinical Endocrinology & Metabolism. 2012 Dec 1;97(12):4454-63.	Prior to 2013	Prior to 2013
Ye X, Zhao H, Liu J, Lu B, Shao J, Wang J. Efficacy and safety of tripterygium glycosides for active moderate to severe Graves' ophthalmopathy: a randomised, observer-masked, single-centre trial. European Journal of Endocrinology. 2021 Feb;184(2):277-87.	Clinical trial design	RCT without utility
Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, Simonetta S, Guastella C, Pignataro L, Avignone S, Beck-Peccoz P. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. The Journal of Clinical Endocrinology & Metabolism. 2015 Feb 1;100(2):422-31.	Clinical trial design	RCT without utility
Lin M, Mao Y, Ai S, Liu G, Zhang J, Yan J, Yang H, Li A, Zou Y, Liang D. Efficacy of Subantimicrobial Dose Doxycycline	Clinical trial design	Single-arm without utility

for Moderate-to-Severe and Active Graves' Orbitopathy. International Journal of Endocrinology. 2015 Jun 29;2015.		
Bradley EA, Sloan JA, Novotny PJ, Garrity JA, Woog JJ, West SK. Evaluation of the National Eye Institute visual function questionnaire in Graves' ophthalmopathy. Ophthalmology. 2006 Aug 1;113(8):1450-4.	Prior to 2013	Prior to 2013
Vannucchi G, Campi I, Covelli D, Currò N, Lazzaroni E, Palomba A, Soranna D, Zambon A, Fugazzola L, Muller I, Guastella C. Efficacy profile and safety of very low-dose rituximab in patients with Graves' orbitopathy. Thyroid. 2021 May 1;31(5):821-8.	Clinical trial design	Single-arm without utility
Dietrich A, Taylor P, White P, Wilson V, Uddin J, Lee RW, Dayan C, Jackson S. Establishing the usefulness of the GO-QOL in a UK hospital-treated population with thyroid eye disease in the CIRTED trial. Psychology, health & medicine. 2018 Dec 14;23(sup1):1341-55.	Clinical trial design	RCT without utility
Michel O, Oberländer N, Neugebauer P, Neugebauer A, Rüßmann W. Follow-up of transnasal orbital decompression in severe Graves' ophthalmopathy. Ophthalmology. 2001 Feb 1;108(2):400-4.	Prior to 2013	Prior to 2013
Fatourechi V, Garrity JA, Bartley GB, Bergstralh EJ, DeSanto LW, Gorman CA. Graves ophthalmopathy: results of transantral orbital decompression performed primarily for cosmetic indications. Ophthalmology. 1994 May 1;101(5):938-42.	Prior to 2013	Prior to 2013
Terwee CB, Dekker FW, Mourits M, Gerding MN, Baldeschi L, Kalmann R, Prummel MF, Wiersinga WM. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. Clinical endocrinology. 2001 Mar;54(3):391-8.	Prior to 2013	Prior to 2013
Baschieri L, Antonelli A, Nardi S, Alberti B, Lepri A, Canapicchi R, Fallahi P. Intravenous immunoglobulin versus corticosteroid in treatment of Graves' ophthalmopathy. Thyroid. 1997 Aug;7(4):579-85.	Prior to 2013	Prior to 2013
Terwee C, Wakelkamp I, Tan S, Dekker F, Prummel MF, Wiersinga W. Long-term effects of Graves' ophthalmopathy on health-related quality of life. European Journal of Endocrinology. 2002 Jun 1;146(6):751-7.	Prior to 2013	Prior to 2013
Marquez SD, Lum BL, McDougall IR, Katkuri S, Levin PS, MacManus M, Donaldson SS. Long-term results of irradiation for patients with progressive GRAVES'ophthalmopathy. International Journal of	Prior to 2013	Prior to 2013

Radiation Oncology* Biology* Physics. 2001 Nov 1;51(3):766-74.		
Bartalena L, Veronesi G, Krassas G, Wiersinga W, Marcocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Azzolini C, Boboridis K, Mourits M, Soeters M, Lelio B, Nardi M, Curro N, Boschi A, Bernard M, Von Arx G, Perros P, Kahaly GJ. European Thyroid Journal. 2016 Aug; 5(S1): 71.	Clinical trial design	RCT without utility
Taylor P, Rajendram R, Lee R, Dayan C. Factors predicting long-term outcome and the need for surgery in graves orbitopathy extended follow-up from the cirted trial. Thyroid. 2021 Sept; 31 (S1): A100.	Clinical trial design	RCT without utility
Taylor P, Rajendram R, Hanna S, Wilson V, Pell J, Li C, Cook A, Gattamaneni R, Plowman N, Jackson S, Hills R. Factors predicting long-term outcome and the need for surgery in Graves Orbitopathy: extended follow-up from the CIRTED Trial.	Clinical trial design	RCT without utility
Fatourechi V, Garrity JA, Bartley GB, Bergstralh EJ, Gorman CA. Orbital decompression in Graves' ophthalmopathy associated with pretibial myxedema. Journal of endocrinological investigation. 1993 Jun;16(6):433-7.	Prior to 2013	Prior to 2013
Mourits MP, Bijl HM, Baldeschi L, Boboridis K, Curro N, Dickinson J, Eckstein AK, Guastella C, Altea M, Kahaly G, Freidel M. Outcome of orbital decompression for disfiguring proptosis in patients with Graves' orbitopathy using various surgical procedures. British Journal of Ophthalmology. 2008 Nov 21.	Prior to 2013	Econ data (LOS hospitalization)
Shen L, Ye L, Zhu W, Jiao Q, Zhou Y, Wang S, Wang W, Ning G. Methotrexate plus reduced or full-dose glucocorticoids for the treatment of active, moderate-to-severe Graves' orbitopathy. European Thyroid Journal. 2022 Oct 1;11(5).	Clinical trial design	RCT without utility
Kahaly GJ, Riedl M, König J, Pitz S, Ponto K, Diana T, Kampmann E, Kolbe E, Eckstein A, Moeller LC, Führer D. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. The Lancet Diabetes & Endocrinology. 2018 Apr 1;6(4):287-98.	Clinical trial design	RCT without utility
Farid M, Roch-Levecq AC, Levi L, Brody BL, Granet DB, Kikkawa DO. Psychological disturbance in graves ophthalmopathy. Archives of Ophthalmology. 2005 Apr 1;123(4):491-6.	Prior to 2013	Prior to 2013

Kahaly GJ, Hardt J, Petrak F, Egle UT. Psychosocial factors in subjects with thyroid-associated ophthalmopathy. Thyroid. 2002 Mar 1;12(3):237-9.	Prior to 2013	Prior to 2013
Kahaly GJ, Petrak F, Hardt J, Pitz S, Egle UT. Psychosocial morbidity of Graves' orbitopathy. Clinical Endocrinology. 2005 Oct;63(4):395-402.	Prior to 2013	Prior to 2013
Kulig G, Andrysiak-Mamos E, Sowińska-Przepiera E, Kulig J, Karakiewicz B, Brodowski J, Robaczyk M, Homa K, Letkiewicz M, Syrenicz A. Quality of life assessment in patients with Graves' disease and progressive infiltrative ophthalmopathy during combined treatment with methylprednisolone and orbital radiotherapy. Endokrynologia Polska. 2009;60(3):158-65.	Prior to 2013	Prior to 2013
Vokurka Topljak S, Galiot Delic M, Mandic K, Peric S, Baretic M, Juri Mandic J. Nonsurgical treatment for upper eyelid retraction in patients with inactive Graves' orbitopathy. International ophthalmology. 2023 Jan 1; 43:2291-2299.	Clinical trial design	RCT without utility
Ćirić J, Žarković M, Beleslin B, Marina D, Bubanja D, Trbojević B. Quality of life assessment in Serbian patients with Graves' orbitopathy. In35th Annual Meeting of the European Thyroid Association 2011 (p. P50).	Prior to 2013	Prior to 2013
Ponto KA, Hommel G, Pitz S, Elflein H, Pfeiffer N, Kahaly GJ. Quality of life in a german graves orbitopathy population. American journal of ophthalmology. 2011 Sep 1;152(3):483-90.	Prior to 2013	Prior to 2013
Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid. 1997 Dec;7(6):885-9.	Prior to 2013	Prior to 2013
Yeatts RP. Quality of life in patients with Graves ophthalmopathy. Transactions of the American Ophthalmological Society. 2005 Dec;103:368.	Prior to 2013	Prior to 2013
Bahmani-Kashkouli M, Pakdel F, Astaraki A, Hashemi M, Honarbakhsh Y, Mirarmandehi B, Jam S. Quality of life in patients with thyroid eye disease. Journal of Ophthalmic & Vision Research. 2009 Jul;4(3):164.	Prior to 2013	Prior to 2013
Sisson JC, Schipper MJ, Nelson CC, Freitas JE, Frueh BR. Radioiodine therapy and Graves' ophthalmopathy. Journal of Nuclear Medicine. 2008 Jun 1; 49(6): 923-930.	Prior to 2013	Prior to 2013
Finamor FE, Martins JR, Nakanami D, Paiva ER, Manso PG, Furlanetto RP. Pentoxifylline (PTX)-an alternative treatment in Graves' ophthalmopathy (inactive phase): assessment by a disease specific quality of life	Prior to 2013	RCT without utility

questionnaire and by exophthalmometry in a prospective randomized trial. European journal of ophthalmology. 2004 Jul;14(4):277-83.		
Draman MS, Morris DS, Evans S, Haridas A, Pell J, Greenwood R, Foy C, Taylor P, Pooprasert P, Muller I, Zhang L. Prostaglandin F2-alpha eye drops (bimatoprost) in graves' orbitopathy: a randomized controlled double-masked crossover trial (BIMA Trial). Thyroid. 2019 Apr 1;29(4):563-72.	Clinical trial design	RCT without utility
Ekdawi NS, Bradley EA, Hatt SR, Leske DA, Holmes JM. Reduced health-related quality of life correlates to diplopia severity in patients with thyroid eye disease. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2010 Feb 1;14(1):e15-6.	Prior to 2013	Prior to 2013
Leon BG, Stan M, Thapa P, Bahn RS, Bradley EA. Quality of Life Assessment in Patients with Graves' Ophthalmopathy Randomized to Treatment with Rituximab Vs. Placebo. InENDOCRINE REVIEWS 2014 Jun 1 (Vol. 35, No. 3). 2055 L ST NW, SUITE 600, WASHINGTON, DC 20036 US: ENDOCRINE SOC.	Clinical trial design	RCT without utility
Sellari-Franceschini S, Rocchi R, Marinò M, Bajraktari A, Mazzi B, Fiacchini G, Lepri P, Dallan I, Vitti P, Marcocci C. Rehabilitative orbital decompression for Graves' orbitopathy: results of a randomized clinical trial. Journal of Endocrinological Investigation. 2018 Sep;41:1037-42.	Clinical trial design	RCT without utility
Lanzolla G, Sabini E, Leo M, Menconi F, Rocchi R, Sframeli A, Piaggi P, Nardi M, Marcocci C, Marinò M. Statins for Graves' orbitopathy (STAGO): a phase 2, open-label, adaptive, single centre, randomised clinical trial. The Lancet Diabetes & Endocrinology. 2021 Nov 1;9(11):733-42.	Clinical trial design	RCT without utility
Lanzolla G, Sabini E, Leo M, Menconi F, Rocchi R, Maglionico MN, Posarelli C, Figus M, Nardi M, Marcocci C, Marino M. STATINS for GRAVES' ORBITOPATHY (STAGO): PRELIMINARY RESULTS of A PHASE II RANDOMIZED CLINICAL TRIAL. European Thyroid Journal. 2021 Aug;10(S1):1.	Clinical trial design	RCT without utility
Lanzolla G, Sabini E, Leo M, Menconi F, Sframeli A, Rocchi R, Piaggi P, Nardi M, Marcocci C, Marino M. Statins for graves' orbitopathy (stago): Results of a phase ii randomized clinical trial. Thyroid. 2021 Sept;31(S1):A1-A2.	Clinical trial design	RCT without utility
Douglas RS, Kahaly GJ, Ugradar S, Elflein H, Ponto KA, Fowler BT, Dailey R, Harris GJ, Schiffman J, Tang R, Wester S. Teprotumumab efficacy, safety, and durability	Clinical trial design	Single-arm without utility

in longer-duration thyroid eye disease and re-treatment: OPTIC-X study. Ophthalmology. 2022 Apr 1;129(4):438-49.		
Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EH, Perdok R, Fleming JC, Fowler BT, Marcocci C, Marinò M, Antonelli A. Teprotumumab for the treatment of active thyroid eye disease. New England Journal of Medicine. 2020 Jan 23;382(4):341-52.	Clinical trial design	RCT without utility
Douglas RS, Kahaly GJ, Ugradar S, Elflein H, Ponto KA, Fowler BT, Dailey R, Harris GJ, Schiffman J, Tang R, Wester S. Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment: OPTIC-X study. Ophthalmology. 2022 Apr 1;129(4):438-49.	Clinical trial design	Single-arm without utility
Terwee CB, Gerding MN, Dekker FW, Prummel MF, Van der Pol JP, Wiersinga WM. Test-retest reliability of the GO-QOL: a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy. Journal of clinical epidemiology. 1999 Sep 1;52(9):875-84.	Prior to 2013	Prior to 2013
Breitenfeld M, Matheis N, Grus FH, Pitz S, Kahaly GJ. The impact of dry eye syndrome in graves' orbitopathy-a prospective and controlled trial. European Thyroid Journal. 2012 Aug;1(S1):122.	Prior to 2013	Prior to 2013
Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, Harris GJ, Antonelli A, Salvi M, Goldberg RA, Gigantelli JW. Teprotumumab for thyroid-associated ophthalmopathy. New England Journal of Medicine. 2017 May 4;376(18):1748-61.	Clinical trial design	RCT without utility
Tavassoli S, Rajendram R, Wilson V, White P, Uddin J, Dayan C, Lee RW, Jackson S. The negative psychosocial impact of thyroid eye disease-comparing results from the CIRTED trial with strabismus and other facially disfiguring conditions. Investigative Ophthalmology & Visual Science. 2018 Jul 13;59(9):5618-.	Clinical trial design	RCT without utility
Li LF, Xue JL, Guan L, Su FF, Wang H, Zhang DF. Therapeutic outcomes of mycophenolate mofetil and glucocorticoid in thyroid-associated ophthalmopathy patients. Frontiers in Endocrinology. 2023 Mar 21;14:1140196.	Clinical trial design	RCT without utility
Watt T, Hegedüs L, Rasmussen ÅK, Groenvold M, Bonnema SJ, Bjorner JB, Feldt-Rasmussen U. Which domains of thyroid-related quality of life are most relevant? Patients and clinicians provide complementary perspectives. Thyroid. 2007 Jul 1;17(7):647-54.	Prior to 2013	Prior to 2013
Kampmann E, Pitz S, Rosbach J, Kahaly GJ. Demographic, clinical, serological and quality of life data of 100	OUTCOMES	No HRQOL

consecutive euthyroid patients with severe thyroid eye disease. European Thyroid Journal. 2014 Aug;3(S1):109.		
Lee TH, Sundar G. Quality of life in thyroid eye disease: a systematic review. Ophthalmic Plastic & Reconstructive Surgery. 2020 Mar 1;36(2):118-26.	STUDY DESIGN	SLR for cross-checking
Viani GA, Boin AC, De Fendi LI, Fonseca EC, Stefano EJ, Paula JS. Radiation therapy for Graves' ophthalmopathy: a systematic review and meta-analysis of randomized controlled trials. Arquivos brasileiros de oftalmologia. 2012;75:324-32.	STUDY DESIGN	SLR for cross-checking
Minakaran N, Ezra DG. Rituximab for thyroid-associated ophthalmopathy. Cochrane Database of Systematic Reviews. 2013(5).	STUDY DESIGN	SLR for cross-checking
Kang S, Azzam SH, Minakaran N, Ezra DG. Rituximab for thyroid-associated ophthalmopathy. Cochrane Database of Systematic Reviews. 2022(6).	STUDY DESIGN	SLR for cross-checking
Ashutosh K, Michael K, Mark M, Stephen T, Lanny GC. “Balanced” orbital decompression for severe Graves' orbitopathy: technique with treatment algorithm. Otolaryngology—Head and Neck Surgery. 2003 Feb;128(2):228-35.	OUTCOMES	No HRQOL
Kahaly GJ, Douglas R, Holt RJ, Perdok R, Ball J, Smith TJ. 48-week follow-up of a multicenter, randomized, double-masked, placebo-controlled treatment trial of teprotumumab in thyroid-associated ophthalmopathy. Thyroid. 2018;28:A1.	OUTCOMES	No HRQOL
WANG L. 99 Tc-MDP combined with methylprednisolone sodium succinate in treatment of thyroid-associated ophthalmopathy: An analysis of clinical efficacy. Academic Journal of Second Military Medical University. 2012:808-9.	LANGUAGE	Article in Chinese
Sun B, Zhang Z, Dong C, Zhang Y, Yan C, Li S. 99Tcm-octreotide scintigraphy and serum eye muscle antibodies in evaluation of active thyroid-associated ophthalmopathy. Eye. 2017 May;31(5):668-76.	OUTCOMES	No HRQOL
Negro R, Hegedüs L, Attanasio R, Papini E, Winther KH. A 2018 European Thyroid Association survey on the use of selenium supplementation in Graves’ hyperthyroidism and Graves’ orbitopathy. European Thyroid Journal. 2019 Jan 1;8(1):7-15.	OUTCOMES	No HRQOL
Sun R, Yang M, Lin C, Wu Y, Sun J, Zhou H. A clinical study of topical treatment for thyroid-associated ophthalmopathy with dry eye syndrome. BMC ophthalmology. 2023 Feb 20;23(1):72.	OUTCOMES	No HRQOL
Goncalves AC, Nogueira T, Monteiro MR. A comparative study of full-thickness blepharotomy vs.	OUTCOMES	No extractable PROs

transconjunctival eyelid lengthening in the correction of upper eyelid retraction in Graves' Orbitopathy. Investigative Ophthalmology & Visual Science. 2017 Jun 23;58(8):3834-.		
Nogueira TM, Goncalves AP, GONCALVES AC, Silva LD, MONTEIRO ML. A Comparative Study of Pre-and Postoperative Quantification of Upper Eyelid Retraction in Graves Orbitopathy Using Margin Reflex Distance and Digital Eyelid Image Processing Methods. InEndocrine Reviews 2014. ENDOCRINE SOC.	OUTCOMES	No HRQOL
Haggerty H, Richardson S, Mitchell KW, Dickinson AJ. A modified method for measuring uniocular fields of fixation: reliability in healthy subjects and in patients with Graves orbitopathy. Archives of ophthalmology. 2005 Mar 1;123(3):356-62.	OUTCOMES	No HRQOL
Prummel MF, Suttorp-Schulten MS, Wiersinga WM, Verbeek AM, Mourits MP, Koornneef L. A new ultrasonographic method to detect disease activity and predict response to immunosuppressive treatment in Graves ophthalmopathy. Ophthalmology. 1993 Apr 1;100(4):556-61.	OUTCOMES	No HRQOL
Baldeschi L. A novel method for measuring outcome of orbital decompression in Graves' orbitopathy. Acta Ophthalmologica. 2015 Oct;93.	OUTCOMES	No HRQOL
Pinto ED, Lopes FP, de Souza SA, da Fonseca LM, Vaisman M, Gutfilen B, dos Santos Teixeira PD. A Pilot Study Evaluating 99mTc-anti-TNF-alpha Scintigraphy in Graves' Ophtalmopathy Patients with Different Clinical Activity Score. Hormone and Metabolic Research. 2013 Aug 5:765-8.	OUTCOMES	No HRQOL
Perros P, Kendall-Taylor P, Neoh C, Frewin S, Dickinson J. A prospective study of the effects of radioiodine therapy for hyperthyroidism in patients with minimally active Graves' ophthalmopathy. The Journal of Clinical Endocrinology & Metabolism. 2005 Sep 1;90(9):5321-3.	OUTCOMES	No HRQOL
Zhu W, Ye L, Shen L, Jiao Q, Huang F, Han R, Zhang X, Wang S, Wang W, Ning G. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with Graves' ophthalmopathy. The Journal of Clinical Endocrinology & Metabolism. 2014 Jun 1;99(6):1999-2007.	OUTCOMES	No HRQOL
Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Bergstralh EJ, Offord KP. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for	OUTCOMES	No HRQOL

