Overview and Management of Thyroid Eye Disease

Thyroid Eye Disease (TED) is an Orphan Disease

Descriptive epidemiology

	Men	Women
Incidence rate	2.9 cases per 100,000	16 cases per 100,000
Peak age range	45 to 49 years and 65 to 69 years[1]	40 to 44 years and 60 to 64 years[1]

TED vs. Graves' Disease

- TED and Graves' Disease are not synonymous. TED may coexist, precede, or follow Graves' Disease[2]
- TED can exist without hyperthyroidism[1,2,3]

Hyperthyroidism, TED & Graves' Disease

- TED not directly related to high serum thyroid concentrations[4]
- However, euthyroid patients with Graves' Disease tend to have less severe TED[4]

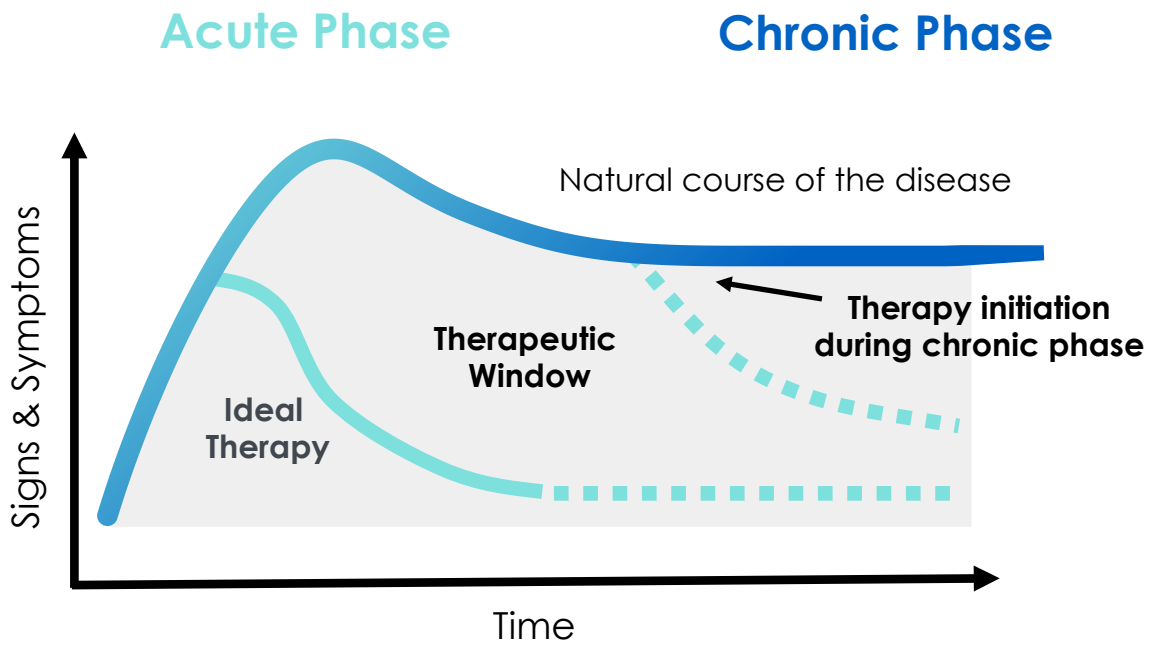
Risk factors for the development and progression of TED[2]

Nonmodifiable Factors	Modifiable Factors
Age • Advanced Aging **Gender** • Women (more frequent) • Men (more severe) **Genetics**	**Environment** • Smoking • Radioactive Iodine Therapy **Thyroid Dysfunction** • Hypothyroidism • Hyperthyroidism

Bartley, G.B. *Trans Am Ophthalmal Soc.* 1994;92:477-588. 2. Eckstein AK *et al. Br J Ophthalmol.* 2009;93(8):1052-1056. 3. Leo M *et al. Thyroid.* 2015;25(3):347-351. 4. Gwinup G *et al. JAMA.* 1982;247(15):2135-2138.