Graves' ophthalmopathy. Ophthalmology. 2020 Apr 1;127(4):S160-71.		
Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Bergstralh EJ, Offord KP, Rademacher DM, Stanley NM, Bartley GB. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. Ophthalmology. 2001;108(9):1523-1534.	OUTCOMES	No HRQOL
Pereira TD, Leite CD, Kuniyoshi CH, Gebrim EM, Monteiro ML, Pieroni Gonçalves AC. A randomized comparative study of inferomedial vs. balanced orbital decompression. Analysis of changes in orbital volume, eyelid parameters, and eyeball position. Eye. 2022 Mar;36(3):547-54.	OUTCOMES	No HRQOL
Goncalves AC, Nogueira TM, Goncalves AC, Silva LD, Monteiro ML. A RANDOMIZED COMPARATIVE STUDY OF SURGICAL CORRECTION OF GRAVES UPPER EYELID RETRACTION THROUGH CONJUNCTIVAL OR BLEPHAROTOMY APPROACH. Investigative Ophthalmology & Visual Science. 2014 Apr 30;55(13):4104-.	OUTCOMES	No HRQOL
Prummel M, Terwee C, Gerding M. A randomized placebocontrolled study on radiotherapy for mild Graves' ophthalmopathy. J Endocrinol. 2000;47:183-9.	POPULATION	Mild GO
Farag S, Feeney C, Lee V, Nagendran S, Jain R, Aziz A, Akishar R, Bravis V, Meeran K. A 'real life'service evaluation model for multidisciplinary thyroid eye services. Frontiers in Endocrinology. 2021 May 7;12:669871.	OUTCOMES	No HRQOL
Johnson KT, Wittig A, Loesch C, Esser J, Sauerwein W, Eckstein AK. A retrospective study on the efficacy of total absorbed orbital doses of 12, 16 and 20 Gy combined with systemic steroid treatment in patients with Graves' orbitopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2010 Jan;248:103-9.	OUTCOMES	No HRQOL
Wang Y, Zhang S, Zhang Y, Liu X, Gu H, Zhong S, Huang Y, Fang S, Sun J, Zhou H, Fan X. A single-center retrospective study of factors related to the effects of intravenous glucocorticoid therapy in moderate-to-severe and active thyroid-associated ophthalmopathy. BMC Endocrine Disorders. 2018 Dec;18:1-7.	OUTCOMES	No HRQOL
Beshyah SA, Khalil AB, Sherif IH, Benbarka MM, Raza SA, Hussein W, Alzahrani AS, Chadli A. A survey of clinical practice patterns in management of Graves disease in	OUTCOMES	No HRQOL

the Middle East and North Africa. Endocrine Practice. 2017 Mar 1;23(3):299-308.		
Leong SC, Karkos PD, MacEwen CJ, White PS. A systematic review of outcomes following surgical decompression for dysthyroid orbitopathy. The Laryngoscope. 2009 Jun;119(6):1106-15.	STUDY DESIGN	SLR, No HRQOL
Wong CK, Lang BH, Lam CL. A systematic review of quality of thyroid-specific health-related quality-of-life instruments recommends ThyPRO for patients with benign thyroid diseases. Journal of Clinical Epidemiology. 2016 Oct 1;78:63-72.	STUDY DESIGN	SLR for cross-checking
Akbarian S, Chaibakhsh S, Kashkouli MB, Karimi N, Abdolalizadeh P, Ghahvehchian H. A systematic review on the role of antioxidants in thyroid eye disease. Journal of Current Ophthalmology. 2022 Jan;34(1):16.	STUDY DESIGN	SLR for cross-checking
Hare T, Luckey D, Miller C, Prosser B, Ross K, Stratton Z, Walton T. Abstract# 1182744: Home Infusion Administration and Clinical Monitoring Experience of Teprotumumab-trbw in Thyroid Eye Disease (TED) Patients by a Home Infusion Specialty Pharmacy. Endocrine Practice. 2022 May 1;28(5):S145.	OUTCOMES	No HRQOL
Smith TJ, Fu Q, Holt RJ. Abstract# 1407025: Hearing-Related Adverse Events and Quality of Life Assessments in Thyroid Eye Disease Patients Treated with Teprotumumab. Endocrine Practice. 2023 May 1;29(5):S110.	STUDY DESIGN	Pooled analysis
Park SW, Khwarg SI, Kim N, Lee MJ, Choung HK. Acquired lower eyelid epiblepharon in thyroid-associated ophthalmopathy of Koreans. Ophthalmology. 2012 Feb 1;119(2):390-5.	OUTCOMES	No HRQOL
á Rogvi-Hansen B, Perrild H, Christensen T, Detmar SE, Siersbaek-Nielsen K, Hansen JE. Acupuncture in the treatment of Graves' ophthalmopathy. A blinded randomized study. European Journal of Endocrinology. 1991 Feb 1;124(2):143-5.	OUTCOMES	No HRQOL
Papageorgiou KI, Ang M, Chang SH, Kohn J, Martinez S, Goldberg RA. Aesthetic considerations in upper eyelid retraction surgery. Ophthalmic Plastic & Reconstructive Surgery. 2012 Nov 1;28(6):419-23.	OUTCOMES	No HRQOL
Akpolat C, Kurt MM, Yılmaz M, Ordulu F, Evliyaoglu F. Analysis of foveal and parafoveal microvascular density and retinal vessel caliber alteration in inactive graves' ophthalmopathy. Journal of Ophthalmology. 2020 Mar 19;2020.	OUTCOMES	No HRQOL
Sánchez-Bilbao L, Martínez-López D, Revenga M, López-Vázquez Á, Valls-Pascual E, Atienza-Mateo B, Valls-	OUTCOMES	No HRQOL

Espinosa B, Maiz-Alonso O, Blanco A, Torre-Salaberri I, Rodríguez-Méndez V. Anti-IL-6 receptor tocilizumab in refractory Graves' orbitopathy: national multicenter observational study of 48 patients. Journal of Clinical Medicine. 2020 Aug 31;9(9):2816.		
Bouzas EA, Karadimas P, Mastorakos G, Koutras DA. Antioxidant agents in the treatment of Graves' ophthalmopathy. American journal of ophthalmology. 2000 May 1;129(5):618-22.	OUTCOMES	No HRQOL
Sarnat-Kucharczyk M, Świerkot M, Handzlik G, Kulawik G, Jagoda K, Grochoła-Małecka I, Fryżewska J, Mrukwa-Kominek E, Chudek J. Antithymocyte Globulin as Second-Line Therapy in Graves Orbitopathy—Preliminary Results From a Prospective Single-Center Study. Frontiers in Endocrinology. 2022 May 9;13:871009.	OUTCOMES	No HRQOL
Akcay M, Akcay E, Yeter E, Durmaz T, Keles T, Bayram NA, Yuksel I, Yuksel Kalkan G, Ayhan H, Simavli H, Simsek S. Aortic elastic properties are impaired in patients with Graves' ophtalmopathy. Vasa. 2011 Jan 1;40(1):41-8.	OUTCOMES	Changes in choroidal thickness and choroidal vascularity index
Edmunds MR, Huntbach JA, Durrani OM. Are ethnicity, social grade, and social deprivation associated with severity of thyroid-associated ophthalmopathy?. Ophthalmic Plastic and Reconstructive Surgery. 2014 May;30(3):241.	OUTCOMES	No HRQOL
Douglas R, Holt R, Barretto N, Wiens B, Francis-Sedlak M, Dailey R. Assessing long-term response to teprotumumab in thyroid eye disease. Journal of Managed Care and Specialty Pharmacy. 2020;26:S52.	OUTCOMES	No HRQOL
Gerding MN, Prummel MF, Wiersinga WM. Assessment of disease activity in Graves' ophthalmopathy by orbital ultrasonography and clinical parameters. Clinical Endocrinology. 2000 May 19;52(5):641-6.	OUTCOMES	No HRQOL
Sizmaz S, Altan-Yaycioglu R, Bakiner OS, Bozkirli E, Coban-Karatas M, Ulas B. Assessment of tear meniscus with optical coherence tomography in thyroid-associated ophtalmopathy. Current Eye Research. 2014 Apr 1;39(4):323-8.	OUTCOMES	No HRQOL
Kaur H, Hodge DO, Bradley EA. Association between subjective and objective measurements of diplopia in patients with Graves' ophthalmopathy. Investigative Ophthalmology & Visual Science. 2005 May 1;46(13):2950-.	OUTCOMES	No HRQOL
Kelada M, Avari P, Farag S, Akishar R, Jain R, Aziz A, Feeney C, Bravis V, Meeran K, Lee V. Association of	OUTCOMES	No HRQOL

other autoimmune diseases with thyroid eye disease. Frontiers in Endocrinology. 2021 Mar 5;12:644200.		
Habib LA, Godfrey KJ, Mathews P, De Rojas J, Kazim M. Association of risk of obstructive sleep apnea with thyroid eye disease: compressive optic neuropathy. Ophthalmic Plastic & Reconstructive Surgery. 2019 May 1;35(3):232-4.	OUTCOMES	No HRQOL
Subekti I, Boedisantoso A, Moeloek ND, Waspadji S, Mansyur M. Association of TSH receptor antibody, thyroid stimulating antibody, and thyroid blocking antibody with clinical activity score and degree of severity of Graves ophthalmopathy. Acta Medica Indonesiana. 2012 Apr 1;44(2):114-21.	OUTCOMES	No HRQOL
Perros P, Žarković MP, Panagiotou GC, Azzolini C, Ayvaz G, Baldeschi L, Bartalena L, Boschi AM, Nardi M, Brix TH, Covelli D. Asymmetry indicates more severe and active disease in Graves' orbitopathy: results from a prospective cross-sectional multicentre study. Journal of endocrinological investigation. 2020 Dec;43:1717-22.	OUTCOMES	No HRQOL
Lanzolla G, Menconi F, Nicolì F, Posarelli C, Maglionico MN, Figus M, Nardi M, Marcocci C, Marinò M. Beneficial effect of low-dose radioiodine ablation for Graves' orbitopathy: results of a retrospective study. Journal of Endocrinological Investigation. 2021 Dec 1:1-5.	OUTCOMES	No HRQOL
Kashkouli MB, Kaghazkanani R, Heidari I, Ketabi N, Jam S, Azarnia S, Pakdel F. Bilateral versus unilateral thyroid eye disease. Indian journal of ophthalmology. 2011 Sep;59(5):363.	OUTCOMES	No HRQOL
Ugradar S, Goldberg RA, Rootman DB. Bony orbital volume expansion in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2019 Sep 1;35(5):434-7.	OUTCOMES	No HRQOL
Olver J. Botulinum toxin A treatment of overactive corrugator supercilii in thyroid eye disease. The British Journal of Ophthalmology. 1998 May;82(5):528.	OUTCOMES	No extractable outcomes (qualitative subjective improvement)
Ugradar S, Zimmerman E, Parunakian E, Kang J, Cockerham K, Douglas RS. Change in lacrimal gland volume and aqueous tear production following treatment with teprotumumab. Clinical & Experimental Ophthalmology. 2023 Feb 1.	OUTCOMES	No HRQOL
Takahashi Y, Vaidya A, Kakizaki H. Changes in Dry Eye Status after Steroid Pulse and Orbital Radiation Therapies in Active Thyroid Eye Disease. Journal of Clinical Medicine. 2022 Jun 22;11(13):3604.	OUTCOMES	No HRQOL

Chen DY, Schneider PF, Zhang XS, Luo XY, He ZM, Chen TH. Changes in Graves' ophthalmopathy after radioiodine and anti-thyroid drug treatment of Graves' disease from 2 prospective, randomized, open-label, blinded end point studies. Experimental and clinical endocrinology & diabetes. 2013 Nov 7:1-6.	OUTCOMES	No HRQOL (TED epidemiology)
Fu W. Changes of Volume Parameters in the Treatment of Graves Ophthalmopathy by Endoscopic Transethmoidal Decompression of the Orbital Inner Wall Combined with Fat Decompression. Scanning. 2022 Aug 24;2022.	OUTCOMES	No HRQOL
Lee H, Lee YH, Suh SI, Jeong EK, Baek S, Seo HS. Characterizing intraorbital optic nerve changes on diffusion tensor imaging in thyroid eye disease before dysthyroid optic neuropathy. Journal of Computer Assisted Tomography. 2018 Mar 1;42(2):293-8.	OUTCOMES	No HRQOL
Krassas GE, Segni M, Wiersinga WM. Childhood Graves' ophthalmopathy: results of a European questionnaire study. European Journal of Endocrinology. 2005 Oct;153(4):515-21.	OUTCOMES	No HRQOL
Çalışkan S, Acar M, Gürdal C. Choroidal thickness in patients with Graves' ophthalmopathy. Current eye research. 2017 Mar 4;42(3):484-90.	OUTCOMES	No HRQOL
Kahaly G, Schrezenmeir J, Krause U, Schweikert B, Meuer S, Muller W, Denneraum R, Beyer J. Ciclosporin and prednisone v. prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. European journal of clinical investigation. 1986 Oct;16(5):415-22.	OUTCOMES	No HRQOL
Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A. Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Annals of internal medicine. 1998 Oct 15;129(8):632-5.	OUTCOMES	No HRQOL
Sui J, Sun L, Cui W, Guo H, Shi B. Circadian Impact of High-Dose Methylprednisolone Pulse Therapy on the Acute Phase of Glucose. InENDOCRINE REVIEWS 2014 Jun 1 (Vol. 35, No. 3). 2055 L ST NW, SUITE 600, WASHINGTON, DC 20036 US: ENDOCRINE SOC.	OUTCOMES	No HRQOL
Salvi M, Dazzi D, Pellistri I, Neri F, Wall JR. Classification and prediction of the progression of thyroid-associated ophthalmopathy by an artificial neural network. Ophthalmology. 2002 Sep 1;109(9):1703-8.	OUTCOMES	No HRQOL
Mourits MP, Prummel MF, Wiersinga WM, Koornneef LJ. Clinical activity score as a guide in the management of	OUTCOMES	No HRQOL

patients with Graves' ophthalmopathy. Clinical endocrinology. 1997 Jul;47(1):9-14.		
Woo YJ, Jang SY, Lim TH, Yoon JS. Clinical association of thyroid stimulating hormone receptor antibody levels with disease severity in the chronic inactive stage of Graves' orbitopathy. Korean Journal of Ophthalmology. 2015 Aug 1;29(4):213-9.	OUTCOMES	No HRQOL
Li Q, Ye H, Ding Y, Chen G, Liu Z, Xu J, Chen R, Yang H. Clinical characteristics of moderate-to-severe thyroid associated ophthalmopathy in 354 Chinese cases. PLoS One. 2017 May 4;12(5):e0176064.	OUTCOMES	No HRQOL
Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, Van Der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. The British journal of ophthalmology. 1989 Aug;73(8):639.	OUTCOMES	No HRQOL
Du Y, Ye H, Chen R, Luo WJ, Yang H. Clinical differences between predominantly fat increase and muscle increase subtypes of thyroid eye disease in Chinese patients. Kuwait Med J. 2018 Mar 1;50(1):87-91.	OUTCOMES	No HRQOL
Expósito MR, Moreno MÁ, Moreno PM, Sánchez IP, Jiménez CM, López PB. Clinical efficacy of intravenous glucocorticoid treatment in Graves' ophthalmopathy. Endocrinología y Nutrición (English Edition). 2013 Jan 1;60(1):10-4.	LANGUAGE	Spanish
de Almeida CA, Neto LV, Buescu A, Vaisman M. Clinical evaluation of the long-term response to intravenous pulses of methylprednisolone in patients with moderate to severe Graves ophthalmopathy. The Endocrinologist. 2006 Jul 1;16(4):193-6.	OUTCOMES	No HRQOL
Lazarus JH, McKeag D, Lane C, Baldeschi L, Boboridis K, Dickinson JA, Hullo A, Krassas G, Marcocci C, Marino M, Mourits M. Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. British Journal of Ophthalmology. 2006 Oct 11.	OUTCOMES	No HRQOL
Muralidhar A, Das S, Tiple S. Clinical profile of thyroid eye disease and factors predictive of disease severity. Indian journal of ophthalmology. 2020 Aug;68(8):1629.	OUTCOMES	No HRQOL
Kościuszko M, Popławska-Kita A, Pawłowski P, Lipińska D, Hryniewicka J, Jankowska D, Górska M, Krętowski A, Myśliwiec J. Clinical relevance of estimating circulating interleukin-17 and interleukin-23 during methylprednisolone therapy in Graves' orbitopathy: A preliminary study. Advances in Medical Sciences. 2021 Sep 1;66(2):315-20.	OUTCOMES	No HRQOL

Li Y, Luo B, Zhang J, Zhou X, Shao S, Xu W, Yang Y, Yuan G. Clinical relevance of serum immunoglobulin G4 in glucocorticoid therapy of Graves' ophthalmopathy. Clinical Endocrinology. 2021 Oct;95(4):657-67.	OUTCOMES	No HRQOL
Diana T, Brown RS, Bossowski A, Segni M, Niedziela M, König J, Bossowska A, Ziora K, Hale A, Smith J, Pitz S. Clinical relevance of thyroid-stimulating autoantibodies in pediatric Graves' disease—a multicenter study. The Journal of Clinical Endocrinology & Metabolism. 2014 May 1;99(5):1648-55.	OUTCOMES	No HRQOL
Zeng L, Xie XQ, Li CH, Shi HS, Wang F. Clinical study of the radiotherapy with EDGE accelerator in the treatment of the moderate and severe thyroid associated ophthalmopathy. European Review for Medical & Pharmacological Sciences. 2019 Apr 15;23(8).	OUTCOMES	No HRQOL
Stamato FJ, Maciel RM, Manso PG, Wolosker ÂM, Paiva ER, Lopes AC, Furlanetto RP. Colchicine in the treatment of the inflammatory phase of Graves' ophthalmopathy: a prospective and randomized trial with prednisone. Arquivos brasileiros de oftalmologia. 2006;69:811-6.	OUTCOMES	No HRQOL
Eckstein A. Combination therapy of intravenous steroids and orbital irradiation is more effective than intravenous steroids alone in patients with Graves' orbitopathy. Hormone and Metabolic Research. 2017 Sep 18;49(10):739-47.	OUTCOMES	No HRQOL
Yinghong Z, Jichao Z, Zhidi Z, Chiyu X, Haipeng Z, Yanrong R, Li Z, Yi W. Combined endonasal and orbital approach for annulus of Zinn area decompression in dysthyroid optic neuropathy. American Journal of Otolaryngology. 2023 Mar 1;44(2):103692.	OUTCOMES	No HRQoL
Kahaly G, Riedl M, Koenig J, Diana T, Pitz S, Eckstein A, Salvi M, Marino M, Marcocci C, Bartalena L, Perros P, Wiersinga W. Combined mycophenolate with intravenous methylprednisolone therapy is more effective than intravenous methyl-prednisolone alone in active and moderate-to-severe graves' orbitopathy-A randomized, observer blind, multicenter trial. Thyroid. 2017 Oct;27(S1):A2.	OUTCOMES	No HRQOL
Trimarchi F, Martino E, Bartalena L. Comics' representation of Graves' orbitopathy, by Emil Ferris. Journal of Endocrinological Investigation. 2021 Aug;44:1799-800.	STUDY DESIGN	Editorial
Cockerham K, Padnick-Silver L, Francis-Sedlak M, Holt R. Comorbidities and thyroid eye disease severity: Which factors are most commonly associated with more severe disease?. Thyroid. 2021 Sept. 31(S1):A75.	OUTCOMES	No HRQOL

Segni M, Bartley GB, Garrity JA, Bergstralh EJ, Gorman CA. Comparability of proptosis measurements by different techniques. American journal of ophthalmology. 2002 Jun 1;133(6):813-8.	OUTCOMES	No HRQOL
Agarwal A, Kumar S, Goel R, Raut A, Khanam S, Chhabra M. Comparative evaluation of peribulbar triamcinolone acetonide and intravenous methylprednisolone in thyroid eye disease. InCLINICAL AND EXPERIMENTAL OPHTHALMOLOGY 2022 Feb 1 (Vol. 49, No. 8, pp. 819-819). 111 RIVER ST, HOBOKEN 07030-5774, NJ US: WILEY.	OUTCOMES	No HRQOL
Nogueira TM, Goncalves AC, Goncalves AC, Silva LD, Monteiro ML. Comparison Between Pre-and Postoperative Quantitative Analysis of Graves Upper Eyelid Retraction Using Margin Reflex Distance and a Digital Eyelid Image Processing Method. Investigative Ophthalmology & Visual Science. 2014 Apr 30;55(13):3107-.	OUTCOMES	No HRQOL
Jellema HM, Baader A, Pitz S, Prick L, Wiersinga WM, Mourits MP. Comparison of cyclodeviation and duction measurement in Graves' orbitopathy patients using different devices. Strabismus. 2011 Jun 1;19(2):43-51.	OUTCOMES	No HRQOL
Alves M, Ribeiro D, Faustino J, Bachette L, Aranha F, Vigorito A, De Souza C, Paula J, Cruz AA, Rocha E. Comparison of diagnostic tests in distinct well-defined diseases related to dry eye syndrome. Investigative Ophthalmology & Visual Science. 2013 Jun 16;54(15):938-.	OUTCOMES	No HRQoL for TED subgroup
Erdogan MF, Demir O, Ersoy RU, Gul K, Unluturk U, Aydogan BI, Uc ZA, Mete T, Ertek S, Caklr B, Aral Y, Guler S, Erdogan G. Comparison of early total thyroidectomy with antithyroid treatment in patients with moderate to severely active graves' orbitopathy, a randomized prospective trial. European Thyroid Journal. 2012;1:173.	OUTCOMES	No HRQOL
Erdogan MF, Demir O, Ersoy RU, Gul K, Unluturk U, Uc ZA, Mete T, Anil C, Ertek S, Caklr B, Aral Y, Guler S, Gursoy A, Erdogan G. Comparison of early total thyroidectomy with antithyroid treatment in patients with moderate to severely active graves' orbitopathy, a randomized prospective trial. European Thyroid Journal. 2013;2:103.	OUTCOMES	No HRQOL
Erdogan MF, Demir O, Ersoy RU, Gul K, Unluturk U, Uc ZA, Mete T, Anil C, Ertek S, Caklr B, Aral Y, Guler S, Gursoy A, Erdogan G. European Thyroid Journal. 2011:88.	OUTCOMES	No HRQOL

Erdoğan MF, Demir Ö, Ersoy RÜ, Gül K, Aydoğan Bİ, Üç ZA, Mete T, Ertek S, Ünlütürk U, Çakır B, Aral Y. Comparison of Early Total Thyroidectomy with Antithyroid Treatment in Patients with Moderate-Severe Graves' Orbitopathy: A Randomized Prospective Trial. European Thyroid Journal. 2016 Jul 1;5(2):106-11.	OUTCOMES	No HRQOL
Choe CH, Cho RI, Elner VM. Comparison of lateral and medial orbital decompression for the treatment of compressive optic neuropathy in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2011 Jan 1;27(1):4-11.	OUTCOMES	No HRQOL
Sagiv O, Satchi K, Kinori M, Fabian ID, Rosen N, Ben Simon GJ, McNab A. Comparison of lateral orbital decompression with and without rim repositioning in thyroid eye disease. Graefe's Archive for Clinical and Experimental Ophthalmology. 2016 Apr;254:791-6.	OUTCOMES	No HRQOL
He Y, Mu K, Liu R, Zhang J, Xiang N. Comparison of two different regimens of intravenous methylprednisolone for patients with moderate to severe and active Graves' ophthalmopathy: a prospective, randomized controlled trial. Endocrine Journal. 2017;64(2):141-9.	OUTCOMES	No HRQOL
Mu PW, Tang XX, Wang YN, Lin S, Wang MM, Yin QL, Shu J, Zhu BL, Li JR, Zhou L, Zeng LY. Comparison of two regimens for patients with thyroid-associated ophthalmopathy receiving intravenous methyl prednisolone: A single center prospective randomized trial. Experimental and Therapeutic Medicine. 2020 Dec 1;20(6):1-.	OUTCOMES	No HRQOL
Khan SH, Malik U, Ahmed F, Siddiqui ZK, Munir S, Rashid N. Conservative Management of Thyroid Eye Disease. J Coll Physicians Surg Pak. 2021 May 1;30(5):599-601.	OUTCOMES	No HRQOL
Pascoe A, Baig IF, Lee AG. Considering use of teprotumumab in thyroid eye disease patients: There is need for alternative treatment to circumvent current treatment limitations. Ophthalmology Times. 2018 Oct 1;43(16):24-6.	STUDY DESIGN	Narrative Review
Sun B, Zhang Z, Yan C. Contribution of 99mTc-DTPA SPECT/CT in the evaluation of thyroid-associated ophthalmopathy in patients with thyroid carcinoma. Investigative Ophthalmology & Visual Science. 2021 Jun 21;62(8):3340-.	OUTCOMES	No extractable outcomes
Zhou M, Wu D, Yu F, Hong S, Ye J, Wang C, Li Y, Du M, Xiao H, Wan P. Corneal Endothelium: A Promising Quantitative Index for Graves Ophthalmopathy Activity Evaluation. American Journal of Ophthalmology. 2021 Oct 1;230:216-23.	OUTCOMES	No HRQOL