The Natural History of TED

Refined understanding of TED natural course



Acute (active) Stage

- Characterized by inflammation including periorbital chemosis, orbital congestion, and tissue expansion associated with eyelid retraction, proptosis, and diplopia for a variable period up to three years[1-3]

Chronic (inactive) Disease

- Inflammation will subside but the changes may remain and result in permanent damage

1. Bhatti MT, et al. *J Neuroophthalmol*. 2014;34(2):186-197. 2. Bothun ED, et al. *Clin Ophthalmol.* 2009; 3:543-551. 3. Bartalena L, et al. *Endocr Rev*. 2000; 21(2):168-199.

Clinical Presentation of TED

Conjunctiva and Cornea[1-4]

Figure adapted from Briceño CA, et al. *Int Ophthalmol Clin.* 2013; 53(3): 93-101.

- Chemosis
- Conjunctival redness
- Tearing
- Photophobia
- Foreign body sensation

Eyelid[1-4]

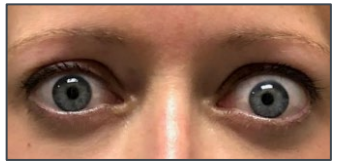
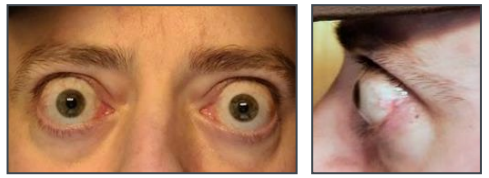


Figure adapted from Briceño CA, et al. *Int Ophthalmol Clin.* 2013; 53(3):93-101.

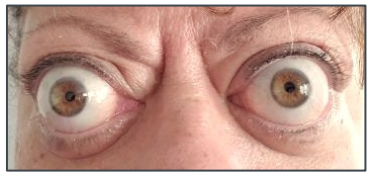
- **Upper eyelid retraction 91%[8]**
- Eyelid swelling
- Pain
- Lagophthalmos
- Exposure keratopathy

Orbital Fat[2-3]



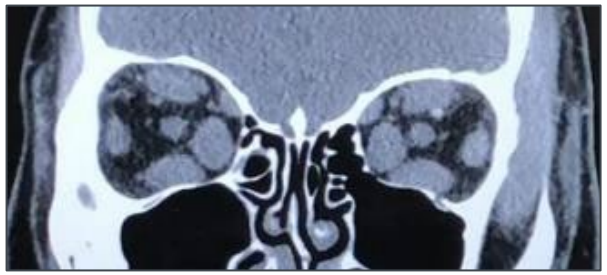
- **Proptosis 60%[8]**
- Pain
- Disfigurement
- Exposure keratopathy
- Vision loss

Extraocular Muscle[2-3]



- Restricted ocular motility
- **Diplopia 51%[9]**
- Pain
- Decreased vision & depth perception

Optic nerve[5-7]



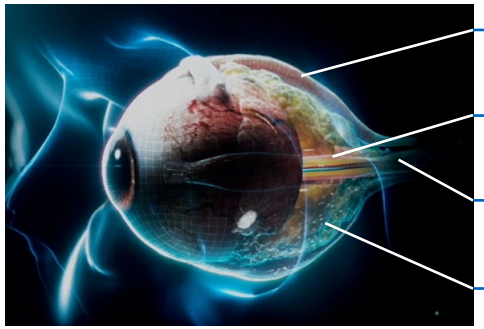
- **Compressive Optic Neuropathy 6-9%[8]**
- Loss of vision
- Impairment of color vision
- Optic disc swelling
- Visual field defect