Sasim IV, de Graaf ME, Berendschot TT, Kalmann R, van Isterdael C, Mourits MP. Coronal or Swinging Eyelid Decompression for Patients with Disfiguring Proptosis in Graves' Orbitopathy?: Comparison of Results in One Center. Ophthalmology. 2005 Jul 1;112(7):1310-5.	OUTCOMES	No HRQOL Econ data (length hospitalization)
Olver J, Rose G, Khaw P, Collin J. Correction of lower eyelid retraction in thyroid eye disease: a randomised controlled trial of retractor tenotomy with adjuvant antimetabolite versus scleral graft. The British Journal of Ophthalmology. 1998 Feb;82(2):174.	OUTCOMES	No HRQOL
Kim KY, Woo YJ, Jang SY, Lee EJ, Yoon JS. Correction of lower eyelid retraction using acellular human dermis during orbital decompression. Ophthalmic plastic and reconstructive surgery. 2017 May 1;33(3):168-72.	OUTCOMES	No HRQOL
Liao SL, Wei YH. Correction of lower lid retraction using tarSys bioengineered grafts for graves ophthalmopathy. American Journal of Ophthalmology. 2013 Aug 1;156(2):387-92.	OUTCOMES	No extractable outcomes (PRO)
Nguyen VT, Park DJ, Levin L, Feldon SE. Correction of restricted extraocular muscle motility in surgical management of strabismus in Graves' ophthalmopathy. Ophthalmology. 2002 Feb 1;109(2):384-8.	OUTCOMES	No HRQOL
Stoyanova NS, Konareva-Kostianeva M, Mitkova-Hristova V, Angelova I. Correlation between Intraocular Pressure and Thickness of Extraocular Muscles, the Severity and Activity of Thyroid-associated Orbitopathy. Folia Medica. 2019 Mar 1;61(1).	OUTCOMES	No HRQOL
Law JJ, Mundy KM, Kupcha AC, Chaganti S, Nelson KM, Harrigan RL, Landman BA, Mawn LA. Correlation of automated computed tomography volumetric analysis metrics with motility disturbances in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2021 Jul 1;37(4):372-6.	STUDY DESIGN	Analysis of CT images
Kirsch EC, Kaim AH, De Oliveira MG, von Arx G. Correlation of signal intensity ratio on orbital MRI-TIRM and clinical activity score as a possible predictor of therapy response in Graves' orbitopathy—a pilot study at 1.5 T. Neuroradiology. 2010 Feb;52:91-7.	OUTCOMES	No HRQOL
Lee DC, Young SM, Kim YD, Woo KI. Course of upper eyelid retraction in thyroid eye disease. British Journal of Ophthalmology. 2019 May 10.	OUTCOMES	No HRQOL
Boboridis KG, Uddin J, Mikropoulos DG, Bunce C, Mangouritsas G, Voudouragkaki IC, Konstas AG. Critical appraisal on orbital decompression for thyroid eye disease: a systematic review and literature search. Advances in Therapy. 2015 Jul;32:595-611.	OUTCOMES	No HRQOL

Giaconi JA, Kazim M, Rho T, Pfaff C. CT scan evidence of dysthyroid optic neuropathy. Ophthalmic Plastic & Reconstructive Surgery. 2002 May 1;18(3):177-82.	OUTCOMES	No HRQOL
Goncalves AC, Gupta S, Monteiro ML, Douglas RS. Customized minimally invasive orbital decompression surgery improves lower eyelid retraction and contour in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2017 Nov 1;33(6):446-51.	OUTCOMES	No HRQOL
Regensburg NI, Wiersinga WM, Berendschot TTJM, Saeed P, Mourits MP. Densities of orbital fat and extraocular muscles in graves orbitopathy patients and controls. Ophthalmic Plastic and Reconstructive Surgery. 2011 July-Aug;27(4):236-240.	OUTCOMES	No HRQOL
Wong MH, Fenwick E, Aw AT, Lamoureux EL, Seah LL. Development and validation of the Singapore thyroid eye disease quality of life questionnaire. Translational Vision Science & Technology. 2018 Sep 4;7(5):14-.	STUDY DESIGN	Validity study
Keene KR, de Nie JM, Brink MJ, Notting IC, Verschuuren JJ, Kan HE, Beenakker JW, Tannemaat MR. Diagnosing myasthenia gravis using orthoptic measurements: assessing extraocular muscle fatiguability. Journal of Neurology, Neurosurgery & Psychiatry. 2023 Feb 1;94(2):151-.	STUDY DESIGN	Diagnosis
Mitchell AL, Goss L, Mathiopoulou L, Morris M, Vaidya B, Dickinson AJ, Quinn A, Dayan C, McLaren J, Hickey JL, Lazarus JH. Diagnosis of Graves' orbitopathy (DiaGO): results of a pilot study to assess the utility of an office tool for practicing endocrinologists. The Journal of Clinical Endocrinology & Metabolism. 2015 Mar 1;100(3):E458-62.	OUTCOMES	No HRQOL
Savku E, Gündüz K. Diagnosis, follow-up and treatment results in thyroid ophthalmopathy. Turkish Journal of Ophthalmology. 2015 Aug;45(4):156.	OUTCOMES	No HRQOL
Dragomir A, Dumitrascu A, Marinescu I, Dumitrache C, Dalea A, Hristea R, Iconaru L, Oros S. Diagnostic ability of computed tomography to assess Graves ophthalmopathy. InEndocrine Abstracts 2009 Apr 1 (Vol. 20). Bioscientifica.	OUTCOMES	No HRQOL
Tortora F, Prudente M, Cirillo M, Elefante A, Belfiore MP, Romano F, Cappabianca S, Carella C, Cirillo S. Diagnostic accuracy of short-time inversion recovery sequence in Graves' ophthalmopathy before and after prednisone treatment. Neuroradiology. 2014 May;56:353-61.	OUTCOMES	No HRQOL
Ting MA, Ozzello DJ, Topilow NJ, Yoon JS, Liu CY, Korn BS, Kikkawa DO. Differential effects of teprotumumab	OUTCOMES	No HRQoL

treatment based on fat-to-muscle ratio in patients with thyroid eye disease. Orbit. 2023 Jul 4;42(4):418-25.		
Ozturk Karabulut G, Fazil K, Ozturker C, Gunaydin ZK, Altan C, İnal A, Taskapili M, Kaynak P. Do ocular pulse amplitude and choroidal thickness change in patients with thyroid eye disease?. Orbit. 2019 Sep 3;38(5):347-52.	OUTCOMES	No HRQOL
Regensburg NI, Wiersinga WM, Berendschot TT, Potgieser P, Mourits MP. Do subtypes of graves' orbitopathy exist?. Ophthalmology. 2011 Jan 1;118(1):191-6.	OUTCOMES	No HRQOL
Sabini E, Leo M, Menconi F, Mazzi B, Ionni I, Nardi M, Vitti P, Marcocci C, Marino M. Does Graves' orbitopathy (GO) ever disappear? Answers to an old question. European Thyroid Journal. 2017 Aug;6(S1):27.	OUTCOMES	No HRQOL
Laurberg P, Berman DC, Pedersen IB, Andersen S, Carlé A. Double vision is a major manifestation in moderate to severe graves' orbitopathy, but it correlates negatively with inflammatory signs and proptosis. The Journal of Clinical Endocrinology & Metabolism. 2015 May 1;100(5):2098-105.	OUTCOMES	No HRQOL
Laurberg P, Berman DC, Pedersen IB, Andersen S, Carle AS. Double vision is the most common indication for therapy in moderate to severe Graves' orbitopathy but it correlates negatively with inflammatory signs and proptosis: A single center prospective cohort study (N= 215) with objective quantitation of diplopia. Thyroid. 2014;24(Suppl 1):A-2.	OUTCOMES	No HRQOL
Dickinson AJ, Vaidya B, Miller M, Coulthard A, Perros P, Baister E, Andrews CD, Hesse L, Heverhagen JT, Heufelder AE, Kendall-Taylor P. Double-blind, placebo-controlled trial of octreotide long-acting repeatable (LAR) in thyroid-associated ophthalmopathy. The Journal of Clinical Endocrinology & Metabolism. 2004 Dec 1;89(12):5910-5.	OUTCOMES	No extractable outcomes
Achtsidis V, Tentolouris N, Theodoropoulou S, Panagiotidis D, Vaikoussis E, Saldana M, Gouws P, Theodossiadis PG. Dry eye in Graves' ophthalmopathy: correlation with corneal hypoesthesia. European journal of ophthalmology. 2013 Jul;23(4):473-9.	POPULATION	Mild GO
Szatmary G, Polgar T. Dti of extraocular muscles in diplopia: A pilot study. Neuro-Ophthalmology. 2013 Apr;37(S1):102-103.	OUTCOMES	No HRQOL
Insull EA, Sipkova Z, David J, Turner HE, Norris JH. Early low-dose rituximab for active thyroid eye disease: an	OUTCOMES	No extractable outcomes

effective and well-tolerated treatment. Clinical endocrinology. 2019 Jul;91(1):179-86.		
Hart RH, Kendall-Taylor P, Crombie A, Perros P. Early response to intravenous glucocorticoids for severe thyroid-associated ophthalmopathy predicts treatment outcome. Journal of Ocular Pharmacology & Therapeutics. 2005 Aug 1;21(4):328-36.	STUDY DESIGN	Case series
Baldeschi L, Wakelkamp IM, Lindeboom R, Prummel MF, Wiersinga WM. Early versus late orbital decompression in Graves' orbitopathy: a retrospective study in 125 patients. Ophthalmology. 2006 May 1;113(5):874-8.	OUTCOMES	No HRQOL
Kim SA, Jung SK, Paik JS, Yang SW. Effect of orbital decompression on corneal topography in patients with thyroid ophthalmopathy. PLoS One. 2015 Sep 9;10(9):e0133612.	OUTCOMES	No HRQOL
Kim SA, Kang KD, Paik JS, Jung SK, Yang SW. Effect of orbital decompression on corneal topography in patients with thyroid ophthalmopathy. Investigative Ophthalmology and Visual Science. 2015 Jun;56(7):S69.	OUTCOMES	No HRQOL
Boulanouar L, Grunenwald S, Imbert P, Khalifa J, Dekeister C, Boutault F, Caron P. Effect of orbital radiotherapy on the outcome of surgical orbital decompression for thyroid-associated orbitopathy (TAO): a retrospective study in 136 patients. Endocrine. 2020 Mar;67:605-12.	OUTCOMES	No HRQOL
Krause M, Kamal M, Kruber D, Sterker I, Sander AK, Zimmerer R, Lethaus B, Bartella AK. Effect of orbital wall resection areas in the treatment of patients with endocrine orbitopathy. British Journal of Oral and Maxillofacial Surgery. 2022 Jun 1;60(5):610-6.	OUTCOMES	No HRQoL
Van Acker BA, Prummel MF, Weberc JA, Wiersinga WM, Arisz L. Effect of prednisone on renal function in man. Nephron. 1993 Dec 12;65(2):254-9.	OUTCOMES	No HRQOL
Russell DJ, Dutton JJ, Baca RL. Effect of radiation therapy on intraocular pressure in patients with Graves' orbitopathy. Orbit. 2013 Aug 1;32(4):219-24.	OUTCOMES	No HRQOL
Wu Y, Tong B, Luo Y, Xie G, Xiong W. Effect of radiotherapy on moderate and severe thyroid associated ophthalmopathy: a double blind and self-controlled study. International Journal of Clinical and Experimental Medicine. 2015;8(2):2086.	OUTCOMES	No HRQOL
Ohtsuka K, Sato A, Kawaguchi S, Hashimoto M, Suzuki Y. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. American journal of ophthalmology. 2003 Mar 1;135(3):285-90.	OUTCOMES	No HRQOL

Siomkajło M, Mizera Ł, Szymczak D, Kolačkov K, Grzegrzółka J, Bolanowski M, Daroszewski J. Effect of systemic steroid therapy in Graves' orbitopathy on regulatory T cells and Th17/Treg ratio. Journal of Endocrinological Investigation. 2021 Nov;44:2475-84.	OUTCOMES	No HRQOL
Adetunji MO, Nguyen BJ, McGeehan B, Tamhankar MA, Briceño CA. Effect of teprotumumab on intraocular pressure in thyroid-associated ophthalmopathy. Taiwan Journal of Ophthalmology. 2022 Jul;12(3):325.	OUTCOMES	No HRQOL
Adetunji MO, Nguyen BJ, Meer E, Kwong B, McGeehan B, Maguire MG, Tamhankar M, Briceño CA. Effect of teprotumumab on intraocular pressure in thyroid-associated ophthalmopathy. Investigative Ophthalmology & Visual Science. 2021 Jun 21;62(8):3327-.	OUTCOMES	No HRQOL
Gomi CF, Yates B, Kikkawa DO, Levi L, Weinreb RN, Granet DB. Effect on intraocular pressure of extraocular muscle surgery for thyroid-associated ophthalmopathy. American journal of ophthalmology. 2007 Nov 1;144(5):654-7.	OUTCOMES	No HRQOL
de-Arriba-Palomero P, Sales-Sanz M, Fuentemilla E, Won-Kim HR, de-Arriba-Palomero F, Muñoz-Negrete FJ. Effectiveness of oral counselling for smoke cessation in Graves orbitopathy patients. Archivos de la Sociedad Española de Oftalmología (English Edition). 2019 Jul 1;94(7):323-30.	OUTCOMES	Smoke cessation
Shaomin SH, Yebing HE. Effectiveness of SomaTotalatin Analogs versus Placebo for Graves' Ophthalmopathy: A Meta-Analysis. Chinese Journal of Evidence-Based Medicine. 2013;13(1):106-11.	STUDY DESIGN	Meta Analysis for cross checking - FT not found
O'Dell JM, Mussatto CC, Chu RL, Al-Sabbagh MQ, Timoney PJ, Sokol JA. Effects of Smoking on Outcomes of Thyroid Eye Disease Treated with Teprotumumab: A Retrospective Cohort Study. Kansas Journal of Medicine. 2023;16:62.	OUTCOMES	No HRQOL
Covelli D, Vannucchi G, Campi I, Curro N, Dazzi D, Rodari M, Pepe G, Chiti A, Beck-Peccoz P, Salvi M. Effects of steroid prophylaxis for graves' orbitopathy on the radioiodine (RAI) therapeutic outcome and thyroid function. European Thyroid Journal. 2013;2:135.	POPULATION	Hyperthyroid patients without TED
Menconi F, Marinò M, Pinchera A, Rocchi R, Mazzi B, Nardi M, Bartalena L, Marcocci C. Effects of total thyroid ablation versus near-total thyroidectomy alone on mild to moderate Graves' orbitopathy treated with	POPULATION	Mild to moderate TED

intravenous glucocorticoids. The Journal of Clinical Endocrinology & Metabolism. 2007 May 1;92(5):1653-8.		
Lai KK, Aljufairi FM, Li CL, Ngai AK, Yeung CS, Fong RH, Yip WW, Young AL, Pang CP, Chong KK. Efficacy and Safety of 6-Weekly versus 12-Weekly Intravenous Methylprednisolone in Moderate-to-Severe Active Thyroid-Associated Ophthalmopathy. Journal of Clinical Medicine. 2023 May 1;12(9):3244.	OUTCOMES	No HRQOL
Roy A, Dutta D, Ghosh S, Mukhopadhyay P, Mukhopadhyay S, Chowdhury S. Efficacy and safety of low dose oral prednisolone as compared with pulse intravenous methylprednisolone in managing moderate severe Graves' orbitopathy: a randomized controlled trial. Indian journal of endocrinology and metabolism. 2015 May;19(3):351.	OUTCOMES	No HRQOL
Ye X, Bo X, Hu X, Cui H, Lu B, Shao J, Wang J. Retracted: Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. Clinical Endocrinology. 2017 Feb;86(2):247-55.	OUTCOMES	No HRQOL
Young SM, Lim AY, Lang SS, Lee KO, Sundar G. Efficacy and safety of pulsed intravenous methylprednisolone in early active thyroid eye disease. Orbit. 2019 Sep 3;38(5):362-9.	OUTCOMES	No HRQOL
Shen WC, Lee CH, Loh EW, Hsieh AT, Chen L, Tam KW. Efficacy and safety of rituximab for the treatment of Graves' orbitopathy: a meta-analysis of randomized controlled trials. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2018 May;38(5):503-10.	STUDY DESIGN	SLR for cross-checking
Paridaens D, Lie A, Grootendorst RJ, Van den Bosch WA. Efficacy and side effects of 'swinging eyelid'orbital decompression in Graves' orbitopathy: a proposal for standardized evaluation of diplopia. Eye. 2006 Feb;20(2):154-62.	OUTCOMES	No HRQOL
Khataminia GR, Moosavian J. Efficacy of a single subconjunctival injection with disport for lid retraction treatment. PAKISTAN JOURNAL OF MEDICAL SCIENCES. 2007 Jul 1;23(4):620-4.	OUTCOMES	No HRQOL
Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, Simonetta S, Guastella C, Pignataro L, Avignone S, Beck-Peccoz P. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. The Journal of Clinical Endocrinology & Metabolism. 2015 Feb 1;100(2):422-31.	DUPLICATE	Duplicate CID 586

Kim JW, Han SH, Son BJ, Rim TH, Keum KC, Yoon JS. Efficacy of combined orbital radiation and systemic steroids in the management of Graves' orbitopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2016 May;254:991-8.	OUTCOMES	No HRQOL
Zoumalan CI, Cockerham KP, Turbin RE, Volpe NJ, Kazim M, Douglas RS, Feldon SE. Efficacy of corticosteroids and external beam radiation in the management of moderate to severe thyroid eye disease. Journal of Neuro-Ophthalmology. 2007 Sep 1;27(3):205-14.	STUDY DESIGN	SLR for cross-checking
Choi JH, Lee JK. Efficacy of orbital radiotherapy in moderate-to-severe active graves' orbitopathy including long-lasting disease: a retrospective analysis. Radiation Oncology. 2020 Dec;15(1):1-8.	OUTCOMES	No HRQOL
Lazzaroni E, Covelli D, Campi I, Vannucchi G, Curro N, Pirola G, Guastella C, Muller I, Dolci A, Arosio M, Salvi M. Efficacy of rituximab in patients with active moderate-severe grave's orbitopathy: Outcomes of different dose regimens. European Thyroid Journal. 2019 Aug;8(S1):22.	OUTCOMES	No HRQOL
Deltour JB, d'Assigny Flamen M, Ladsous M, Giovansili L, Cariou B, Caron P, Drui D, Lebranchu P. Efficacy of rituximab in patients with Graves' orbitopathy: a retrospective multicenter nationwide study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2020 Sep;258:2013-21.	OUTCOMES	No HRQOL
Kahaly GJ, Smith TJ, Sile S, Thompson EH, Vescio T, Perdok R, Sherman JW, Douglas RS. Efficacy of teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in patients with active thyroid eye disease: Pooled results from two placebo-controlled trials. Thyroid. 2019 Oct;29(S1):A1.	STUDY DESIGN	Pooled analysis
Vannucchi G, Campi I, Covelli D, Currò N, Lazzaroni E, Palomba A, Soranna D, Zambon A, Fugazzola L, Muller I, Guastella C. Efficacy profile and safety of very low-dose rituximab in patients with Graves' orbitopathy. Thyroid. 2021 May 1;31(5):821-8.	DUPLICATE	Duplicate CID 87
Malik R, Cormack G, MacEwen C, White P. Endoscopic orbital decompression for dyscosmetic thyroid eye disease. The Journal of Laryngology & Otology. 2008 Jun;122(6):593-7.	OUTCOMES	PRO correlation only
Pham TM, Nguyen CT, Mai QT, Bui TH, Do DH, McCluskey P, Pham TV. Endoscopic Orbital Decompression for Graves' Orbitopathy–A Vietnam Study. Clinical Ophthalmology. 2021 Apr 22:1685-90.	OUTCOMES	No HRQOL
Tu Y, Wu S, Pan Z, Hu X, Zhou G, Shi J, Xu M, Liu W, Wu W. Endoscopic transconjunctival deep lateral wall	OUTCOMES	No HRQoL

decompression for thyroid-associated orbitopathy: a minimally invasive alternative: transconjunctival endoscopic with wall decompression for TAO. American Journal of Ophthalmology. 2022 Mar 1;235:71-9.		
Eckstein A, Loesch C, Glowacka D, Schott M, Mann K, Esser J, Morgenthaler NG. Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetric Graves ophthalmopathy. British Journal of Ophthalmology. 2009 Feb 15.	OUTCOMES	No HRQOL
Yu W, Zheng L, Shuo Z, Xingtong L, Mengda J, Lin Z, Ziyang S, Huifang Z. Evaluation of extraocular muscles in patients with thyroid associated ophthalmopathy using apparent diffusion coefficient measured by magnetic resonance imaging before and after radiation therapy. Acta Radiologica. 2022 Sep;63(9):1180-6.	OUTCOMES	No HRQOL
Forte R, Bonavolontà P, Vassallo P. Evaluation of retinal nerve fiber layer with optic nerve tracking optical coherence tomography in thyroid-associated orbitopathy. Ophthalmologica. 2010 Sep 2;224(2):116-21.	OUTCOMES	No HRQOL
Latusek T, Miszczyk L. Eye cyclotorsion after deep lateral orbital wall decompression (DLOWD) in Grave's orbitopathy. Onkologia i Radioterapia. 2015;24(4):29-33.	LANGUAGE	Polish
Nezzar H, Bordas R, Sabadel A, Al Hazzaa S, Chiambaretta F. Eye cyclotorsion after deep lateral orbital wall decompression (DLOWD) in Grave’s orbitopathy. Investigative Ophthalmology & Visual Science. 2014 Apr 30;55(13):4101-.	OUTCOMES	No HRQOL
Savar LM, Menghani RM, Chong KK, Garneau HC, Goldberg RA. Eyebrow tissue expansion: an underappreciated entity in thyroid-associated orbitopathy. Archives of Ophthalmology. 2012 Dec 1;130(12):1566-9.	OUTCOMES	No HRQOL
Gaddipati RV, Meyer DR. Eyelid Retraction, Lid Lag, Lagophthalmos, and von Graefe's Sign: Quantifying the Eyelid Features of Graves' Ophthalmopathy. Ophthalmology. 2008 Jun 1;115(6):1083-8.	OUTCOMES	No HRQOL
Terwee CB, Dekker FW, Bonsel GJ, Heisterkamp SH, Prummel MF, Baldeschi L, Wiersinga WM. Facial disfigurement: is it in the eye of the beholder? A study in patients with Graves’ ophthalmopathy. Clinical Endocrinology. 2003 Feb;58(2):192-8.	OUTCOMES	No HRQOL
Lei C, Qu M, Sun H, Huang J, Huang J, Song X, Zhai G, Zhou H. Facial expression of patients with Graves’ orbitopathy. Journal of Endocrinological Investigation. 2023 Apr 1:1-2.	STUDY DESIGN	Assessment of facial expressions

Hsieh MW, Hsu CK, Kuo PC, Chang HC, Chen YH, Chien KH. Factors Predicting the Success of Combined Orbital Decompression and Strabismus Surgery in Thyroid-Associated Orbitopathy. Journal of Personalized Medicine. 2022 Jan 31;12(2):186.	POPULATION	Mild to moderate TED
Li EY, Kwok TY, Cheng AC, Wong AC, Yuen HK. Fat-removal orbital decompression for disfiguring proptosis associated with Graves' ophthalmopathy: safety, efficacy and predictability of outcomes. International ophthalmology. 2015 Jun;35:325-9.	OUTCOMES	No HRQOL
Kampmann E, Diana T, Kanitz M, Hoppe D, Kahaly GJ. Thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy: a prospective study. International journal of endocrinology. 2015 Oct;2015.	OUTCOMES	No HRQOL
Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. Thyroid. 2014 Oct 1;24(10):1515-23.	STUDY DESIGN	SLR, No HRQOL
Längericht J, Krämer I, Kahaly GJ. Glucocorticoids in Graves' orbitopathy: mechanisms of action and clinical application. Therapeutic Advances in Endocrinology and Metabolism. 2020 Dec;11:2042018820958335.	STUDY DESIGN	SLR for cross-checking
Sawicka-Gutaj N, Bednarczuk T, Daroszewski J, Waligórska-Stachura J, Miśkiewicz P, Sowiński J, Bolanowski M, Ruchała M. GO-QOL—disease-specific quality of life questionnaire in Graves' orbitopathy. Endokrynologia Polska. 2015;66(4):362-6.	OUTCOMES	No HRQOL, GO-QOL construction
Ribeiro SF, Garcia DM, Leal V, Faria-Correia F, Rocha-Sousa A, Falcão-Reis F, e Cruz AA. Graded müllerectomy for correction of graves upper eyelid retraction: effect on eyelid movements. Ophthalmic Plastic & Reconstructive Surgery. 2014 Sep 1;30(5):384-7.	OUTCOMES	No HRQOL
Dolman PJ. Grading severity and activity in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2018 Jul 1;34(4S):S34-40.	STUDY DESIGN	Narrative Review
Järhult J, Rudberg C, Larsson E, Selvander H, Sjövall K, Winsa B, Rastad J, Karlsson FA, TEO Study Group. Graves' disease with moderate–severe endocrine ophthalmopathy–long term results of a prospective, randomized study of total or subtotal thyroid resection. Thyroid. 2005 Oct 1;15(10):1157-64.	OUTCOMES	No HRQOL
Bartalena L, Tanda ML. Graves' ophthalmopathy. New England Journal of Medicine. 2009 Mar 5;360(10):994-1001.	STUDY DESIGN	Case report

Tallstedt L, Lundell G, Taube A. Graves' ophthalmopathy and tobacco smoking. European Journal of Endocrinology. 1993 Aug 1;129(2):147-50.	OUTCOMES	No HRQOL
Arora S, Damle NA, Meel R, Lata K, Tandon N, Sharma S, Bal C. Graves' Ophthalmopathy on 68Ga-DOTANOC Positron Emission Tomography/Computed Tomography. Indian Journal of Nuclear Medicine: IJNM: the Official Journal of the Society of Nuclear Medicine, India. 2019 Oct;34(4):338.	STUDY DESIGN	Case series
Shaikh MP, Alite F, Wu M, Welsh J, Emami B, Melian E, Harkenrider MM. PO-0639: Graves ophthalmopathy: a network meta-analysis of treatments. Radiotherapy and Oncology. 2016 Apr 1;119:S299-300.	STUDY DESIGN	SLR, no references listed
Nakahara H, Noguchi S, Murakami N, Morita M, Tamaru M, Ohnishi T, Hoshi H, Jinnouchi S, Nagamachi S, Futami S. Graves ophthalmopathy: MR evaluation of 10-Gy versus 24-Gy irradiation combined with systemic corticosteroids. Radiology. 1995 Sep;196(3):857-62.	OUTCOMES	No HRQOL
Chan LL, Tan HE, Fook-Chong S, Teo TH, Lim LH, Seah LL. Graves ophthalmopathy: the bony orbit in optic neuropathy, its apical angular capacity, and impact on prediction of risk. American journal of neuroradiology. 2009 Mar 1;30(3):597-602.	OUTCOMES	No HRQOL
Villagelin D, Dos Santos RB, Romaldini JH, Comarella AP, Bufalo N, Peres KC, Ward L. Graves orbitopathy affects visual function and appearance in different manners. European Thyroid Journal. 2016 Aug;5(S1):73.	POPULATION	Graves' disease
Mbarek S, Abid F, Ammari W, Alaya W, Mahmoud A, Messaoud R. Graves' Orbitopathy: Report of 82 cases. Tunisie Medicale. 2021 Feb;99(2):243-251.	LANGUAGE	French
Mladenovic M, Buchberger M, Qerimi V, Puntscher S, Siebert U, Rochau U. Health state utilities in individuals with goiter, hypothyroidism, hyperthyroidism and graves' disease as an example for thyroid disorders–a systematic review. Value in Health. 2017 Oct 1;20(9):A483.	STUDY DESIGN	SLR, no references listed
Park NR, Moon JH, Lee JK. Hertel exophthalmometer versus computed tomography scan in proptosis estimation in thyroid-associated orbitopathy. Clinical Ophthalmology. 2019 Aug 2:1461-7.	OUTCOMES	No HRQOL
Kauppinen-Mäkelin R, Karma A, Leinonen E, Löyttyniemi E, Salonen O, Sane T, Setälä K, Viikari J, Heufelder A, Välimäki M. High dose intravenous methylprednisolone pulse therapy versus oral prednisone for thyroid-	OUTCOMES	No HRQOL

associated ophthalmopathy. Acta Ophthalmologica Scandinavica. 2002 Jun;80(3):316-21.		
Macchia PE, Bagattini M, Lupoli G, Vitale M, Vitale G, Fenzi G. High-dose intravenous corticosteroid therapy for Graves' ophthalmopathy. Journal of endocrinological investigation. 2001 Mar;24:152-8.	OUTCOMES	No extractable outcomes (figure 2A)
Goswami R. High-dose intravenous immunoglobulin treatment in Graves' ophthalmopathy. Acta Endocrinologica. 1992 May 1;126(5):474-.	OUTCOMES	No HRQOL
Kikkawa DO. Histopathologic analysis of palpebral conjunctiva in thyroid-related orbitopathy (an american ophthalmological society thesis). Transactions of the American Ophthalmological Society. 2010 Dec;108:46.	OUTCOMES	No HRQOL
Young SM, Kim JH, Kim YD, Karnsiritanont V, Lang SS, Woo KI. Hyaluronic acid gel injection for dysthyroid upper eyelid retraction in Asian patients. Orbit. 2023 Jul 4;42(4):389-96.	OUTCOMES	No HRQoL
Kashkouli MB, Pakdel F, Kiavash V, Heidari I, Heirati A, Jam S. Hyperthyroid vs hypothyroid eye disease: the same severity and activity. Eye. 2011 Nov;25(11):1442-6.	OUTCOMES	No HRQOL
Bartalena L, Tanda ML. Immunotherapy for Graves' orbitopathy: easy enthusiasm, but let's keep trying. Journal of endocrinological investigation. 2006 Dec;29:1012-6.	STUDY DESIGN	Narrative Review
Ugradar S, Wang Y, Mester T, Kahaly G, Douglas R. Improvement of asymmetric thyroid eye disease with teprotumumab. British Journal of Ophthalmology. 2021 Feb 12.	OUTCOMES	No HRQOL
Ma Z, Ozaki H, Ishikawa Y, Jingu K. Improvement of the MRI and clinical features of Asian Graves' ophthalmopathy by radiation therapy with steroids. Japanese Journal of Radiology. 2019 Aug 20;37:612-8.	OUTCOMES	No HRQOL
Laurberg P, Berman DC, Bülow Pedersen I, Andersen S, Carlé A. Incidence and clinical presentation of moderate to severe Graves' orbitopathy in a Danish population before and after iodine fortification of salt. The Journal of Clinical Endocrinology & Metabolism. 2012 Jul 1;97(7):2325-32.	OUTCOMES	No HRQOL
Munshi N, Goldberg R, Rootman D. Incidence and Predictors of SLK in Thyroid Eye Disease. Investigative Ophthalmology & Visual Science. 2022 Jun 1;63(7):4000-A0342.	OUTCOMES	No HRQOL
Carrasco JR, Castillo I, Bilyk JR, Pribitkin EA, Savino PJ. Incidence of infraorbital hypesthesia and sinusitis after orbital decompression for thyroid-related orbitopathy: a	OUTCOMES	No HRQOL

comparison of surgical techniques. Ophthalmic Plastic & Reconstructive Surgery. 2005 May 1;21(3):188-91.		
Nexo MA, Watt T, Pedersen J, Bonnema SJ, Hegedüs L, Rasmussen AK, Feldt-Rasmussen U, Bjorner JB. Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study. The Journal of Clinical Endocrinology & Metabolism. 2014 Sep 1;99(9):3184-92.	OUTCOMES	No HRQOL
Lantz M, Planck T, Åsman P, Hallengren B. Increased TRAb and/or low anti-TPO titers at diagnosis of Graves' disease are associated with an increased risk of developing ophthalmopathy after onset. Experimental and Clinical Endocrinology & Diabetes. 2014 Feb;122(02):113-7.	OUTCOMES	No HRQOL
Chen X, Abudukerimu B, Li Q, Li Q, Qiao J, Lin D, Sui C, Ye L, Zhai H, Jiang B, Wang N. Influence of 4-week or 12-week glucocorticoid treatment on metabolic changes in patients with active moderate-to-severe thyroid-associated ophthalmopathy. Clinical and Translational Science. 2021 Sep;14(5):1734-46.	OUTCOMES	No HRQOL
Stahr K, Schluter A, Holtmann L, Kasper F, Eckstein A, Lang S, Mattheis S. Influence of orbital decompression to nasal function. Laryngo- Rhino- Otologie. 2018 Apr;97(S2):S345-S346.	OUTCOMES	No HRQOL
Thorne AW, Rootman DB. Influence of surgical approach for decompression on lower eyelid position in thyroid eye disease. Orbit. 2020 Mar 3;39(2):84-6.	OUTCOMES	No HRQOL
Bradley E, Gorman CA, Bergstralh EJ, Bartley GB. Interobserver Reliability of Rating Color Slides to Measure Change in Graves' Ophthalmopathy. Investigative Ophthalmology & Visual Science. 2003 May 1;44(13):158-.	OUTCOMES	No HRQOL
Dal Canto AJ, Crowe S, Perry JD, Traboulsi EI. Intraoperative relaxed muscle positioning technique for strabismus repair in thyroid eye disease. Ophthalmology. 2006 Dec 1;113(12):2324-30.	OUTCOMES	No HRQOL
Ahn HY, Lee JK. Intravenous glucocorticoid treatment for Korean graves' ophthalmopathy patients. Journal of Korean Medical Science. 2020 Jun 15;35(23).	OUTCOMES	No HRQOL
Salvi M, Colucci G, Masetti G, Covelli D, Koehling H, Garaiova I, Michael D, Zhang L, Ludgate M, Marchesi J, Biscarini F, Plummer S. Investigation of novel biomarkers and definition of role of the microbiome in graves' orbitopathy (INDIGO): the probiotic trial. European Thyroid Journal. 2018;7:24.	OUTCOMES	No HRQOL

Jankauskiene J, Imbrasiene D. Investigations of ocular changes, extraocular muscle thickness, and eye movements in Graves' ophthalmopathy. Medicina (Kaunas). 2006;42(11):900-3.	OUTCOMES	No HRQOL
Irradiation and surgery of Graves' ophthalmopathy - primary research. Healthcare Insurance Board/ College Voor Zorgverzekeringen (CVZ). http://www.cvz.nl/	STUDY DESIGN	Health Insurance document
Limone PP, Bianco L, Mellano M, Garino F, Giannoccaro F, Rossi A, Airaldi C, Nassisi D, Gino E, Deandrea M, Oldani B. Is concomitant treatment with steroids and radiotherapy more favorable than sequential treatment in moderate-to-severe graves orbitopathy?. La radiologia medica. 2021 Feb;126:334-42.	OUTCOMES	No HRQOL
Kim JW, Woo YJ, Yoon JS. Is modified clinical activity score an accurate indicator of diplopia progression in Graves' orbitopathy patients?. Endocrine Journal. 2016;63(12):1133-40.	OUTCOMES	No HRQOL
MOON KT. Is Selenium a Beneficial Treatment for Graves Orbitopathy?. American Family Physician. 2012 Jun 1;85(11):1100-.	POPULATION	Mild TED
Wiersinga WM, Bleumink M, Saeed P, Baldeschi L, Prummel MF. Is sleeping position related to asymmetry in bilateral Graves' ophthalmopathy?. Thyroid. 2008 May 1;18(5):541-4.	OUTCOMES	No HRQOL
Edmunds MR, Boelaert K. Knowledge of thyroid eye disease in Graves' disease patients with and without orbitopathy. Thyroid. 2019 Apr 1;29(4):557-62.	OUTCOMES	No HRQOL
Vannucchi GM, Covelli D, Campi I, Curro N, Dazzi D, Rodari M, Pepe G, Chiti A, Beck-Peccoz P, Salvi M. Lack of occurrence of graves' orbitopathy (GO) after radioiodine (RAI) therapy with and without steroid prophylaxis: a prospective study. European Thyroid Journal. 2013;2:103.	POPULATION	No TED subgroup
Gagliardo C, Radellini S, Morreale Bubella R, Falanga G, Richiusa P, Vadalà M, Ciresi A, Midiri M, Giordano C. Lacrimal gland herniation in Graves ophthalmopathy: a simple and useful MRI biomarker of disease activity. European Radiology. 2020 Apr;30:2138-41.	OUTCOMES	No HRQOL
Krassas GE, Kaltsas TH, Dumas A, Pontikides N, Tolis G. Lanreotide in the treatment of patients with thyroid eye disease. European journal of endocrinology. 1997 Apr;136(4):416-22.	OUTCOMES	No HRQOL
Ko J, Kook KH, Yoon JS, Woo KI, Yang JW. Longitudinal association of thyroid-stimulating immunoglobulin levels with clinical characteristics in thyroid eye disease. BMJ open. 2022 Jun 1;12(6):e050337.	OUTCOMES	No HRQOL

Dragan LR, Seiff SR, Lee DC. Longitudinal correlation of thyroid-stimulating immunoglobulin with clinical activity of disease in thyroid-associated orbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2006 Jan 1;22(1):13-9.	OUTCOMES	No HRQOL
Xu DD, Chen Y, Xu HY, Li H, Zhang ZH, Liu YH. Long-term effect of triamcinolone acetonide in the treatment of upper lid retraction with thyroid associated ophthalmopathy. International Journal of Ophthalmology. 2018;11(8):1290.	POPULATION	Mild to moderate TED
Chang M, Baek S, Lee TS. Long-term outcomes of unilateral orbital fat decompression for thyroid eye disease. Graefe's Archive for Clinical and Experimental Ophthalmology. 2013 Mar;251:935-9.	OUTCOMES	No HRQOL
Kinyoun JL. Long-term visual acuity results of treated and untreated radiation retinopathy (an AOS thesis). Transactions of the American Ophthalmological Society. 2008 Dec;106:325.	OUTCOMES	No HRQOL
Kahaly GJ, Rösler HP, Pitz S, Hommel G. Low-versus high-dose radiotherapy for Graves' ophthalmopathy: a randomized, single blind trial. Cancer/Radiothérapie. 2001;2(5):194-5.	OUTCOMES	No HRQOL
Weissmann T, Lettmaier S, Donaubauer AJ, Bert C, Schmidt M, Kruse F, Ott O, Hecht M, Fietkau R, Frey B, Putz F. Low-vs. high-dose radiotherapy in Graves' ophthalmopathy: a retrospective comparison of long-term results. Strahlentherapie und Onkologie. 2021 Oct;197:885-94.	OUTCOMES	No HRQOL
Benzimra JD, Quinn AG, Kersey T, McGrane D, Goss L, Vaidya B. Management of patients in a combined thyroid eye clinic in secondary care. International ophthalmology. 2014 Feb;34:1-6.	OUTCOMES	No HRQOL
Bruscolini A, La Cava M, Gharbiya M, Sacchetti M, Restivo L, Nardella C, Marenco M, Lambiase A. Management of patients with Graves' disease and orbital involvement: role of spectral domain optical coherence tomography. Journal of Immunology Research. 2018 Feb 18;2018.	OUTCOMES	No HRQOL
Antisdel JL, Gumber D, Holmes J, Sindwani R. Management of sinonasal complications after endoscopic orbital decompression for Graves' orbitopathy. The Laryngoscope. 2013 Sep;123(9):2094-8.	OUTCOMES	No HRQOL
Mellington FE, Dayan CM, Dickinson AJ, Hickey JL, MacEwen CJ, McLaren J, Perros P, Rose GE, Uddin J, Vaidya B, Foley P. Management of thyroid eye disease in the United Kingdom: a multi-centre thyroid eye disease audit. Orbit. 2017 May 4;36(3):159-69.	OUTCOMES	No HRQOL

Bokman CL, Ugradar S, Rootman DB. Measurement of medial wall bowing and clinical associations in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2018 Nov 1;34(6):557-9.	OUTCOMES	No HRQOL
Terwee CB, Prummel MF, Gerding MN, Kahaly GJ, Dekker FW, Wiersinga WM. Measuring disease activity to predict therapeutic outcome in Graves' ophthalmopathy. Clinical Endocrinology. 2005 Feb;62(2):145-55.	OUTCOMES	No HRQOL
Marfowaa GD, Friedland DR, Adams JA, Osinski K, Poetker DM. Medial orbital wall decompression: Demographics influencing surgical follow-up and complications: Impacts on follow-up and complications. American Journal of Otolaryngology. 2022 Sep 1;43(5):103578.	OUTCOMES	No HRQoL
Yi-jun WU, Gen-gui XU, Wen SH, Wen-sheng LI. Meta analysis of 99technetium-methylene bisphosphonate for treatment of thyroid-associated ophthalmopathy. Chinese Journal of Experimental Ophthalmology. 2013:282-7.	LANGUAGE	Chinese
Gao G, Dai J, Qian Y, Ma F. Meta-analysis of methylprednisolone pulse therapy for Graves' ophthalmopathy [Preview]. Clinical and Experimental Ophthalmology. 2014.	STUDY DESIGN	SLR, No HRQOL
Yong KL, Chng CL, Sie NM, Lang S, Yang M, Looi A, Choo CT, Shen S, Seah LL. Methotrexate as an adjuvant in severe thyroid eye disease: does it really work as a steroid-sparing agent?. Ophthalmic Plastic & Reconstructive Surgery. 2019 Jul 1;35(4):369-73.	OUTCOMES	No HRQOL
van Geest RJ, Sasim IV, Koppeschaar HP, Kalmann R, Stravers SN, Bijlsma WR, Mourits MP. Methylprednisolone pulse therapy for patients with moderately severe Graves' orbitopathy: a prospective, randomized, placebo-controlled study. European journal of endocrinology. 2008 Feb;158(2):229-37.	OUTCOMES	No HRQOL
Maalouf T, Vedrine PO, Coffinet L, George JL. Mid-term rhinosinusal consequences of bony orbital decompression in Graves' disease: a retrospective study. Orbit. 2008 Jan 1;27(3):169-73.	OUTCOMES	No HRQOL
Bone HC. Minimally invasive orbital decompression. Arch Ophthalmol. 2005;123:1671-5.	OUTCOMES	No HRQOL
Sales-Sanz M, Huelin FJ, Ye-Zhu C, Cruz AA, Muñoz-Negrete FJ, Rebolleda G. Müllerotomy with anterior graded Müller muscle disinsertion for Graves upper eyelid retraction: validation of surgical outcomes using	OUTCOMES	No HRQoL