1. Liaboe C *et al. Thyroid eye disease: an introductory tutorial and overview of disease.* EyeRounds.org. https://webeye.ophth.uiowa.edu/eyeforum/tutorials/thyroid-eye-disease/ Thyroid-Eye-Disease.pdf Published November 18, 2016. Accessed January 10, 2022. 2. Bothun ED *et al. Clin Ophthalmol.* 2009;3:543-551. 3. Bahn RS. *N Engl J Med.* 2010;362(8):726-738. 4. Briceño CA et al. *Int Ophthalmol Clin.* 2013;53(3):93-101. 5. Neigel JM et al. *Ophthalmology.* 1988;95(11):1515-1521. 6. McKeag D et al. *J Ophthalmol.* 2007;91:455-458. 7. Fernandez E et al. *Ann Thyroid Res.* 2016;2:63-65. 8. Bartley GB et al. *Am J Ophthalmol.* 1996;121(4):426-434. 9. Terwee C et al. *Eur J Endocrinol*. 2002;146(6):751-757.

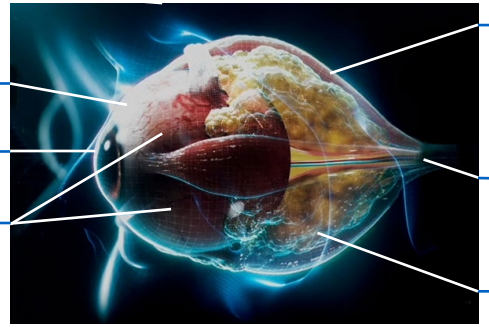
TED Is an Autoimmune Inflammatory Eye Disease

Healthy Eye and Orbital Tissue[3]

- Eye is well protected by lid
- Optic nerve can easily pass through apex
- Orbit contains a small amount of tissue and fat



In Presence of Moderate to Severe TED[3]



While the exact autoimmune triggers for TED are unknown, autoantibody activation leads to inflammation and tissue expansion/remodeling in the eye[1,2]

Multifactorial causes:

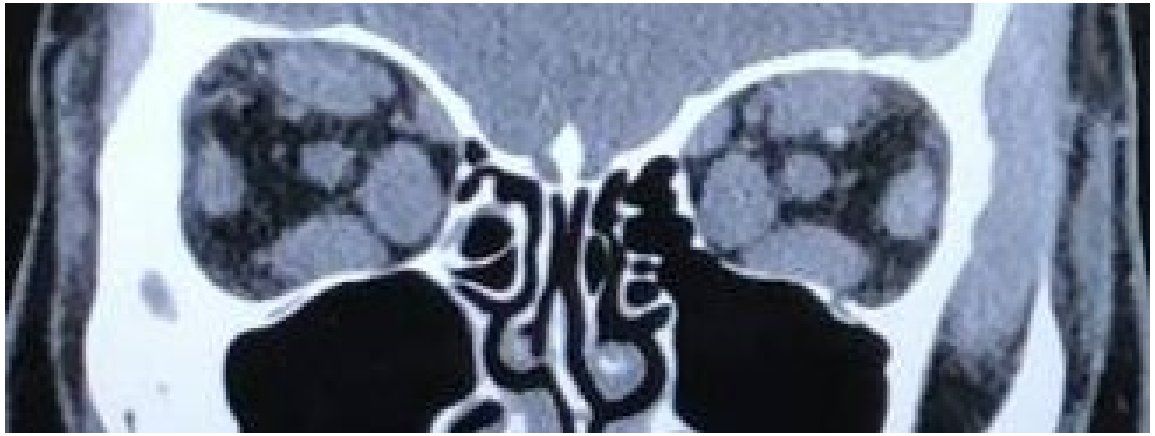
- IGF-1R is overexpressed in TED orbital fibroblasts[4]
- Autoantibodies activate the IGF-1R and TSHR-signaling complex, which stimulates orbital fibroblasts[1] and leads to the release of inflammatory cytokines and hyaluronan production[5-7]
- Once activated, orbital fibroblasts cause inflammation and expansion of tissue, muscle, and fat cells behind the eye[7,8]