Bézier curves. Graefe's Archive for Clinical and Experimental Ophthalmology. 2023 Apr;261(4):1141-9.		
Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, Perros P, Neoh C, Dickinson AJ, Lazarus JH, Lane CM. Multi-center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience. European Journal of Endocrinology. 2003 May;148(5):491-5.	OUTCOMES	No HRQOL
Hu H, Chen L, Zhou J, Chen W, Chen HH, Zhang JL, Hsu YC, Xu XQ, Wu FY. Multiparametric magnetic resonance imaging for differentiating active from inactive thyroid-associated ophthalmopathy: Added value from magnetization transfer imaging. European Journal of Radiology. 2022 Jun 1;151:110295.	OUTCOMES	No HRQoL
Boulakh L, Nygaard B, Bek T, Faber J, Heegaard S, Toft PB, Poulsen HE, Toft-Petersen AP, Hesgaard HB, Ellervik C. Nationwide incidence of thyroid eye disease and cumulative incidence of strabismus and surgical interventions in Denmark. JAMA ophthalmology. 2022 Jul 1;140(7):667-73.	OUTCOMES	No HRQOL
Lo C, Yang M, Rootman D. Natural history of inflammatory and non-inflammatory dry eye in thyroid eye disease. Orbit. 2021 Sep 3;40(5):389-93.	OUTCOMES	Correlation results only
Jia J, Dong J, Deng L. Network Meta-Analysis of Different Intravenous Glucocorticoid Regimes for the Treatment of Graves' Orbitopathy. Frontiers in Pharmacology. 2022 Apr 26;13:785757.	STUDY DESIGN	SLR, No HRQOL
Lee J, Seo W, Park J, Lim WS, Oh JY, Moon NJ, Lee JK. Neural network-based method for diagnosis and severity assessment of Graves' orbitopathy using orbital computed tomography. Scientific Reports. 2022 Jul 15;12(1):12071.	OUTCOMES	No HRQOL
Szydełko J, Litwińczuk M, Szydełko M, Matyjaszek-Matuszek B. Neutrophil-to-Lymphocyte, Monocyte-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Relation to Clinical Parameters and Smoking Status in Patients with Graves' Orbitopathy—Novel Insight into Old Tests. Journal of Clinical Medicine. 2020 Sep 26;9(10):3111.	OUTCOMES	No HRQOL
Moncayo R, Moncayo H, Ulmer H, Kainz H. New diagnostic and therapeutic approach to thyroid-associated orbitopathy based on applied kinesiology and homeopathic therapy. Journal of Alternative & Complementary Medicine. 2004 Aug 1;10(4):643-50.	OUTCOMES	No HRQOL

Di Maria C, Allen J, Dickinson J, Neoh C, Perros P. Novel thermal imaging analysis technique for detecting inflammation in thyroid eye disease. The Journal of Clinical Endocrinology & Metabolism. 2014 Dec 1;99(12):4600-6.	OUTCOMES	No HRQOL
Lingam RK, Mundada P, Lee V. Novel use of non-echo-planar diffusion weighted MRI in monitoring disease activity and treatment response in active Grave's orbitopathy: an initial observational cohort study. Orbit. 2018 Sep 3;37(5):325-30.	OUTCOMES	No HRQOL
Liao D, Ishii M, Darrach HM, Bater KL, Smith J, Joseph AW, Douglas RS, Joseph SS, Ishii LE. Objectively Measuring Observer Attention in Severe Thyroid-Associated Orbitopathy: A 3 D Study. The Laryngoscope. 2019 May;129(5):1250-4.	OUTCOMES	No HRQOL
Li D, Sun F. Observations on the efficacy of two methods for the treatment of upper eyelid retraction in thyroid-associated ophthalmopathy. BioMed Research International. 2021 Mar 19;2021.	OUTCOMES	No HRQOL
Wemeau JL, Caron P, Beckers A, Rohmer V, Orgiazzi J, Borson-Chazot F, Nocaudie M, Perimenis P, Bisot-Locard S, Bourdeix I, Dejager S. Octreotide (long-acting release formulation) treatment in patients with graves' orbitopathy: clinical results of a four-month, randomized, placebo-controlled, double-blind study. The Journal of Clinical Endocrinology & Metabolism. 2005 Feb 1;90(2):841-8.	POPULATION	Mild to moderate TED
Karhanová M, Kalitová J, Kovář R, Schovánek J, Karásek D, Čivrný J, Hübnerová P, Mlčák P, Šín M. Ocular hypertension in patients with active thyroid-associated orbitopathy: a predictor of disease severity, particularly of extraocular muscle enlargement. Graefe's Archive for Clinical and Experimental Ophthalmology. 2022 Dec;260(12):3977-84.	OUTCOMES	No HRQoL
Leite CD, Pereira TD, Chiang J, Moritz RB, Gonçalves AC, Monteiro ML. Ocular motility changes after inferomedial wall and balanced medial plus lateral wall orbital decompression in Graves' orbitopathy: a randomized prospective comparative study. Clinics. 2021 Apr 9;76.	OUTCOMES	No HRQOL
Kan EK, Kan E, Ecemiş GC, Bahadır ÇT, Çolak R. Ophthalmopathy Consciousness Level in Graves Patients: Graves Ophthalmopathy. Erciyes tıp dergisi= Erciyes Medical Journal. 2014;36(3):104.	POPULATION	Graves' disease
Baril C, Pouliot D, Molgat Y. Optic neuropathy in thyroid eye disease: results of the balanced decompression	OUTCOMES	No HRQOL

technique. Canadian Journal of Ophthalmology. 2014 Apr 1;49(2):162-6.		
De-Pablo-Gómez-de-Liaño L, Fernández-Vigo JI, Ventura-Abreu N, Troyano-Rivas J, Niño-Rueda C, Romo-López Á, Gómez-de-Liaño R. Optical Coherence Tomography Thickness Measurements of the Extraocular Rectus Muscle Tendons in Graves' Ophthalmopathy. Journal of Pediatric Ophthalmology & Strabismus. 2018 Nov 19;55(6):356-62.	STUDY DESIGN	Optical coherence tomography measurements
Lee JK, Loi MX, Wei YH, Liao SL. Optimizing esthetic outcomes in graded full-thickness anterior blepharotomy for Graves' ophthalmopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2019 Jun 4;257:1303-8.	OUTCOMES	No HRQOL
Marcocci C, Bartalena L, Panicucci M, Marconcini C, Cartei F, Cavallacci G, Laddaga M, Campobasso G, Baschieri L, Pinchera A. ORBITAL COBALT IRRADIATION COMBINED WITH RETROBULBAR OR SYSTEMIC CORTICOSTEROIDS FOR GRAVES'OPHTHALMOPATHY: A COMPARATIVE STUDY. Clinical endocrinology. 1987 Jul;27(1):33-42.	OUTCOMES	No HRQOL
Bartalena L, Marcocci C, Chiovato L, Laddaga M, Lepri G, Andreani D, Cavallacci G, Baschieri L, Pinchera A. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. The Journal of Clinical Endocrinology & Metabolism. 1983 Jun 1;56(6):1139-44.	OUTCOMES	No HRQOL
Perros P, Chandler T, Dayan CM, Dickinson AJ, Foley P, Hickey J, MacEwen CJ, Lazarus JH, McLaren J, Rose GE, Uddin JM. Orbital decompression for Graves' orbitopathy in England. Eye. 2012 Mar;26(3):434-7.	OUTCOMES	No HRQOL
Girod DA, Orcutt JC, Cummings CW. Orbital decompression for preservation of vision in Graves' ophthalmopathy. Archives of Otolaryngology–Head & Neck Surgery. 1993 Feb 1;119(2):229-33.	OUTCOMES	No HRQOL
Kingdom TT, Davies BW, Durairaj VD. Orbital decompression for the management of thyroid eye disease: an analysis of outcomes and complications. The Laryngoscope. 2015 Sep;125(9):2034-40.	OUTCOMES	No HRQOL
Weisman RA, Osguthorpe JD. Orbital decompression in Graves' disease. Archives of Otolaryngology–Head & Neck Surgery. 1994 Aug 1;120(8):831-4.	OUTCOMES	No HRQOL
LARES NA, Abdala A, Olvera-Morales O, CANALES JL. Orbital Decompression in Thyroid Eye Disease, A 5 year review in a reference center in Mexico City. Investigative	OUTCOMES	No HRQOL

Ophthalmology & Visual Science. 2016 Sep 26;57(12):709-.		
Ramesh S, Nobori A, Wang Y, Rootman D, Goldberg RA. Orbital expansion in cranial vault after minimally invasive extradural transorbital decompression for thyroid orbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2019 Jan 1;35(1):17-21.	OUTCOMES	No HRQOL
Ugradar S, Rootman DB. Orbital fat expansion in thyroid eye disease is related to age. European Journal of Ophthalmology. 2020 Sep;30(5):1004-7.	OUTCOMES	No HRQOL
Wakelkamp IM, Tan H, Saeed P, Schlingemann RO, Verbraak FD, Blank LE, Prummel MF, Wiersinga WM. Orbital irradiation for Graves' ophthalmopathy: Is it safe? A long-term follow-up study. Ophthalmology. 2004 Aug 1;111(8):1557-62.	OUTCOMES	No HRQOL
Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y, Noguchi S. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for Graves' ophthalmopathy. Endocrine journal. 2010;57(10):853-61.	OUTCOMES	No HRQOL
García-Rojas L, Adame-Ocampo G, Mendoza-Vázquez G, Alexánderson E, Tovilla-Canales JL. Orbital positron emission tomography/computed tomography (PET/CT) imaging findings in graves ophthalmopathy. BMC Research Notes. 2013 Dec;6:1-7.	OUTCOMES	No HRQOL
Bradley EA, Gower EW, Bradley DJ, Meyer DR, Cahill KV, Custer PL, Holck DE, Woog JJ. Orbital radiation for graves ophthalmopathy: a report by the American Academy of Ophthalmology. Ophthalmology. 2008 Feb 1;115(2):398-409.	STUDY DESIGN	SLR for cross-checking
Ainbinder DJ, Halligan JB. Orbital radiation therapy for Graves' ophthalmopathy. Ophthalmology. 2003;110(3):449-450.	STUDY DESIGN	Letter to the editor
Chundury RV, Weber AC, Perry JD. Orbital radiation therapy in thyroid eye disease. Ophthalmic Plastic and Reconstructive Surgery. 2016 Mar 1;32(2):83-9.	STUDY DESIGN	SLR for cross-checking
Stoynova M, Kovatcheva R, Shinkov A, Dimitrova I, Ivanova G, Angelova M, Ivanova R, Novoselski M, Nakova N, Zahariev Z, Gocheva L. Orbital radiotherapy as a first-choice treatment in selected cases of thyroid-associated ophthalmopathy. European Thyroid Journal. 2018;7(S1):70.	OUTCOMES	No extractable outcomes

Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. Journal of endocrinological investigation. 1991 Nov;14(10):853-60.	OUTCOMES	No HRQOL
Rajendram R, Bunce C, Lee RW, Morley AM. Orbital radiotherapy for adult thyroid eye disease. Cochrane Database of Systematic Reviews. 2012(7).	STUDY DESIGN	SLR for cross-checking
Rajendram R, Bunce C, Lee RW, Morley AM. Orbital radiotherapy for adult thyroid eye disease. Cochrane Database of Systematic Reviews. 2012(7).	STUDY DESIGN	Protocol
Nicosia L, Reverberi C, Agolli L, Marinelli L, De Sanctis V, Minniti G, Valeriani M, Osti MF. Orbital radiotherapy plus concomitant steroids in moderate-to-severe Graves' ophthalmopathy: good results after long-term follow-up. International journal of endocrinology and metabolism. 2019 Jan;17(1).	OUTCOMES	No HRQOL
Colao A, Lastoria S, Ferone D, Pivonello R, Macchia PE, Vassallo P, BonavolontÁ G, Muto P, Lombardi G, Fenzi G. Orbital scintigraphy with [111In-diethylenetriamine pentaacetic acid-D-phe1]-octreotide predicts the clinical response to corticosteroid therapy in patients with Graves' ophthalmopathy. The Journal of Clinical Endocrinology & Metabolism. 1998 Nov 1;83(11):3790-4.	OUTCOMES	No HRQOL
Alkawas AA, Hussein AM, Shahien EA. Orbital steroid injection versus oral steroid therapy in management of thyroid-related ophthalmopathy. Clinical & experimental ophthalmology. 2010 Oct;38(7):692-7.	OUTCOMES	No HRQOL
Leo M, Marcocci C, Pinchera A, Nardi M, Megna L, Rocchi R, Latrofa F, Altea MA, Mazzi B, Sisti E, Profilo MA. Outcome of Graves' orbitopathy after total thyroid ablation and glucocorticoid treatment: follow-up of a randomized clinical trial. The Journal of Clinical Endocrinology & Metabolism. 2012 Jan 1;97(1):E44-8.	OUTCOMES	No extractable QOL outcomes
Elbers L, Mourits M, Wiersinga W. Outcome of very long-term treatment with antithyroid drugs in Graves' hyperthyroidism associated with Graves' orbitopathy. Thyroid. 2011 Mar 1;21(3):279-83.	OUTCOMES	No HRQOL
Prevost A, Dekeister C, Caron P, Imbert P, Cavallier Z, Lauwers F, Boutault F. Outcomes of orbital decompression using surgical navigation in thyroid-associated ophthalmopathy. International Journal of	OUTCOMES	No HRQOL

Oral and Maxillofacial Surgery. 2020 Oct 1;49(10):1279-85.		
Ueda-Sakane Y, Kanamoto N, Fushimi Y, Tanaka-Mizuno S, Yasuno S, Miura M, Sone M, Yasoda A, Okada T, Togashi K, Nakao K. Overall safety and efficacy of high-dose and low-dose intravenous glucocorticoid therapy in patients with moderate-to-severe active Graves' ophthalmopathy. Endocrine Journal. 2016;63(8):703-14.	OUTCOMES	No HRQOL
Nassar MM, Dickinson AJ, Neoh C, Powell C, Buck D, Galal E, Clarke MP. Parameters predicting outcomes of strabismus surgery in the management of Graves' ophthalmopathy. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2009 Jun 1;13(3):236-40.	OUTCOMES	No HRQOL
Ramey NA, Butt Z, Burkat CN, Rose JG, Lucarelli MJ. Patient-Reported outcomes: comprehensive analysis for the oculofacial clinician. Ophthalmic Plastic & Reconstructive Surgery. 2014 Jul 1;30(4):279-89.	STUDY DESIGN	SLR for cross-checking
Ionescu IC, van Trotsenburg PA, Paridaens D, Tanck M, Mooij CF, Cagienard E, Kalmann R, Pakdel F, van der Meeren S, Saeed P. Pediatric Graves' orbitopathy: a multicentre study. Acta Ophthalmologica. 2022 Sep;100(6):e1340-8.	OUTCOMES	No HRQOL
Heesterbeek TJ, Ionescu C, Trotsenburg P, Paridaens D, Kalmann R, Hartong D, van der Meeren SW, Saeed P. Pediatric Greaves Orbitopathy, a multicenter study. InACTA OPHTHALMOLOGICA 2022 Jun 1 (Vol. 100, pp. 40-40). 111 RIVER ST, HOBOKEN 07030-5774, NJ US: WILEY.	OUTCOMES	No HRQOL
Ponto KA, Zwiener I, Al-Nawas B, Kahaly GJ, Otto AF, Karbach J, Pfeiffer N, Pitz S. Piezosurgery for orbital decompression surgery in thyroid associated orbitopathy. Journal of Cranio-Maxillofacial Surgery. 2014 Dec 1;42(8):1813-20.	OUTCOMES	No HRQOL
Sasim IV, Berendschot TT, van Isterdael C, Mourits MP. Planning health care for patients with Graves' orbitopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2008 Sep;246:1315-21.	OUTCOMES	No HRQOL
Asad R, Tewari HK, Ahuja MM, Mithal A. Postural variation of exophthalmometry in Graves' ophthalmopathy. Indian journal of ophthalmology. 1990 Oct 1;38(4):166-8.	OUTCOMES	No HRQOL
Watt T, Groenvold M, Cramon P, Feldt-Rasmussen U, Rasmussen AK, Bonnema SJ, Hegedus L, Bjorner JB. Predicting results on a generic PRO from a disease-specific: SF-36 MCS scale was predicted with high	POPULATION	No TED subgroup

agreement from the thyroid-specific ThyPRO instrument. InQUALITY OF LIFE RESEARCH 2016 Oct 1 (Vol. 25, pp. 32-32). VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS: SPRINGER.		
Fatourechi V, Bergstralh EJ, Garrity JA, Bartley GB, Beatty CW, Offord KP, Gorman CA. Predictors of response to transantral orbital decompression in severe Graves' ophthalmopathy. InMayo Clinic Proceedings 1994 Sep 1 (Vol. 69, No. 9, pp. 841-848). Elsevier.	OUTCOMES	No HRQOL
Prummel MF, Mourits MP, Berghout A, Krenning EP, van der Gaag R, Koornneef L, Wiersinga WM. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. New England Journal of Medicine. 1989 Nov 16;321(20):1353-9.	OUTCOMES	No HRQOL
Schworm HD, Boergen KP. Preliminary report: Saccade analysis in acute Graves' ophthalmopathy. Strabismus. 2000 Jan 1;8(3):179-85.	OUTCOMES	No HRQOL
Soroudi AE, Goldberg RA, McCann JD. Prevalence of asymmetric exophthalmos in Graves orbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2004 May 1;20(3):224-5.	OUTCOMES	No HRQOL
Vannucchi G, Covelli D, Campi I, Currò N, Dazzi D, Rodari M, Pepe G, Chiti A, Guastella C, Lazzaroni E, Salvi M. Prevention of orbitopathy by oral or intravenous steroid prophylaxis in short duration Graves' disease patients undergoing radioiodine ablation: a prospective randomized control trial study. Thyroid. 2019 Dec 1;29(12):1828-33.	OUTCOMES	No HRQOL
Eckstein A, Oeverhaus M, Dekowski D, Stöhr M, Merckel-Timmer E, Saeed P, Jellema HM. Primary and secondary superior rectus recessions to correct vertical deviations in Graves' orbitopathy patients. Acta Ophthalmologica. 2021 Dec;99(8):850-60.	OUTCOMES	No HRQOL
Jefferis JM, Raoof N, Burke JP. Prioritising downgaze alignment in the management of vertical strabismus for thyroid eye disease: principles and outcomes. Eye. 2020 May;34(5):906-14.	OUTCOMES	No HRQOL
Lin TY, Li N, Yeh MW, Leung AM, Rootman DB. Prognostic indicators for the development of strabismus among patients with graves' ophthalmopathy. Journal of Clinical & Translational Endocrinology. 2017 Sep 1;9:38-40.	OUTCOMES	No HRQOL
Park J, Kim J, Kim SS, Choi HY. Prognostic significance of thyroid-stimulating hormone receptor antibodies in moderate-to-severe graves' orbitopathy. Frontiers in Endocrinology. 2023 May 8;14:1153312.	OUTCOMES	No HRQOL

Bartalena L, Wiersinga WM. Proposal for standardization of primary and secondary outcomes in patients with active, moderate-to-severe Graves' orbitopathy. European Thyroid Journal. 2020 Dec 1;9(1_Suppl):3-16.	STUDY DESIGN	Narrative Review
Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, Qadeer RA, Cameron C. Proptosis and diplopia response with teprotumumab and placebo vs the recommended treatment regimen with intravenous methylprednisolone in moderate to severe thyroid eye disease: a meta-analysis and matching-adjusted indirect comparison. JAMA ophthalmology. 2022 Apr 1;140(4):328-35.	OUTCOMES	No HRQOL
Godfrey KJ, Schmuter G, Hu B, Tooley AA, Dunbar KE, Basner RC, Kazim M. Prospective correlation of risk of obstructive sleep apnea with severe clinical features of thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2021 May 1;37(3S):S58-61.	STUDY DESIGN	Correlation Study
Riedl M, Kolbe E, Kampmann E, Krämer I, Kahaly GJ. Prospectively recorded and MedDRA-coded safety data of intravenous methylprednisolone therapy in Graves' orbitopathy. Journal of endocrinological investigation. 2015 Feb;38:177-82.	OUTCOMES	No HRQOL
Draman MS, Morris D, Evans S, Haridas A, Pell J, Greenwood R, Foy C, Taylor P, Pooprasert P, Muller I, Zhang L, Lane C, Okosieme O, Ludgate M, Dayan C. Prostaglandin F2-alpha eye drops (Bimatoprost) in thyroid eye disease: a randomised controlled double blind crossover trial (Bima study). European Thyroid Journal. 2017;6(S1):25.	OUTCOMES	No HRQOL
Draman MS, Morris DS, Evans S, Haridas A, Pell J, Greenwood R, Foy C, Taylor P, Pooprasert P, Muller I, Zhang L. Prostaglandin F2-alpha eye drops (bimatoprost) in graves' orbitopathy: a randomized controlled double-masked crossover trial (BIMA Trial). Thyroid. 2019 Apr 1;29(4):563-72.	OUTCOMES	No HRQOL
Zhang Q, Shao Y, Guan Y, Liu S, Chen Q. Protective effects of standard dose prednisone combined with glutamine on Graves' ophthalmopathy after radioiodine therapy.	OUTCOMES	No HRQOL
de Deus Cardoso CC, Giordani AJ, Wolosker ÂM, Souhami L, Manso PG, Dias RS, Segreto HR, Segreto RA. Protracted hypofractionated radiotherapy for Graves' ophthalmopathy: A pilot study of clinical and radiologic response. International Journal of Radiation Oncology* Biology* Physics. 2012 Mar 1;82(3):1285-91.	OUTCOMES	No HRQOL

Tsai CC, Kau HC, Tsai HH, Kao SC, Hsu WM. Pulsatile ocular blood flow change after treatment with systemic steroid in patients with Graves' ophthalmopathy. Eye. 2006 Sep;20(9):1025-9.	OUTCOMES	No HRQOL
Higashiyama T, Iwasa M, Ohji M. Quantitative analysis of inflammation in orbital fat of thyroid-associated ophthalmopathy using MRI signal intensity. Scientific Reports. 2017 Dec 4;7(1):16874.	OUTCOMES	No HRQOL
Byun JS, Moon NJ, Lee JK. Quantitative analysis of orbital soft tissues on computed tomography to assess the activity of thyroid-associated orbitopathy. Graefe's Archive for Clinical and Experimental Ophthalmology. 2017 Feb;255:413-20.	OUTCOMES	No HRQOL
Hyer J, Murta F, Haridas A, Rose G, Ezra D. Quantitative assessment of orbital decompression surgery for thyroid eye disease using three-dimensional stereo photogrammetric imaging. Clinical and Experimental Ophthalmology. 2019 Nov;47(S1):52.	OUTCOMES	No HRQOL
Murta F, Hyer JN, Haridas A, Rose GE, Ezra DG. Quantitative assessment of orbital decompression surgery using Photogrammetric Stereoimaging. Ophthalmic Plastic and Reconstructive Surgery. 2021 Feb 15;37(5):420-3.	OUTCOMES	periorbital volume changes
Weis E, Heran MK, Jhamb A, Chan AK, Chiu JP, Hurley MC, Rootman J. Quantitative computed tomographic predictors of compressive optic neuropathy in patients with thyroid orbitopathy: a volumetric analysis. Ophthalmology. 2012 Oct 1;119(10):2174-8.	OUTCOMES	No HRQOL
Farach A, Carpenter LS. Radiation therapy for orbitopathy of thyroid eye disease. International Ophthalmology Clinics. 2016 Jan 1;56(1):81-93.	STUDY DESIGN	Narrative Review
Moleti M, Violi MA, Montanini D, Trombetta C, Di Bella B, Sturniolo G, Presti S, Alibrandi A, Campennì A, Baldari S, Trimarchi F. Radioiodine ablation of postsurgical thyroid remnants after treatment with recombinant human TSH (rhTSH) in patients with moderate-to-severe graves' orbitopathy (GO): a prospective, randomized, single-blind clinical trial. The Journal of Clinical Endocrinology & Metabolism. 2014 May 1;99(5):1783-9.	OUTCOMES	No HRQOL
Marcocci C, Bartalena L, Bogazzi F, Panicucci M, Bruno-Bossio G, Lepri A. Radioiodine treatment of Grave's hyperthyroidis, and progression of ophthalmopathy: protective effect of systemic corticosteroids. Acta endocrinologica. Supplementum (Oslo). 1989;121(2):145-8.	OUTCOMES	No HRQOL

Watanabe N, Noh JY, Kozaki A, Iwaku K, Sekiya K, Kosuga Y, Matsumoto M, Suzuki M, Yoshihara A, Ohye H, Kobayashi S, Kunii Y, Mukasa K, Sugino K, Inoue T, Ito K. Radioiodine-associated exacerbation of Graves' orbitopathy in the Japanese population: randomized prospective study. Translational Endocrinology and Metabolism. 2015;100(7):2700-2708.	OUTCOMES	No HRQOL
Watanabe N, Noh JY, Kozaki A, Iwaku K, Sekiya K, Kosuga Y, Matsumoto M, Suzuki M, Yoshihara A, Ohye H, Kobayashi S. Radioiodine-associated exacerbation of Graves' orbitopathy in the Japanese population: randomized prospective study. The Journal of Clinical Endocrinology & Metabolism. 2015 Jul 1;100(7):2700-8.	DUPLICATE	Duplicate CID 1969
Mourits MP, van Kempen-Harteveld ML, García MB, Koppeschaar HP, Tick L, Terwee CB. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. The Lancet. 2000 Apr 29;355(9214):1505-9.	OUTCOMES	No HRQOL
Seegenschmiedt MH, Keilholz L, Becker W, Gusek G, Naumann GO, Wolf F, Hensen J, Sauer R. Radiotherapy for severe, progressive thyroid-associated ophthalmopathy: long-term results with comparison of scoring systems. Frontiers of Radiation Therapy and Oncology. 1997 Jan 1;30:218-28.	OUTCOMES	No HRQOL
Grassi P, Strianese D, Piscopo R, Pacelli R, Bonavolonta G. Radiotherapy for the treatment of thyroid eye disease—a prospective comparison: Is orbital radiotherapy a suitable alternative to steroids?. Irish Journal of Medical Science (1971-). 2017 Aug;186:647-52.	OUTCOMES	No HRQOL
Ferris JD, Dawson EL, Plowman N, Adams GG, Fells P, Lee JP. Radiotherapy in thyroid eye disease: the effect on the field of binocular single vision. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2002 Apr 1;6(2):71-6.	OUTCOMES	No HRQOL
Prummel MF, Berghout A, Wiersinga WM, Mourits MP, Koornneef L, Blank L. Randomised double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. The Lancet. 1993 Oct 16;342(8877):949-54.	OUTCOMES	No HRQOL
Muller I, Curro N, Campi I, Favero V, Dazzi B, Montacchini B, Bagnaresi F, Vannucchi G, Dazzi D, Arosio M, Salvi M. Randomized controlled trial of belimumab and methylprednisolone in active moderate severe graves' orbitopathy. Thyroid. 2021;31(S1):A9.	OUTCOMES	No HRQOL

Salvi M, Muller I, Curro N, Bagnaresi F, Maioli S, Dazzi B, Montacchini B, Covelli D, Campi I, Vannucchi G, Dazzi D, Arosio M. RANDOMIZED CONTROLLED TRIAL OF BELIMUMAB AND METHYLPREDNISOLONE IN ACTIVE MODERATESEVERE GRAVES' ORBITOPATHY: EFFECTS ON DISEASE INACTIVATION AND ON TSH-RECEPTOR STIMULATING ANTIBODIES. Thyroid. 2022;32:A49.	OUTCOMES	No HRQOL
Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. The Journal of Clinical Endocrinology & Metabolism. 2015 Feb 1;100(2):432-41.	DUPLICATE	Duplicate CID 593
Kahaly G, Pitz S, Müller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. Clinical & Experimental Immunology. 1996 Nov;106(2):197-202.	OUTCOMES	No HRQOL
Stan MN, Garrity JA, Bradley EA, Woog JJ, Bahn MM, Brennan MD, Bryant SC, Achenbach SJ, Bahn RS. Randomized, double-blind, placebo-controlled trial of long-acting release octreotide for treatment of Graves' ophthalmopathy. The Journal of Clinical Endocrinology & Metabolism. 2006 Dec 1;91(12):4817-24.	OUTCOMES	No HRQOL
Quah Qin Xian N, Alnahrawy A, Akshikar R, Lee V. Real-world efficacy and safety of mycophenolate mofetil in active moderate-to-sight-threatening thyroid eye disease. Clinical Ophthalmology. 2021 May 10:1921-32.	OUTCOMES	No HRQOL
Abramoff MD, Kalmann R, de Graaf ME, Stilma JS, Mourits MP. Rectus extraocular muscle paths and decompression surgery for Graves orbitopathy: mechanism of motility disturbances. Investigative ophthalmology & visual science. 2002 Feb 1;43(2):300-7.	OUTCOMES	No HRQOL
Shams PN, Ma R, Pickles T, Rootman J, Dolman PJ. Reduced risk of compressive optic neuropathy using orbital radiotherapy in patients with active thyroid eye disease. American Journal of Ophthalmology. 2014 Jun 1;157(6):1299-305.	OUTCOMES	No HRQOL
Oeverhaus M, Witteler T, Lax H, Esser J, Eckstein A. Reducing Diplopia in patients with graves orbitopathy–efficacy of intravenous glucocorticoids with and without combination of orbital radiotherapy. Investigative Ophthalmology & Visual Science. 2017 Jun 23;58(8):5153-.	OUTCOMES	No HRQOL
Oh SR, Tung JD, Priel A, Levi L, Granet DB, Korn BS, Kikkawa DO. Reduction of orbital inflammation following decompression for thyroid-related orbitopathy. BioMed Research International. 2013 Jun 18;2013.	OUTCOMES	No HRQOL

Chang TC, Huang KM, Hsiao YL, Tzeng SS, Kao SC. Relationships of orbital computed tomographic findings and activity scores to the prognosis of corticosteroid therapy in patients with Graves' ophthalmopathy. Acta Ophthalmologica Scandinavica. 1997 Jun;75(3):301-4.	OUTCOMES	No HRQOL
Khong JJ, Goldstein RF, Schneider H, Pope J, Sanders KM, Burdon K, Craig JE, Ebeling PR. Relative selenium deficiency in Graves' orbitopathy.	OUTCOMES	No HRQOL
Dolman PJ, Cahill K, Czyz CN, Douglas RS, Elner VM, Feldon S, Kazim M, Lucarelli M, Sivak-Collcott J, Stacey AW, Strianese D. Reliability of estimating ductions in thyroid eye disease: an International Thyroid Eye Disease Society multicenter study. Ophthalmology. 2012 Feb 1;119(2):382-9.	OUTCOMES	No HRQOL
McAlister CN, Oestreicher JH. Repeat posterior lamellar grafting for recalcitrant lower eyelid retraction is effective. Orbit. 2012 Oct 1;31(5):307-12.	OUTCOMES	No HRQOL
Xu D, Liu Y, Xu H, Li H. Repeated triamcinolone acetonide injection in the treatment of upper-lid retraction in patients with thyroid-associated ophthalmopathy. Canadian Journal of Ophthalmology. 2012 Feb 1;47(1):34-41.	OUTCOMES	No HRQOL
Wu CH, Chang TC, Liao SL. Results and predictability of fat-removal orbital decompression for disfiguring graves exophthalmos in an Asian patient population. American journal of ophthalmology. 2008 Apr 1;145(4):755-9.	OUTCOMES	No HRQOL
Linnet J, Hegedüs L, Bjerre P. Results of a neurosurgical two-wall orbital decompression in the treatment of severe thyroid associated ophthalmopathy. Acta ophthalmologica Scandinavica. 2001 Feb;79(1):49-52.	OUTCOMES	No HRQOL
Roncevic R, Savkovic Z, Roncevic D. Results of diplopia and strabismus in patients with severe thyroid ophthalmopathy after orbital decompression. Indian Journal of Ophthalmology. 2014 Mar;62(3):268.	OUTCOMES	No HRQOL
Pinas D, OB De Keizer R, Wubbels RJ, van den Bosch WA, Paridaens D. Results of surgical correction of upper eyelid retraction in Graves' Orbitopathy. Acta Ophthalmologica. 2021 Jun;99(4):e608-13.	OUTCOMES	No HRQOL
Tallstedt L, Papatziamos G, Lundblad L, Änggård A. Results of transantral orbital decompression in patients with thyroid-associated ophthalmopathy. Acta Ophthalmologica Scandinavica. 2000 Apr;78(2):206-10.	OUTCOMES	No HRQOL
Robertson DM, Buettner H, Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW. Retinal microvascular abnormalities in patients treated with external radiation	OUTCOMES	No HRQOL

for Graves ophthalmopathy. Archives of ophthalmology. 2003 May 1;121(5):652-7.		
Ye L, Zhou SS, Yang WL, Bao J, Jiang N, Min YL, Yuan Q, Tan G, Shen M, Shao Y. Retinal microvasculature alteration in active thyroid-associated ophthalmopathy. Endocrine Practice. 2018 Jul 1;24(7):658-67.	OUTCOMES	No HRQOL
Gerling J, Kommerell G, Henne K, Laubenberger J, Schulte-Mönting J, Fells P, TAO Multicenter Study Group. Retrobulbar irradiation for thyroid-associated orbitopathy: double-blind comparison between 2.4 and 16 Gy. International Journal of Radiation Oncology* Biology* Physics. 2003 Jan 1;55(1):182-9.	OUTCOMES	No HRQOL
Gerling J, Kommerell G, Henne K. Retrobulbar irradiation in Graves' ophthalmopathy: Double blind comparison between 2.4 and 16 Gy. InINVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 2000 Mar 15 (Vol. 41, No. 4, pp. S416-S416). 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 US: ASSOC RESEARCH VISION OPHTHALMOLOGY INC.	OUTCOMES	No HRQoL
Pérez-López M, Sales-Sanz M, Rebolleda G, Casas-Llera P, González-Gordaliza C, Jarrín E, Munoz-Negrete FJ. Retrobulbar ocular blood flow changes after orbital decompression in Graves' ophthalmopathy measured by color Doppler imaging. Investigative ophthalmology & visual science. 2011 Jul 1;52(8):5612-7.	OUTCOMES	No HRQOL
Schovanek J, Cibickova L, Karhanova M, Kovarova D, Frysak Z, Karasek D. Retrospective analysis of patients with graves orbitopathy treated by pulses of methylprednisolone, with a focus on adverse events. Endocrine Practice. 2018 Jul 1;24(7):652-7.	OUTCOMES	No HRQOL
Leung MK, Platt MP, Metson R. Revision endoscopic orbital decompression in the management of Graves' orbitopathy. Otolaryngology—Head and Neck Surgery. 2009 Jul;141(1):46-51.	OUTCOMES	No HRQOL
Pham TA, Simmons B, Potter NJ, Al-Qurayshi Z, Carter KD, Graham SM. Revision orbital decompression for thyroid eye disease. American Journal of Otolaryngology. 2022 Jan 1;43(1):103196.	OUTCOMES	No HRQOL
Lee JH, Lee SY, Yoon JS. Risk factors associated with the severity of thyroid-associated orbitopathy in Korean patients. Korean Journal of Ophthalmology. 2010 Oct 1;24(5):267-73.	OUTCOMES	No HRQOL
Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, Ebeling PR. Risk factors for Graves' orbitopathy; the Australian thyroid-associated orbitopathy research	OUTCOMES	No HRQOL

(ATOR) study. The Journal of Clinical Endocrinology & Metabolism. 2016 Jul 1;101(7):2711-20.		
Yokoyama N, Nagataki S, Uetani M, Ashizawa K, Eguchi K. Role of magnetic resonance imaging in the assessment of disease activity in thyroid-associated ophthalmopathy. Thyroid. 2002 Mar 1;12(3):223-7.	OUTCOMES	No HRQOL
HIROMATSU Y, KOJIMA K, ISHISAKA N, TANAKA K, SATO M, NONAKA K, NISHIMURA H, NISHIDA H. Role of magnetic resonance imaging in thyroid-associated ophthalmopathy: its predictive value for therapeutic outcome of immunosuppressive therapy. Thyroid. 1992;2(4):299-305.	OUTCOMES	No HRQOL
Ventura M, Melo M, Carrilho F. Selenium and thyroid disease: from pathophysiology to treatment. International journal of endocrinology. 2017 Jan 31;2017.	STUDY DESIGN	SLR for cross-checking
Nexø MA, Watt T, Bonnema SJ, Hegedüs L, Rasmussen ÅK, Feldt-Rasmussen U, Bjørner JB. Self-reported work ability varies according to type of thyroid disease. In38th Annual Meeting of the European Thyroid Association 2014 2014.	POPULATION	No TED subgroup
Mayer E, Herdman G, Burnett C, Kabala J, Goddard P, Potts MJ. Serial STIR magnetic resonance imaging correlates with clinical score of activity in thyroid eye disease. Eye. 2001 May;15(3):313-8.	OUTCOMES	No HRQOL
Owji N, Moradi F, Khalili MR, Jahanbani-Ardakani H. Serum Selenium Levels in Patients With Graves Disease With or Without Thyroid Ophthalmopathy. Endocrine Practice. 2022 Dec 1;28(12):1216-20.	OUTCOMES	Serum Selenium Levels
Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, Craig JE, Ebeling PR. Serum selenium status in G raves' disease with and without orbitopathy: a case–control study. Clinical endocrinology. 2014 Jun;80(6):905-10.	OUTCOMES	No HRQOL
Heisel CJ, Riddering AL, Andrews CA, Kahana A. Serum vitamin D deficiency is an independent risk factor for thyroid eye disease. Ophthalmic plastic and reconstructive surgery. 2020 Jan 1;36(1):17-20.	OUTCOMES	No HRQOL
Rath S, Pattnaik M, Tripathy D, Mohapatra S, Panigrahy B, Ali MH. Sight-threatening thyroid eye disease: role of diabetes mellitus and interaction with other risk factors. Ophthalmic Plastic & Reconstructive Surgery. 2021 Jul 1;37(4):352-60.	STUDY DESIGN	Interaction Study
Lee NG, Habib L, Hall J, Freitag SK. Simultaneous ipsilateral transconjunctival repair of upper and lower	OUTCOMES	No HRQOL

eyelid retraction in thyroid-associated ophthalmopathy. Orbit. 2019 Mar 4;38(2):124-9.		
Simon GJ, Mansury AM, Schwarcz RM, Lee S, McCann JD, Goldberg RA. Simultaneous orbital decompression and correction of upper eyelid retraction versus staged procedures in thyroid-related orbitopathy. Ophthalmology. 2005 May 1;112(5):923-32.	OUTCOMES	No HRQOL
Chang TC, Liao SL. Slow-release lanreotide in Graves' ophthalmopathy: a double-blind randomized, placebo-controlled clinical trial. Journal of endocrinological investigation. 2006 May;29:413-22.	OUTCOMES	No HRQOL
Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. Jama. 1993 Jan 27;269(4):479-82.	OUTCOMES	No HRQOL
Rajendram R, Bunce C, Adams GG, Dayan CM, Rose GE. Smoking and strabismus surgery in patients with thyroid eye disease. Ophthalmology. 2011 Dec 1;118(12):2493-7.	OUTCOMES	No HRQOL
Xing L, Ye L, Zhu W, Shen L, Huang F, Jiao Q, Zhou X, Wang S, Wang W, Ning G. Smoking was associated with poor response to intravenous steroids therapy in Graves' ophthalmopathy. British Journal of Ophthalmology. 2015 Jun 10.	OUTCOMES	No HRQOL
Simon GJ, Syed AM, Lee S, Wang DY, Schwarcz RM, McCann JD, Goldberg RA. Strabismus after deep lateral wall orbital decompression in thyroid-related orbitopathy patients using automated hess screen. Ophthalmology. 2006 Jun 1;113(6):1050-5.	OUTCOMES	No HRQOL
Fabian ID, Rosen N, Ben Simon GJ. Strabismus after inferior-medial wall orbital decompression in thyroid-related orbitopathy. Current Eye Research. 2013 Feb 1;38(1):204-9.	OUTCOMES	No HRQOL
Chaganti S, Nelson K, Mundy K, Luo Y, Harrigan RL, Damon S, Fabbri D, Mawn L, Landman B. Structural functional associations of the orbit in thyroid eye disease: Kalman filters to track extraocular rectal muscles. InMedical Imaging 2016: Image Processing 2016 Mar 21 (Vol. 9784, pp. 391-397). SPIE.	OUTCOMES	No HRQOL
Lee JM, Lee H, Park M, Baek S. Subconjunctival injection of triamcinolone for the treatment of upper lid retraction associated with thyroid eye disease. Journal of Craniofacial Surgery. 2012 Nov 1;23(6):1755-8.	OUTCOMES	No HRQOL
Kashkouli MB, Alemzadeh SA, Aghaei H, Pakdel F, Abdolalizadeh P, Ghazizadeh M, Moradpasandi F. Subjective versus objective dry eye disease in patients with moderate-severe thyroid eye disease. The ocular surface. 2018 Oct 1;16(4):458-62.	OUTCOMES	No HRQOL

Wakelkamp IM, Baldeschi L, Saeed P, Mourits M, Prummel MF, Wiersinga WM. Surgical or medical decompression as a first-line treatment of optic neuropathy in Graves' ophthalmopathy? A randomized controlled trial. Clinical endocrinology. 2005 Sep;63(3):323-8.	OUTCOMES	No HRQOL
Boboridis KG, Bunce C. Surgical orbital decompression for thyroid eye disease. Cochrane Database of Systematic Reviews. 2011(12).	STUDY DESIGN	SLR for cross-checking
Boboridis KG, Bunce C. Surgical orbital decompression for thyroid eye disease. Cochrane Database of Systematic Reviews. 2011(12).	DUPLICATE	CID 760
Korkmaz S, Konuk O. Surgical treatment of dysthyroid optic neuropathy: long-term visual outcomes with comparison of 2-wall versus 3-wall orbital decompression. Current Eye Research. 2016 Feb 1;41(2):159-64.	OUTCOMES	No HRQOL
Laurberg P, Berman DC, Andersen S, Bülow Pedersen I. Sustained control of Graves' hyperthyroidism during long-term low-dose antithyroid drug therapy of patients with severe Graves' orbitopathy. Thyroid. 2011 Sep 1;21(9):951-6.	OUTCOMES	No HRQOL
Zhai L, Wang Q, Liu P, Luo B, Yuan G, Zhang J. T2 mapping with and without fat-suppression to predict treatment response to intravenous glucocorticoid therapy for thyroid-associated ophthalmopathy. Korean Journal of Radiology. 2022 Jun;23(6):664.	OUTCOMES	No HRQOL
Chang EL, Piva AP. Temporal fossa orbital decompression for treatment of disfiguring thyroid-related orbitopathy. Ophthalmology. 2008 Sep 1;115(9):1613-9.	OUTCOMES	No HRQOL
Ozzello DJ, Dallalzadeh LO, Liu CY. Teprotumumab for chronic thyroid eye disease. Orbit. 2022 Sep 3;41(5):539-46.	OUTCOMES	No HRQOL
Bartalena L, Marinò M, Marcocci C, Tanda ML. Teprotumumab for Graves' orbitopathy and ototoxicity: moving problems from eyes to ears?. Journal of Endocrinological Investigation. 2022 Jul;45(7):1455-7.	STUDY DESIGN	Narrative Review
Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. The Lancet Diabetes & Endocrinology. 2021 Jun 1;9(6):360-72.	STUDY DESIGN	Pooled analysis for cross-checking