1. Smith TJ et al. *Front Endocrinol (Lausanne)*. 2016; 7:167. 2. Wang Y et al. *Invest Ophthalmol Vis Sci*. 2014; 55(3): 1735-1748. 3. Horizon Pharma. Events & presentations. https://ir.horizontherapeutics.com/static-files/c153d2c9-fae6-4e3b-ab18-7e8485e2c2d4. Accessed January 10, 2022. 4. Tsui S, et al. J Immunol. 2008;181:4397-4405. 5. Pritchard J, et al. J Immunol. 2003;170:6348-6354. 6. Smith TJ, et al. J Clin Endocrinol Metab. 2004;89:5076-5080. 7. Wang Y, et al. Ther Clin Risk Manag. 2019;15:1305-1318. 8. Patel A, et al. Am J Ophthalmol. 2019;208:281-288.

Compressive Optic Neuropathy (CON) Can Result in Irreversible Vision Loss

- Compressive Optic Neuropathy (CON) is a rare, serious complication of TED, affecting 4 to 8% of patients with TED[1-3]
- Caused by compression of optic nerve due to enlargement of rectus muscles and increased volume of periorbital tissue[3]
- May require urgent treatment with medical or surgical decompression to avoid permanent or progressive vision loss[3]
- Clinical features include[3,4]:
  - Slow, progressive loss of vision
  - Impairment of color vision
  - Optic disc swelling
  - Radiologic evidence of apical optic nerve compression
  - Relative afferent pupillary defect
  - Visual field defect
  - Optic atrophy (or edema)

Compressive Optic Neuropathy in a patient with TED



EOM, extraocular muscle; MRI, magnetic resonance imaging.

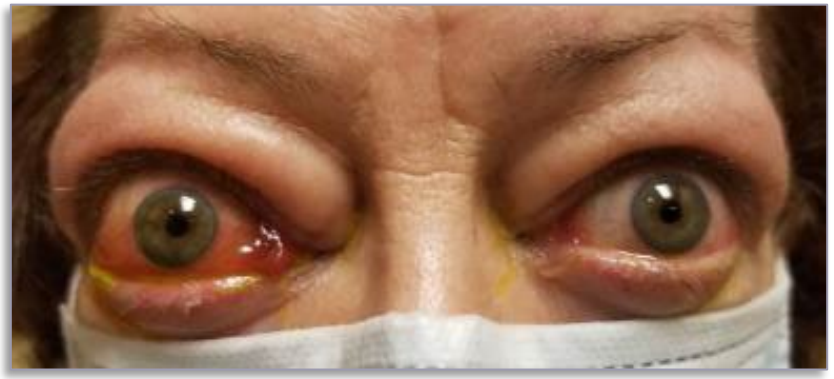
1. Bartley GB. *Trans Am Ophthalmol Soc*. 1994; 92:477-588. 2. Bartley GB, et al. *Am J Ophthalmol.* 1996; 121(3):284-290. 3. Neigel JM, et al. *Ophthalmology*. 1988; 95(11):1515-1521. 4. McKeag D, et al. *J Ophthalmol*. 2007; 91:455-458. 5. Fernandez E, et al. *Ann Thyroid Res.* 2016; 2:63-65.

TED Has Broad Implications for Patients' Lives

Diminished Quality of Life

TED impacts the way patients see, the way they look, and the way they feel.[1-3]

In a study of 41 TED patients, **75.6% had altered visual function.**[4]



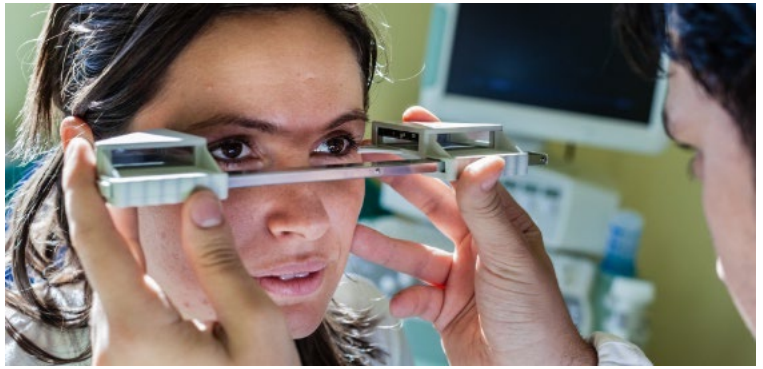
In a study of 41 TED patients, **95.1% perceived a disturbance in their appearance.**[4]