Wang Y, Mester T, Ugradar S, Douglas R. Teprotumumab for the treatment of thyroid eye disease: clinical experience from expanded access program (EAP). Investigative Ophthalmology & Visual Science. 2021 Jun 21;62(8):3339-.	OUTCOMES	No HRQOL
Ugradar S, Wang Y, Mester T, Kahaly GJ, Douglas RS. Teprotumumab for thyroid eye disease: early response is not required for benefit. Eye. 2022 Jul;36(7):1403-8.	OUTCOMES	No HRQOL
Jain AP, Gellada N, Ugradar S, Kumar A, Kahaly G, Douglas R. Teprotumumab reduces extraocular muscle and orbital fat volume in thyroid eye disease. British Journal of Ophthalmology. 2020 Nov 10.	OUTCOMES	No HRQOL
Kahaly G, Sile S, Thompson EH, Vescio T, Perdok R, Sherman JW, Smith TJ, Douglas RS. Teprotumumab, a novel biologic for active thyroid eye disease. InARTHRITIS & RHEUMATOLOGY 2019 Oct 1 (Vol. 71). 111 RIVER ST, HOBOKEN 07030-5774, NJ US: WILEY.	STUDY DESIGN	Pooled analysis for cross-checking
Piantanida E, Bartalena L. Teprotumumab: a new avenue for the management of moderate-to-severe and active Graves' orbitopathy?. Journal of endocrinological investigation. 2017 Aug;40:885-7.	STUDY DESIGN	Narrative Review
Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL, Earle JD, Forbes GS, Kline RW, Buettner H, Robertson DM. The aftermath of orbital radiotherapy for graves' ophthalmopathy. Ophthalmology. 2002 Nov 1;109(11):2100-7.	POPULATION	Mild to moderate TED
Huh HD, Kim JH, Kim SJ, Yoo JM, Seo SW. The change of lacrimal gland volume in Korean patients with thyroid-associated ophthalmopathy. Korean Journal of Ophthalmology. 2016 Oct 1;30(5):319-25.	OUTCOMES	No HRQOL
Zu Horste MM, Pateronis K, Walz MK, Alesina P, Mann K, Schott M, Esser J, Eckstein AK. The effect of early thyroidectomy on the course of active Graves' orbitopathy (GO): a retrospective case study. Hormone and Metabolic Research. 2016 Jul;48(07):433-9.	OUTCOMES	No HRQOL
Paridaens D, Van den Bosch WA, Van der Loos TL, Krenning EP, Van Hagen PM. The effect of etanercept on Graves' ophthalmopathy: a pilot study. Eye. 2005 Dec;19(12):1286-9.	OUTCOMES	No HRQOL
Li X, Bai X, Liu Z, Cheng M, Li J, Tan N, Yuan H. The effect of inferior rectus muscle thickening on intraocular pressure in thyroid-associated ophthalmopathy. Journal of Ophthalmology. 2021 Jan 30;2021.	OUTCOMES	No HRQOL
Prummel MF, Wiersinga WM, Oosting H, Endert E. The effect of long-term prednisone treatment on growth	OUTCOMES	No HRQOL

hormone and insulin-like growth factor-I. Journal of endocrinological investigation. 1996 Oct;19:620-3.		
CORIN S, GOEL A. THE EFFECT OF NEOSYNEPHRINE ON LID RETRACTION IN PATIENTS WITH THYROID EYE DISEASE. InINVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 1991 Mar 15 (Vol. 32, No. 4, pp. 1088-1088). 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106: LIPPINCOTT-RAVEN PUBL.	OUTCOMES	No HRQoL
Woo T, Li C, Ganesananthan S, Rajendram R, Uddin J, Lee R, Dayan C, Taylor P. 178 The Effect of Ophthalmic Surgery for Graves' Orbitopathy on Quality of Life–A Systematic Review and Meta-Analysis. British Journal of Surgery. 2022 Sep 1;109(Supplement_6):znac268-004.	STUDY DESIGN	SLR, no references listed
Woo T, Li C, Ganesananthan S, Rajendram R, Uddin J, Lee RW, Dayan C, Taylor P. The effect of ophthalmic surgery for Graves' orbitopathy on quality of life: A systematic review and meta-analysis. Thyroid. 2022 Feb 1;32(2):177-87.	STUDY DESIGN	SLR for cross-checking
Cho RI, Elner VM, Nelson CC, Frueh BR. The effect of orbital decompression surgery on lid retraction in thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2011 Nov 1;27(6):436-8.	OUTCOMES	No HRQOL
Van Ruyven RL, Van Den Bosch WA, Mulder PG, Eijkenboom WM, Paridaens AD. The effect of retrobulbar irradiation on exophthalmos, ductions and soft tissue signs in Graves' ophthalmopathy: a retrospective analysis of 90 cases. Eye. 2000 Sep;14(5):761-4.	OUTCOMES	No HRQOL
Kung AW, Michon J, Tai KS, Chan FL. The effect of somaTotalatin versus corticosteroid in the treatment of Graves' ophthalmopathy. Thyroid. 1996 Oct;6(5):381-4.	OUTCOMES	No HRQOL
Kim JW, Lee KH, Woo YJ, Kim J, Keum KC, Yoon JS. The effect of systemic steroids and orbital radiation for active Graves orbitopathy on postdecompression extraocular muscle volume. American Journal of Ophthalmology. 2016 Nov 1;171:11-7.	OUTCOMES	No HRQOL
Michon J, Tso M, Kung A, Tai K, Chan F. The effects of somaTotalatin versus corticosteroiods in graves' ophthalmopathy. Investigative Ophthalmology & Visual Science. 1998;39.	OUTCOMES	No HRQoL
Li J, Xiao Z, Hu X, Li Y, Zhang X, Zhang S, Gong W, Zhao J, Ye X. The efficacy of rituximab combined with 131I for ophthalmic outcomes of Graves' ophthalmopathy patients. Pharmacology. 2017 Jan 4;99(3-4):144-52.	OUTCOMES	No HRQOL
Medghalchi A, Akbari M, Alizadeh Y, Moghadam RS. The epidemiological characteristics of patients with thyroid	OUTCOMES	No HRQOL

eye disease in a referral center in northern Iran. Journal of current ophthalmology. 2018 Dec 1;30(4):353-8.		
Szabados L, Nagy EV, Ujhelyi B, Urbancsek H, Varga J, Nagy E, Galuska L. The impact of 99mTc-DTPA orbital SPECT in patient selection for external radiation therapy in Graves' ophthalmopathy. Nuclear Medicine Communications. 2013 Feb 1;34(2):108-12.	OUTCOMES	No HRQOL
Jensen AL, Harder I. The impact of bodily change on social behaviour in patients with Thyroid-Associated Ophthalmopathy. Scandinavian Journal of Caring Sciences. 2011 Jun;25(2):341-9.	OUTCOMES	No extractable outcomes, qualitative interviews (PROs)
Estcourt S, Vaidya B, Quinn A, Shepherd M. The impact of thyroid eye disease upon patients' wellbeing: a qualitative analysis. Clinical endocrinology. 2008 Apr;68(4):635-9.	OUTCOMES	No extractable outcomes, qualitative interviews (PROs)
Ciric J, Zarkovic M, Nedeljkovic-Beleslin B, Stojiljkovic M, Stojkovic M, Savic S. The implementation of nurse specialist in the motivation for smoking cessation in graves orbitopathy. European Thyroid Journal. 2017 Aug;6(S1):97.	OUTCOMES	No HRQOL
Ambroziak U, Bluszcz G, Bednarczuk T, Miśkiewicz P. The influence of Graves' orbitopathy treatment with intravenous glucocorticoids on adrenal function. Endokrynologia Polska. 2017;68(4):430-3.	OUTCOMES	No HRQOL
Termote K, Decallonne B, Mombaerts I. The influence of prior hyperthyroidism on euthyroid Graves' Ophthalmopathy. Journal of Ophthalmology. 2014 Jan 1;2014.	OUTCOMES	No HRQOL
Kendler DL, Lippa J, Rootman J. The initial clinical characteristics of Graves' orbitopathy vary with age and sex. Archives of ophthalmology. 1993 Feb 1;111(2):197-201.	OUTCOMES	No HRQOL
Ye Y, Hu F, Ji Y, Wang R, Zhu K, Kong Q. The outcomes of endoscopic orbital decompression combined with fat decompression for thyroid-associated ophthalmopathy. BMC ophthalmology. 2023 Dec;23(1):1-3.	OUTCOMES	No HRQOL
Estcourt S, Hickey J, Dayan C, Vaidya B. The patient experience of services for thyroid eye disease in the United Kingdom: a questionnaire survey. InEndocrine Abstracts 2009 Mar 1 (Vol. 19). Bioscientifica.	OUTCOMES	Treatment satisfaction
Estcourt S, Hickey J, Perros P, Dayan C, Vaidya B. The patient experience of services for thyroid eye disease in the United Kingdom: results of a nationwide survey. European Journal of Endocrinology. 2009 Sep;161(3):483-7.	OUTCOMES	Treatment satisfaction

Kavoussi SC, Giacometti JN, Servat JJ, Levin F. The relationship between sex and symmetry in thyroid eye disease. Clinical Ophthalmology. 2014 Jul 10:1295-300.	OUTCOMES	No HRQOL
Egle UT, Kahaly GJ, Petrak F, Hardt J, Batke J, Best J, Rothenbacher M. The relevance of physical and psychosocial factors for the quality of life in patients with thyroid-associated orbitopathy (TAO). Experimental and Clinical Endocrinology & Diabetes. 1999;107(S 05):S168-71.	OUTCOMES	No extractable outcomes (figure 1 needs to be digitized)
Galuska L, Szabados L, Leoevey A, Ujhelyi B, Garai I, Varga J, Nagy E. The role of 99mTc-DTPA orbital SPECT in the management of patients with Graves' orbitopathy. InEUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING 2012 Oct 1 (Vol. 39, pp. S482-S483). 233 SPRING ST, NEW YORK, NY 10013 US: SPRINGER.	OUTCOMES	No HRQOL
Galuska L, Szabados L, Leovey A, Ujhelyi B, Garai I, Varga J, Nagy EV. The role of 99MTC-DTPA SPECT in staging and follow up of disease activity before and after orbital irradiation in graves' orbitopathy. European Thyroid Journal. 2011 Sept:114.	OUTCOMES	No HRQOL
Liao SL, Wei YH, Chuang AY. The role of rectus muscle myectomy in the management of large-angle strabismus for Graves' ophthalmopathy. Eye. 2017 Jul;31(7):1027-33.	OUTCOMES	No HRQOL
Prendiville P, Chopra M, Gauderman WJ, Feldon SE. The role of restricted motility in determining outcomes for vertical strabismus surgery in Graves' ophthalmopathy. Ophthalmology. 2000 Mar 1;107(3):545-9.	OUTCOMES	No HRQOL
Ortapamuk H, Hoşal B, Naldöken S. The role of Tc-99m polyclonal human immunoglobulin G scintigraphy in Graves' ophthalmopathy. Annals of nuclear medicine. 2002 Nov;16:461-5.	OUTCOMES	No HRQOL
Wei RL, Cheng JW, Cai JP. The use of orbital radiotherapy for Graves' ophthalmopathy: quantitative review of the evidence. Ophthalmologica. 2007 Dec 1;222(1):27-31.	STUDY DESIGN	SLR for cross-checking
Đorić I, Žarković M, Radojičić Z, Repac N, Janićijević A, Rotim K, Tasić G, Rasulić L. The value of multidetector computed tomography of orbits in globe protrusion in comparison to Hertel exophthalmometry. Acta clinica Croatica. 2017 Mar 1;56(1.):21-7.	OUTCOMES	No HRQOL
Currò N, Covelli D, Vannucchi G, Campi I, Pirola G, Simonetta S, Dazzi D, Guastella C, Pignataro L, Beck-Peccoz P, Ratiglia R. Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. Thyroid. 2014 May 1;24(5):897-905.	OUTCOMES	No HRQOL

Rymuza J, Popow M, Żurecka Z, Przedlacki J, Bednarczuk T, Miśkiewicz P. Therapy of moderate-to-severe Graves' orbitopathy with intravenous methylprednisolone pulses is not associated with loss of bone mineral density. Endocrine. 2019 May 15;64:308-15.	OUTCOMES	No HRQOL
Campi I, Vannucchi G, Muller I, Lazzaroni E, Currò N, Dainese M, Montacchini B, Covelli D, Guastella C, Pignataro L, Fugazzola L. Therapy with different dose regimens of rituximab in patients with active moderate-to-severe Graves' orbitopathy. Frontiers in Endocrinology. 2022 Jan 25;12:790246.	STUDY DESIGN	Pooled analysis from 3 clinical studies Costs of treatment reported
Hou K, Ai T, Hu WK, Luo B, Wu YP, Liu R. Three dimensional orbital magnetic resonance T2-mapping in the evaluation of patients with Graves' ophthalmopathy. Current Medical Science. 2017 Dec;37(6):938-42.	OUTCOMES	No HRQOL
Krause M, Kruber D, Hümpfner-Hierl H, Sterker I, Hierl T. Three-dimensional changes of scleral show after surgical treatment of endocrine orbitopathy. Journal of Cranio-Maxillofacial Surgery. 2018 Jan 1;46(1):44-9.	OUTCOMES	No HRQOL
Träisk F, Tallstedt L. Thyroid associated ophthalmopathy: botulinum toxin A in the treatment of upper eyelid retraction–a pilot study. Acta ophthalmologica Scandinavica. 2001 Dec;79(6):585-8.	OUTCOMES	No extractable outcome (PROs - figure 1)
Uslar V, Becker C, Weyhe D, Tabriz N. Thyroid disease-specific quality of life questionnaires-A systematic review. Endocrinology, Diabetes & Metabolism. 2022 Sep;5(5):e357.	STUDY DESIGN	SLR for cross-checking
Wang Y, Mettu P, Broadbent T, Radke P, Firl K, Shepherd III JB, Couch SM, Nguyen A, Henderson AD, McCulley T, McClelland CM. Thyroid eye disease presenting with superior rectus/levator complex enlargement. Orbit. 2020 Jan 2;39(1):5-12.	OUTCOMES	No HRQOL
Hyman L, Ramesh S, Watson A, Sharpe J, Das AV, Moster M, Alessi K, Peskin E, Naik MN. Thyroid Eye Disease: A US (Wills Eye Hospital) and India (LV Prasad) Comparison. Investigative Ophthalmology & Visual Science. 2022 Jun 1;63(7):4003-A0345.	OUTCOMES	No HRQOL
Bhatti MT, Dutton JJ. Thyroid eye disease: therapy in the active phase. Journal of Neuro-Ophthalmology. 2014 Jun 1;34(2):186-97.	STUDY DESIGN	SLR for cross-checking
Kahaly GJ, Diana T, Glang J, Kanitz M, Pitz S, König J. Thyroid stimulating antibodies are highly prevalent in Hashimoto's thyroiditis and associated orbitopathy. The Journal of Clinical Endocrinology & Metabolism. 2016 May 1;101(5):1998-2004.	OUTCOMES	No HRQOL

Kahaly GJ, Diana T, Kanitz M, Pitz S, Konig J. Thyroid stimulating autoantibodies predict orbitopathy in hashimoto's thyroiditis. Endocrine Reviews. 2016;37(2S1).	OUTCOMES	No HRQOL
Kampmann E, Diana T, Kanitz M, Kahaly GJ. Thyroid stimulating but not blocking autoantibodies are highly prevalent in active/severe thyroid-associated orbitopathy-a prospective study. Thyroid. 2014 Oct;24(S1):A10.	OUTCOMES	No HRQOL
Kampmann E, Diana T, Kanitz M, Hoppe D, Kahaly GJ. Thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy: a prospective study. International journal of endocrinology. 2015 Oct;2015.	OUTCOMES	No HRQOL
Liu ZW, Masterson L, Fish B, Jani P, Chatterjee K. Thyroid surgery for Graves' disease and Graves' ophthalmopathy. Cochrane Database of Systematic Reviews. 2015(11).	STUDY DESIGN	SLR for cross-checking
Kashkouli MB, Jam S, Sabzvari D, Ketabi N, Azarinia S, SeyedAlinaghi S, Mofid A. Thyroid-associated ophthalmopathy in Iranian patients. Acta Medica Iranica. 2011:612-8.	OUTCOMES	No HRQOL
Sun B, Zhang Z, Ji X. Thyroid-associated ophthalmopathy in patients with thyroid carcinoma. Investigative Ophthalmology & Visual Science. 2019 Jul 22;60(9):6207-.	OUTCOMES	No extractable outcomes, qualitative QOL data
Borel M, Grunenwald S, Imbert P, Dekeister C, Caron P. Thyroid-associated orbitopathy and quality of life: correlation of GO-QOLwith clinical activity score and severity in 101 patients. InEndocrine Abstracts 2019 May 1 (Vol. 63). Bioscientifica.	OUTCOMES	Correlation results only
Nakano M, Konishi H, Koshiba M. Thyroid-Stimulating antibody/thyroid-stimulating hormone receptor antibody ratio as a sensitive screening test for active Graves' orbitopathy. Endocrine Practice. 2022 Oct 1;28(10):1050-4.	OUTCOMES	No HRQOL
Azzam SH, Kang S, Salvi M, Ezra DG. Tocilizumab for thyroid eye disease. Cochrane Database of Systematic Reviews. 2018(11).	STUDY DESIGN	SLR for cross-checking
Rahman I, Cannon PS, Sadiq SA. Tonopen versus Goldmann applanation tonometry for detecting restrictive thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2010 Jan 1;26(1):36-8.	OUTCOMES	No HRQOL
Bouzas E, Karadimas P, Kotsiras I, Mastorakos G. Topical cyclosporin 0.05% ophthalmic emulsion in patients with dysthyroid ophthalmopathy. Investigative	POPULATION	Mild to moderate TED

Ophthalmology & Visual Science. 2005 May 1;46(13):2659-.		
Altiparmak UE, Acar DE, Ozer PA, Emec SD, Kasim R, Ustun H, Duman S. Topical cyclosporine A for the dry eye findings of thyroid orbitopathy patients. Eye. 2010 Jun;24(6):1044-50.	OUTCOMES	No HRQOL
Gumińska M, Goś R, Śmigielski J, Nowak MS. Topical treatment of elevated intraocular pressure in patients with graves' orbitopathy. International Journal of Environmental Research and Public Health. 2020 Dec;17(24):9331.	OUTCOMES	No HRQOL
Liao SL, Chang TC, Lin LL. Transcaruncular orbital decompression: an alternate procedure for Graves ophthalmopathy with compressive optic neuropathy. American journal of ophthalmology. 2006 May 1;141(5):810-8.	OUTCOMES	No HRQOL
O'Malley MR, Meyer DR. Transconjunctival fat removal combined with conservative medial wall/floor orbital decompression for Graves orbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2009 May 1;25(3):206-10.	OUTCOMES	No HRQOL
She YY, Chi CC, Chu ST. Transnasal endoscopic orbital decompression: 15-year clinical experience in Southern Taiwan. Journal of the Formosan Medical Association. 2014 Sep 1;113(9):648-55.	OUTCOMES	No HRQOL
Richter DF, Stoff A, Olivari N. Transpalpebral decompression of endocrine ophthalmopathy by intraorbital fat removal (Olivari technique): experience and progression after more than 3000 operations over 20 years. Plastic and Reconstructive surgery. 2007 Jul 1;120(1):109-23.	STUDY DESIGN	Narrative Review
Dongmei QI, Weimin HE. Treatment for thyroid-associated ophthalmopathy with retrobular injection of glucocorticoid: a Meta-analysis. Chinese Journal of Evidence-Based Medicine. 2010;10(6):678-82.	STUDY DESIGN	SLR for cross-checking
Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' ophthalmopathy: systematic review and metaanalysis. The Journal of Clinical Endocrinology & Metabolism. 2009 Aug 1;94(8):2708-16.	STUDY DESIGN	SLR for cross-checking
Witte A, Landgraf R, Markl A, Boergen KP, Hasenfratz G, Pickardt CR. Treatment of Graves' ophthalmopathy with cyclosporin A. Klinische Wochenschrift. 1985 Oct;63:1000-4.	OUTCOMES	No HRQOL
Oestreicher JH, Pang NK, Liao W. Treatment of lower eyelid retraction by retractor release and posterior	OUTCOMES	No HRQOL

lamellar grafting: an analysis of 659 eyelids in 400 patients. Ophthalmic Plastic & Reconstructive Surgery. 2008 May 1;24(3):207-12.		
Stiglmayer N, Lešin M, Juri J, Ivanišević M, Boić L, Rogošić V. Treatment of ocular motility disturbances in Graves' disease with botulinum toxin A. Collegium antropologicum. 2005 Jun 20;29(1):41-6.	OUTCOMES	No HRQOL
Ebner R, Devoto MH, Weil D, Bordaberry M, Mir C, Martinez H, Bonelli L, Niepomniszcze H. Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone. The British journal of ophthalmology. 2004 Nov;88(11):1380.	OUTCOMES	No HRQOL
Uddin JM, Davies PD. Treatment of upper eyelid retraction associated with thyroid eye disease with subconjunctival botulinum toxin injection. Ophthalmology. 2002 Jun 1;109(6):1183-7.	OUTCOMES	Treatment satisfaction
Lee SJ, Rim TH, Jang SY, Kim CY, Shin DY, Lee EJ, Lee SY, Yoon JS. Treatment of upper eyelid retraction related to thyroid-associated ophthalmopathy using subconjunctival triamcinolone injections. Graefe's Archive for Clinical and Experimental Ophthalmology. 2013 Jan;251:261-70.	OUTCOMES	No HRQOL
Elubous KA, Alebous AD, Abous HA, Elubous RA, Alebous LA, Alshammari TO. Trends in Graves' orbitopathy research in the past two decades: a bibliometric analysis. Arquivos Brasileiros de Oftalmologia. 2022 Feb 14;85:590-8.	STUDY DESIGN	SLR for cross-checking
Parekh AS, Mansouri K, Weinreb RN, Tafreshi A, Korn BS, Kikkawa DO. Twenty-four-hour intraocular pressure patterns in patients with thyroid eye disease. Clinical & experimental ophthalmology. 2015 Mar;43(2):108-14.	OUTCOMES	No HRQOL
Le Moli R, Muscia V, Tumminia A, Frittitta L, Buscema M, Palermo F, Sciacca L, Squatrito S, Vigneri R. Type 2 diabetic patients with Graves' disease have more frequent and severe Graves' orbitopathy. Nutrition, Metabolism and Cardiovascular Diseases. 2015 May 1;25(5):452-7.	OUTCOMES	No HRQOL
Cho RI, Choe CH, Elner VM. Ultrasonic bone removal versus high-speed burring for lateral orbital decompression: comparison of surgical outcomes for the treatment of thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery. 2010 Mar 1;26(2):83-7.	OUTCOMES	No HRQOL
Schiff BA, McMullen CP, Farinhas J, Jackman AH, Hagiwara M, McKellop J, Lui YW. Use of computed tomography to assess volume change after endoscopic orbital decompression for Graves' ophthalmopathy.	OUTCOMES	No HRQOL