In another study with 102 TED patients, **45% had anxiety and/or depression.**[3]

1. Bothun ED et al. *Clin Ophthalmol.* 2009; 3:543-551. 2. Barrio-Barrio J et al. *J Ophthalmol*. 2015; 2015:249125. 3. Kahaly GJ et al. *Clin Endocrinol.* 2005; 63:395-402. 4. Delfino LC, et al. *Arch Endocrinol Metab.* 2017;61(4):374-381.

Proptosis Is Quantified With an Exophthalmometer

- Exophthalmometer is a noninvasive tool designed to measure the forward protrusion of the eye[1,2]
- Normal ocular protrusion as measured from the lateral orbital rim to corneal apex has traditionally been considered ≤21 mm in adults[2]
  - Protrusion >21mm or a 2-mm difference unilaterally or between the two eyes is considered abnormal
- However, proptosis upper limits of normal varies by age, sex, and race[2,3]



Upper Limits of Normal (Proptosis)[3]

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

Gorman Bahn Diplopia Scale[4]

Diplopia Score
0. No diplopia
1. Intermittent, i.e., diplopia in primary position of gaze, when tired or when first awakening
2. Inconstant, i.e., diplopia at extremes of gaze
3. Constant, i.e., continuous diplopia in primary or reading position

1. Bothun ED et al. *Clin Ophthalmol.* 2009; 3:543-551. 2. Barrio-Barrio J et al. *J Ophthalmol*. 2015; 2015:249125. 3. Kahaly GJ et al. *Clin Endocrinol.* 2005; 63:395-402.
4. Delfino LC, et al. *Arch Endocrinol Metab.* 2017; 61(4):374-381.

Clinical Activity Score Is a Measurement of TED Activity

For initial CAS, only score items 1-7	
1	Spontaneous orbital pain
2	Gaze-evoked orbital pain
3	Eyelid swelling that is considered to be due to active TED
4	Eyelid erythema
5	Conjunctival redness considered to be due to active TED
6	Chemosis
7	Inflammation of caruncle OR plica
Patients assessed after follow-up (1-3 months) can be scored out of 10 by including items 8-10	
8	Increase of ≥2 mm in proptosis
9	Decrease in uniocular excursion in any one direction of ≥5°
10	Decrease of acuity equivalent to ≥1 Snellen line

7-component scale commonly used to assess changes in disease activity in clinical trial settings.

- Clinical Activity Score (CAS) is based on four classical signs of inflammation: pain, redness, swelling and impaired function[1-3]
  - One point for each item, weight for each item is the same
  - Total CAS may range from 0 to 7 or 0 to 10
  - CAS ≥ 3 out of 7 on initial visit or CAS ≥ 4 out of 10 at follow-up visit implies active inflammatory stage of TED*
- Validated as a predictor of response to immunosuppression[1]
- ATA Guidelines and European Thyroid Association/EUGOGO recommend CAS to determine TED activity[2,3]

ATA, American Thyroid Association; EUGOGO, European Group of Graves' Orbitopathy.
*≥ 3 at initial visit and ≥ 4 at follow-up visit.

1. Mourits MP et al. *Br J Ophthalmol.* 1989; 73(8):639-644. 2. Ross DS et al. *Thyroid.* 2016; 26(10):1343-1421. 3. Bartalena L et al. *Eur Thyroid J.* 2016; 5(1):9-26. 4. Barrio-Barrio J et al. *J Ophthalmol.* 2015; 2015:249125.

American Thyroid Association

TED Severity Grades

Mild TED[1]: Patients whose features of TED have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment.