American Journal of Otolaryngology. 2015 Nov 1;36(6):729-35.		
Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. New England Journal of Medicine. 1989 Nov 16;321(20):1349-52.	OUTCOMES	No HRQOL
Fayers T, Dolman PJ. Validity and reliability of the TED-QOL: a new three-item questionnaire to assess quality of life in thyroid eye disease. British Journal of Ophthalmology. 2011 Jan 1.	OUTCOMES	Correlation, ICC results
Ugradar S, Katz B, O'Shaughnessy D, Summerfelt R, She A, Douglas R. VRDN-001, A NOVEL SELECTIVE INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-1R) ANTAGONIST ANTIBODY FOR THYROID EYE DISEASE (TED): PHASE 1/ 2 PROOF OF CONCEPT IN PATIENTS WITH TED. Thyroid. 2022;32:A154.	OUTCOMES	No HRQOL
Wickwar S, McBain HB, Ezra DG, Hirani SP, Rose GE, Newman SP. What are the psychosocial outcomes of treatment for thyroid eye disease? A systematic review. Thyroid. 2014 Sep 1;24(9):1407-18.	STUDY DESIGN	SLR for cross-checking
Yang M, Wiersinga WM, Soeters MR, Mourits MP. What is the aim of immunosuppressive treatment in patients with Graves' orbitopathy?. Ophthalmic Plastic & Reconstructive Surgery. 2014 Mar 1;30(2):157-61.	OUTCOMES	No HRQOL
Garrido-Hermosilla AM, Kazim M, Méndez-Muros M, Díaz-Ruiz MC. Which scale should we choose to assess activity and severity in Graves orbitopathy?. Archivos de la Sociedad Espanola de Oftalmologia. 2015 May 23;90(10):500-3.	LANGUAGE	Spanish
Laban KG, Kalmann R, Leguit RJ, de Keizer B. Zirconium-89-labelled rituximab PET-CT in orbital inflammatory disease. EJNMMI research. 2019 Dec;9(1):1-7.	POPULATION	Mixed TED, IOI population
Hosojima H, Uchida K. Availability of an anti-platelet aggregation inhibitor, ticlopidine, in the treatment of Graves' ophthalmopathy. JOURNAL OF DRUG DEVELOPMENT AND CLINICAL PRACTICE. 1996;8:129-34.	OUTCOMES	Clinical outcomes manifestations
Chien L, Go CC, Lahaie Luna GM, Briceño CA. Changes in choroidal thickness and choroidal vascularity index in thyroid eye disease: a systematic review. Orbit. 2022 Nov 27:1-9.	OUTCOMES	SLR, No HRQOL
Antonelli A, Saracino A. Comparative evaluation of retrobulbar or systemic corticosteroids and intravenous immunoglobulin in treatment of Graves' ophthalmopathy. European Journal of Clinical Investigation. 1992;22(4 Pt2):A16.	OUTCOMES	No HRQOL

Diniz SB, Cohen LM, Roelofs KA, Rootman DB. Early experience with the clinical use of teprotumumab in a heterogenous thyroid eye disease population. Ophthalmic Plastic & Reconstructive Surgery. 2021 Nov 1;37(6):583-91.	OUTCOMES	No HRQOL
Millar GT. Guanethidine drops in thyroid eye disease. Transactions of the Ophthalmological Societies of the United Kingdom. 1969;88:677-679.	OUTCOMES	No HRQOL
Pampín-Sánchez R, Martínez-Mugica-Barbosa C, Fonseca-Aizpuru EM, Barbazán-Vázquez FJ, Fernández-González B, Buznego-Súárez L. Outcome of tocilizumab treatment in corticosteroid-resistant thyroid eye disease. Medicina Clínica (English Edition). 2023 Feb 10;160(3):113-7.	STUDY DESIGN	Case series
Ho TC, Maamari RN, Kossler AL, Sears CM, Freitag SK, Reshef ER, Shinder R, Rootman DB, Diniz SB, Kahana A, Schlachter D. Outcomes of patients with thyroid eye disease partially treated with teprotumumab. Ophthalmic Plastic & Reconstructive Surgery. 2023 Mar 1;39(2):150-5.	OUTCOMES	No HRQOL
Baldys Waligorska A, Golkowski F. Results of oral and pulse steroid therapy in treatment of thyroid eye disease. European Journal of Clinical Investigation. 1998;28(1):A13.	OUTCOMES	No HRQOL
Mocan MC, Ament C, Azar NF. The characteristics and surgical outcomes of medial rectus recessions in Graves' ophthalmopathy. Journal of pediatric ophthalmology and strabismus. 2007 Mar 1;44(2):93.	OUTCOMES	No HRQOL
Al-Badri WK. Psychological aspects of Graves' ophthalmopathy. Endocrine Connections. 2024;13(9) (no pagination).	REVIEW	
Amarikwa L. Novel Measures of Quality of Life for Patients With Thyroid Eye Disease. Endocrine Practice. 2024;30(7):695-696.	REVIEW	
Anonymous. Erratum: Utility assessment of moderate to severe thyroid eye disease health states (JAMA Ophthalmol (2022) DOI: 10.1001/jamaophthalmol.2022.3225). JAMA Ophthalmology. 2023;141(2):213.	LINKED PUBLICATION	Linked to Smith 2023 (in original SR)
Bello OM. Graves' ophthalmopathy: The clinical and psychosocial outcomes of different medical interventions - A systematic review. BMJ Open Ophthalmology. 2024;9(1) (no pagination).	REVIEW	
Carter MJ. Insight Into Quality of Life in Patients With Moderate to Severe Thyroid Eye Disease. JAMA Ophthalmology. 2023;141(2):166-167.	REVIEW	

Chung CW. Efficacy of selenium supplementation for mild-to-moderate Graves' ophthalmopathy in a selenium-sufficient area (SeGOSS trial): study protocol for a phase III, multicenter, open-label, randomized, controlled intervention trial. Trials. 2023;24(1) (no pagination).	PROTOCOL ONLY	
Cockerham K. Inactive Thyroid Eye Disease Patient Journey. Journal of the Endocrine Society. 2023;7(Supplement 1)	OUTCOMES	No QoL data reported
Eatamadimadi H. EE457 Economic Burden Impact of Thyroid Eye Disease in the United Arab Emirates. Value in Health. 2024;27(6 Supplement)	OUTCOMES	No QoL data reported
Fatani WA. Monoclonal antibodies for the treatment of Graves' ophthalmopathy: A systematic review and meta-analysis. Saudi Journal of Ophthalmology. 2023;37(2):137-148.	REVIEW	
Gildea L. Evidence Gap Analysis of the Burden of Illness and Treatment of Thyroid Eye Disease. Value in Health. 2024;27(6 Supplement)	REVIEW	
Jinhai Y. Bayesian network analysis of drug treatment strategies for thyroid associated ophthalmopathy. International Ophthalmology. 2024;44(1) (no pagination).	REVIEW	
Kahaly G. Teprotumumab Is Associated with Pronounced Improvement in Quality of Life for Thyroid Eye Disease Patients as Compared to Intravenous Methylprednisolone: A Meta-analysis and Matching-Adjusted Indirect Comparison. Thyroid. 2023;33(Supplement 1)	STUDY DESIGN	pooled
Kahaly GJ. Teprotumumab Pooled Efficacy From The European Study Sites Participating In The Phase 2, OPTIC (Phase 3) And OPTIC-X Pivotal Trials. Journal of the Endocrine Society. 2023;7(Supplement 1)	LINKED PUBLICATION	Linked to Kahaly 2024 full text
Kahaly GJ. Long-Term Efficacy of Teprotumumab in Thyroid Eye Disease: Follow-Up Outcomes in Three Clinical Trials. Thyroid. 2024;34(7):880-889.	STUDY DESIGN	pooled
Kim J. Cost-Effectiveness of a Digital Therapeutic for Managing Hyperthyroidism: Evaluation of Glandytm. Thyroid. 2023;33(Supplement 1)	OUTCOMES	No QoL data reported
Lanzolla G. A Prospective, Observational Study on the Effect of an Ablative Vs a Conservative Approach for the Treatment of Graves' Hyperthyroidism in Patients with Moderate-to-Severe, Active Graves' Orbitopathy. Thyroid. 2023;33(Supplement 1)	OUTCOMES	Abstract- no data
Li M. The efficacy of Tripterygium Glycosides in the treatment of Chinese patients with thyroid-associated	REVIEW	

orbitopathy: A systematic review and meta-analysis. medRxiv. 2024;25.		
Lin F. The Efficacy and Safety of Teprotumumab in Thyroid Eye Disease: Evidence from Randomized Controlled Trials. International Journal of Clinical Practice. 2023;2023(no pagination).	REVIEW	
Masaquel C. Evidence Gap Analysis of the Burden of Disease in Thyroid Eye Disease. Value in Health. 2024;27(6 Supplement)	REVIEW	
Ramesh S. Thyroid Eye Disease: Pilot Study Comparison Between Patients in United States-Based and India-Based Practices. American Journal of Ophthalmology. 2024;264:25-35.	OUTCOMES	No QoL data reported
Sharabati I. The efficacy and safety of selenium supplementation versus placebo in the treatment of Graves' orbitopathy: A systematic review and meta-analysis of randomised controlled trials. Clinical Endocrinology. 2024. Background: Selenium is a trace element crucial for thyroid function, and has potential therapeutic benefits in Graves' orbitopathy (GO).	REVIEW	
Smith TJ. Abstract #1407025: Hearing-Related Adverse Events and Quality of Life Assessments in Thyroid Eye Disease Patients Treated with Teprotumumab. Endocrine Practice. 2023;29(5 Supplement)	LINKED PUBLICATION	In original SLR
Smith TJ. Assessment of hearing dysfunction in patients with Graves' disease and thyroid eye disease without or with teprotumumab. The Journal of Clinical Endocrinology and Metabolism. 2024;14.	STUDY DESIGN	pooled
Stokland AEM. Outcomes of Patients With Graves Disease 25 Years After Initiating Antithyroid Drug Therapy. Journal of Clinical Endocrinology and Metabolism. 2024;109(3):827-836.	OUTCOMES	No QOL for TED
Tumlin P. Gender Differences in Quality-of-Life Outcome in Patients undergoing Endoscopic Endonasal Skull Base Surgery. Journal of Neurological Surgery, Part B: Skull Base. 2023. Background: Prior studies showed that female patients with chronic rhinosinusitis (CRS) suffer a worse disease-specific quality of life (QoL).	POPULATION	Data for TED not reported separately
Xi A. Disease Severity Is Associated With Poorer Quality of Life Outcomes and Higher Costs in Thyroid Eye Disease (TED): Evidence From Systematic Literature Reviews (SLRs). Value in Health. 2024;27(6 Supplement)	REVIEW	
Aishwarya, A. Efficacy and safety of various Intravenous Methylprednisolone regimens in Moderate to Severe Thyroid Eye Disease: A systematic review Indian journal of ophthalmology 2025 73(8):1100-1107.	STUDY DESIGN	SLR

Al-Badri, W. K. W. Psychological aspects of Graves' ophthalmopathy Endocrine Connections 2024 13(9) (no pagination).	STUDY DESIGN	
Amarikwa, L. Novel Measures of Quality of Life for Patients With Thyroid Eye Disease Endocrine Practice 2024 30(7):695-696	OUTCOMES	
Bartalena, L. Process to radioactive iodine treatment for Graves' hyperthyroidism: condemned or absolved? Journal of Endocrinological Investigation 2025 48(9):1927-1950.	STUDY DESIGN	SLR
Bello, O. M. Graves' ophthalmopathy: The clinical and psychosocial outcomes of different medical interventions - A systematic review BMJ Open Ophthalmology 2024 9(1) (no pagination).	STUDY DESIGN	
Chen, Y. A Systematic Review of Patient Preferences, Expectations, and Values for the Management and Treatment of Graves Disease Patient Preference and Adherence 2025 19:2949-2957.	STUDY DESIGN	SLR
Choi, S. Comparative Efficacy of Corticosteroids and Teprotumumab in Thyroid Eye Disease Management Thyroid 2024 34(Supplement 1):A91.	OUTCOMES	
Ciarmatori, N. Redefining Treatment Paradigms in Thyroid Eye Disease: Current and Future Therapeutic Strategies Journal of Clinical Medicine 2025 14(15) (no pagination).	STUDY DESIGN	SLR
Cockerham, K. The impacts of thyroid eye disease (TED) extend beyond signs/symptoms, and patients want to discuss more with their physicians: Results from the ElevaTED survey Journal of the Endocrine Society 2025 9(Supplement 1):A1157-A1158.	OUTCOMES	
Cukovic, L. #1706739 Efficacy of Teprotumumab in Phenotype Type I vs Type II Thyroid Eye Disease Endocrine Practice 2024 30(5 Supplement):S161.	OUTCOMES	
Fung, M. H. M. Comparing the Health-Related Quality of Life at Two Years After Successful Treatment of Relapsed Graves' Disease With Radiofrequency Ablation, Surgery, or Radioiodine World journal of surgery 2025 49(11):3142-3151.	POPULATION	
Garrido-Hermosilla, A. M. Evaluation of the clinical management of Graves' Orbitopathy according to severity: a real-life Analysis International Ophthalmology 2025 45(1):116.	STUDY DESIGN	
Giannakogeorgou, A. Prognostic Factors and Outcomes of Intravenous Glucocorticoid Pulse Therapy in Moderate-to-Severe Thyroid Eye Disease Thyroid 2024 34(Supplement 1):A89.	OUTCOMES	

Jinhai, Y. Bayesian network analysis of drug treatment strategies for thyroid associated ophthalmopathy International Ophthalmology 2024 44(1) (no pagination).	STUDY DESIGN	
Kahaly, G. J. Long-Term Efficacy of Teprotumumab in Thyroid Eye Disease: Follow-Up Outcomes in Three Clinical Trials Thyroid 2024 34(7):880-889.	STUDY DESIGN	
Kahaly, G. J. Durability of Teprotumumab for the Treatment of Thyroid Eye Disease (TED) in Clinical Trials Journal of the Endocrine Society 2024 8(Supplement 1):A1016-A1017.	OUTCOMES	
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Lee, A. C. H. Targeted immunotherapies for Graves' thyroidal & orbital diseases Frontiers in Immunology 2025 16(no pagination).	STUDY DESIGN	
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Malik, A. Assessment Of Quality Of Life By Baseline Factors Among Patients With Thyroid Eye Disease (ted) Journal of the Endocrine Society 2025 9(Supplement 1):A1196-A1197.	OUTCOMES	
Manousou, S. Rituximab Treatment as Second-Line Therapy in Glucocorticoid Nonresponsive Graves' Orbitopathy: A Nonrandomized, Controlled, Interventional Study Endocrine Practice 2025 31(4):447-454.	OUTCOMES	No extractable data
Masaquel, C. Evidence Gap Analysis of the Burden of Disease in Thyroid Eye Disease Value in Health 2024 27(6 Supplement):S389.	STUDY DESIGN	
Pramono, L. A. Quality of Life Study in Chronic Diseases: More Needed Than Ever Acta medica Indonesiana 2024 56(4):442-444.	OUTCOMES	
Ramesh, S. Thyroid Eye Disease: Pilot Study Comparison Between Patients in United States-Based and India-Based Practices American Journal of Ophthalmology 2024 264:25-35.	OUTCOMES	
Sanfelippo, W. Anxiety, Depression, and Manifestations of Thyroid Eye Disease Investigative Ophthalmology and Visual Science. Conference: Association for Research in	OUTCOMES	

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Sharabati, I. The efficacy and safety of selenium supplementation versus placebo in the treatment of Graves' orbitopathy: A systematic review and meta-analysis of randomised controlled trials Clinical Endocrinology 2024 101(6):669-681.	STUDY DESIGN	
Smith, T. J. Bridging and Validation of the Specific Graves Ophthalmopathy Quality of Life Questionnaire With Health State Utility Values Endocrine Practice 2024 30(5):470-475.	POPULATION	Pooled analysis
Smith, T. J. Assessment of Hearing Dysfunction in Patients With Graves' Disease and Thyroid Eye Disease Without or With Teprotumumab Journal of Clinical Endocrinology and Metabolism 2025 110(3):811-819.	POPULATION	Pooled analysis
Stokland, A. E. M. Outcomes of Patients With Graves Disease 25 Years After Initiating Antithyroid Drug Therapy Journal of Clinical Endocrinology and Metabolism 2024 109(3):827-836.	POPULATION	
Tamhankar, M. A. Real-World Experience with Teprotumumab in Patients with Dysthyroid Optic Neuropathy Journal of Neuro-Ophthalmology 2024 44(1):74-79.	STUDY DESIGN	SLR
Tamhankar, M. A. The burden of illness in thyroid eye disease: current state of the evidence Frontiers in Ophthalmology 2025 5:1565762.	STUDY DESIGN	SLR
Tumlin, P. Gender Differences in Quality-of-Life Outcome in Patients Undergoing Endoscopic Endonasal Skull Base Surgery Journal of Neurological Surgery Part B Skull Base 2024 85(Suppl 2):e80-e85.	POPULATION	
Ugradar, S. Evaluation of Tobacco Exposure and Teprotumumab Efficacy: Pooled Results from Acute TED Clinical Trials Journal of the Endocrine Society 2024 8(Supplement 1):A1023-A1024.	OUTCOMES	
Xi, A. Disease Severity Is Associated With Poorer Quality of Life Outcomes and Higher Costs in Thyroid Eye Disease (TED): Evidence From Systematic Literature Reviews (SLRs) Value in Health 2024 27(6 Supplement):S405.	STUDY DESIGN	

J.2.3 Quality assessment and generalizability of estimates

In the SLR, there was high heterogeneity in the population assessed. Definitions confirming moderate to severe TED were often not reported, and as such, a large proportion of studies were based on an all-TED population, without further details on the composition of the population, leading to potential heterogeneity. Additionally, this could introduce potential biases that were not considered in the current report and limit inferences that may be made. For example, in the all-TED population, baseline scores in the visual function GO-QOL subscale ranged from 32.82 to 87.18 and may reflect the differences in disease activity or disease severity of the included populations.

Due to a time restriction (i.e., studies published in the last 12 years), relevant literature reporting HRQOL/PRO data may have been missed. Similarly, HRQOL data from clinical trials were limited to two disease-specific instruments (GO-QOL and TED-QOL [thyroid eye disease - quality of life]) and generic instruments that can be mapped to obtain utility values, therefore, potentially limiting the HRQOL data available from clinical trials. The comparison of results in the HRQOL/utilities SLR was limited by several factors, making it difficult to draw conclusions. Specifically, many questionnaires were reported by a single study; overlapping (i.e., similar) evidence was sparse across populations, instruments, treatments, and timepoints measured; and definitions for TED-QOL and TAO-QOL (thyroid associated orbitopathy - quality of life) instruments were inconsistent across studies.

The SLR was limited to English-language publications. While this is generally considered acceptable, it presents a language bias and a risk of exclusion of relevant studies not published in English.

Regarding generalizability to a Danish setting, the study by Smith et al. (2023) presents TTO-derived utility estimates based on a representative sample from the general population in the United States. The methodology adheres to established international standards and is consistent with approaches accepted by HTA agencies, even though it does not report EQ-5D. While the study sample is US-based, the demographic characteristics, particularly in terms of age, gender distribution, and visual function, are reasonably comparable to the Danish population affected by TED. Moreover, the described health states are clinically relevant, reflect real-world TED symptomatology, and have been validated by a Danish clinical expert. In the absence of Danish utility data or EQ-5D-based estimates for these health states, the values reported in this study are considered appropriate for use in the present assessment.

J.2.3.1 Quality appraisal

Quality appraisal of included studies was conducted using a validated checklist, depending upon study design. Studies reporting on HSUV or HRQOL were assessed using the NICE-recommended tool for the quality assessment of individual HSUV studies and are presented in Table 154.

Due to limited information in reporting, quality appraisal was conducted only on full publications and not on conference abstracts or posters.

Quality assessment was performed by a single individual for each included study and independently verified by a second individual once completed. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached. Any unresolved conflicts were decided by a third reviewer.

Table 154: Quality appraisal of all full publications reporting HSUVs included in the HRQOL/Utilities SLR: NICE-recommended tool for the quality assessment of individual HSUV studies

Question	Smith et al. (2023) (59)
1. Is the sample size used to derived utility values adequately powered?	UNCLEAR
2. Do the population characteristics (e.g., age, sex, co-morbidities, diagnosis, severity of disease) in the study match those modelled?	YES
3. Are all relevant individuals included from the sample?	YES
4. If response rates are reported, are they high enough to not be a threat to validity?	YES
5. Are numbers of patients lost to follow up likely low enough to not be a threat to the validity of the estimates?	N/A
6. Are missing data rare enough or statistically accounted for to prevent the validity of the estimates being threatened?	N/A
7. If there are no other over problems, answer 'Yes' and provide further information. Otherwise, answer 'No' (where problems are obvious / already captured in the checklist) or 'Not reported'	YES
8. Do the population characteristics (e.g. age, sex, co-morbidities, diagnosis, severity of disease) in the study match those modelled and those described in the decision problem of the review?	YES
9. What instrument is used to describe the health states?	TTO
10. Is the population reported in which the change in HRQOL undertaken?	YES
11. Is the population reported for which the valuation of changes in patients' HRQOL is undertaken?	NO
12. Was the technique used to value the health states reported?	YES

Abbreviations: HRQOL, health-related quality of life; HSUV, health state utility value; NICE, national institute for health and care excellence; SLR, systematic literature review.

J.2.4 Unpublished data

N/A

J.3 Focused Search

N/A

Appendix K. Justification for Confidential Information

Table 155. Justification for confidential information

Parameter	Justification
Dose distribution OPTIC phase 3, section 3.2	Unpublished data on file from clinical study report
MAIC results, section 7.2., 7.3. and 7.4.	Unpublished data on file, ITC
Transition probabilities for teprotumumab section 9.3 and Appendix E	Unpublished data on file from clinical study report
Modelled means in years, Table 35, section 9.4	Commercial confidentiality considerations
Distribution of patients across health states over the model time horizon for Teprotumumab, Figure 2	Commercial confidentiality considerations
Section 10.2.1.2 Data Collection EQ-5D-5L	Unpublished data on file from clinical study report
Results	Confidential price and commercial confidentiality considerations