Moderate-to-Severe TED: Patients without sight-threatening TED whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).

Sight-Threatening TED: Patients with optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

Grade[1]	Lid retraction	Soft tissues	Proptosis†	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression

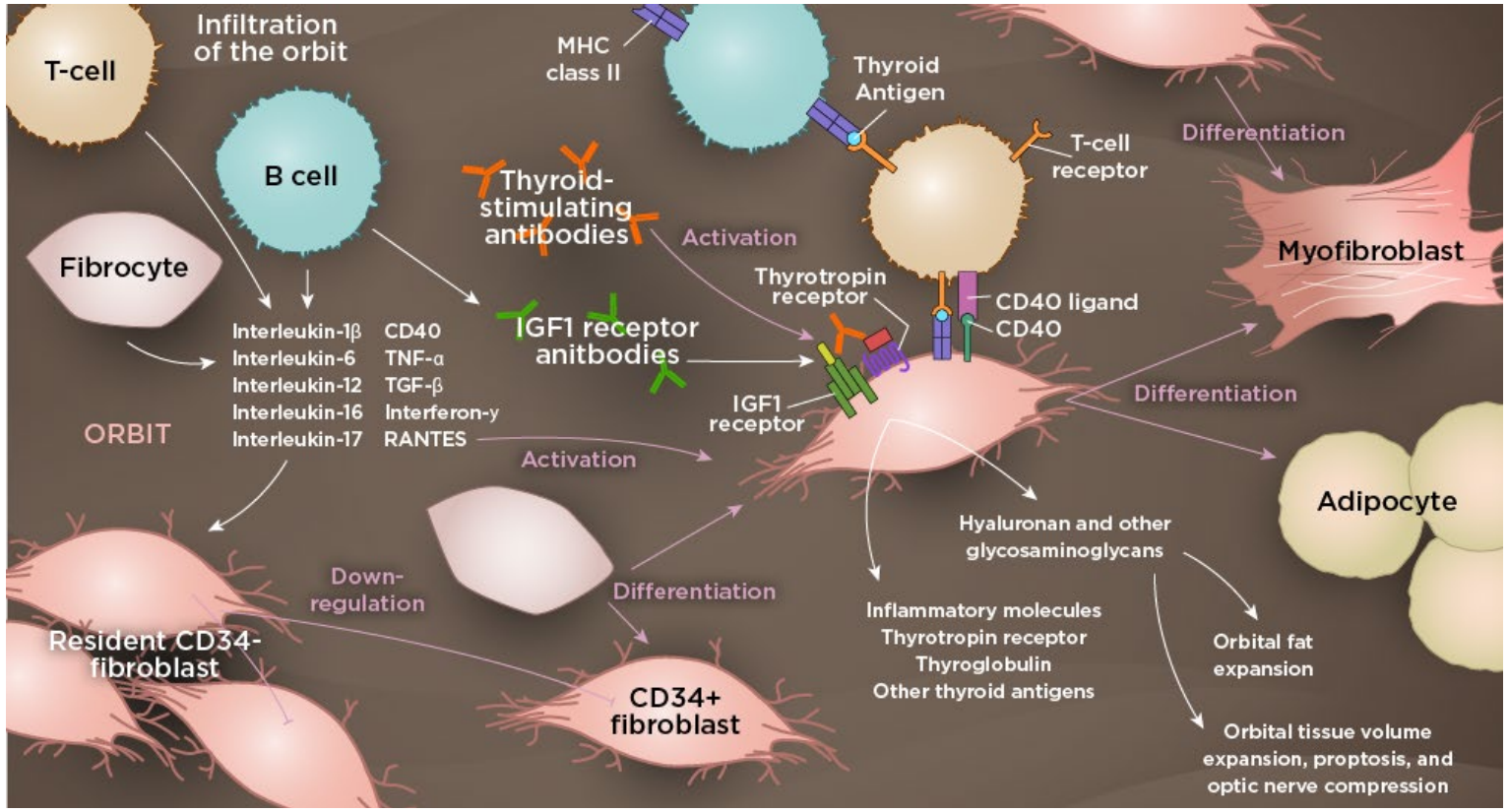
The European Thyroid Association has similar severity grades with one exception. The severity grades of moderate and severe are combined to be Moderate/Severe. All of the signs and symptoms for ATA and ETA are the same.[2]

†Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

1. Ross DS et al. Thyroid. 2016; 26(10):1343-1421. 2. Bartalena, Luigi, et al. "The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy." *European Journal of Endocrinology* 185.4 (2021): G43-G67.

IGF-1R/TSHR Signaling Complex Activation Triggers Inflammatory Response Leading to Tissue Expansion and Remodeling

- Orbital fibroblasts (OFs) are the principal cells that drive the inflammation and expansion of orbital soft tissues[1-4]
- OFs from patients with TED are more prone to activation, leading to proliferation, differentiation into adipocytes and increased hyaluronan secretion than OFs from healthy controls[1,3,4]
- IGF-1R and TSHR are co-localized and form a signaling complex[5]



IGF-1R, insulin-like growth factor-1 receptor; TSHR, thyroid-stimulating hormone receptor.

1. Smith TJ, et al. *Thyroid.* 2008;18(9):983-988. 2. Smith T. *Pharmacological Rev*. 2010;62(2):199-236. 3. Bahn RS. *N Engl J Med.* 2010;362(8):726-738. 4. Shan SJ, et al. *J Neuroophthalmol.* 2014;34(2):177-185. 5. Tsui S et al. *J Immunol*. 2008;181:4397-4405.

Historically, Treatment Options for TED Selected Based on Disease Activity and Severity[1,2]

Disease Severity

	Mild	Moderate-to-severe	Sight-threatening
Acute Stage	• Local measures* • Oral steroids if acute stage or decreased QoL	• IV steroids • Off-label biologics (TOCI, RTX) • Orbital radiation • Orbital decompression surgery or clinical trial enrollment	• IV steroids + urgent orbital decompression surgery
Chronic Disease	• Local measures	• Surgical intervention after ≥3 months observation (as needed)	• Surgical intervention

IV, intravenous; N/A, not applicable; QoL, quality of life; TOCI, tocilizumab, RTX, rituximab.
*With or without selenium supplementation.

1. Ross DS et al. *Thyroid*. 2016;26(10):1343-1421. 2. Bartalena L et al. *Eur Thyroid J*. 2016;5(1):9-26.

Teprotumumab-trbw Overview

FDA Indication

- **Teprotumumab is indicated for the treatment of Thyroid Eye Disease**
- Approved January 21, 2020[1]

Mechanism of Action

- Teprotumumab-trbw is a fully human monoclonal antibody[1] that binds to IGF-1R and blocks its activation and signaling

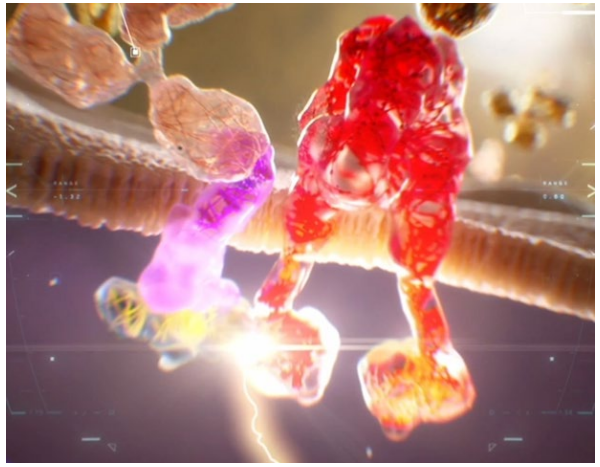
Administration

- One infusion every 3 weeks across 21 weeks (8 total infusions)[1]
- First infusion of 10 mg/kg followed by 7 infusions of 20 mg/kg[1]

IGF-1R, insulin-like growth factor-1 receptor.

1. Horizon Pharma USA, Inc. Treatment of Graves' orbitopathy (thyroid eye disease) to reduce proptosis with teprotumumab-trbw infusions in a randomized, placebo-controlled, clinical study (OPTIC). https://www.clinicaltrials.gov/ct2/show/NCT03298867. Accessed November 15, 2018.

Mechanism of Action of Teprotumumab-trbw for TED



Pathophysiology of TED

- The body attacks its own orbital cells which overexpress IGF-1R.[1,2]
- IGF-1R and TSHR are co-localized and form a signaling complex.[2]
- This leads to severe inflammation and expansion of tissue, muscle and fat cells behind the eye.[1,3]
- May cause proptosis (bulging of the eyes) and optic nerve compression.[1,3]

Teprotumumab-trbw Mechanism of Action[3]

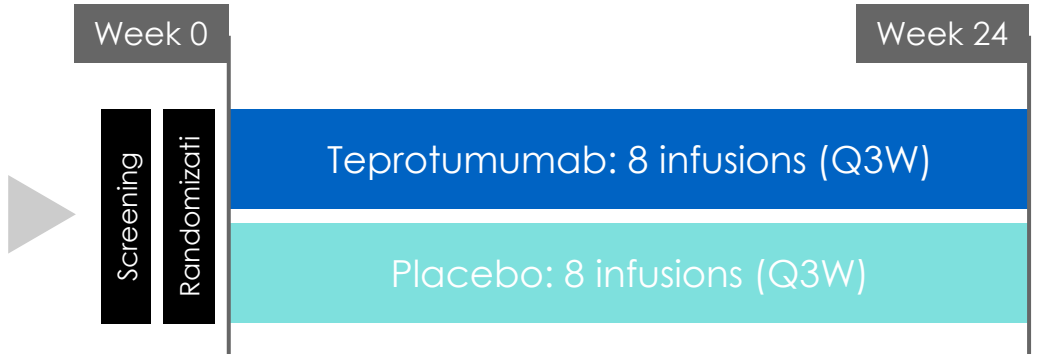
- Fully human monoclonal antibody inhibitor of IGF-1R.
- Blocks IGF-1R and turns off signaling complex at the source of the disease.
- Intended to reduce inflammation and prevent excessive cell growth behind the eye.

1. Bahn RS. *N Engl J Med.* 2010; 362:726-738. 2. Tsui S, et al. *J Immunol*. 2008; 181:4397-4405. 3. Smith TJ, et al. *N Engl J Med.* 2016; 375:1552-1565.

OPTIC Study

Patient Criteria

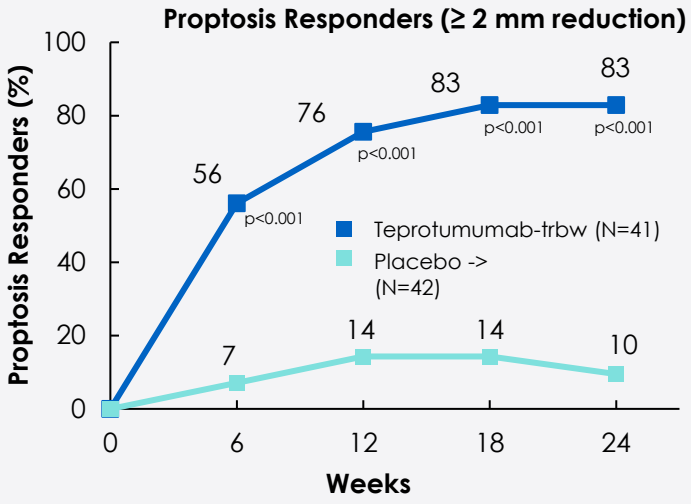
- Active TED
- 18-80 years
- CAS ≥4
- <9 months since active TED onset with no prior treatment
- FT4 and FT3 <50% above or below normal limits

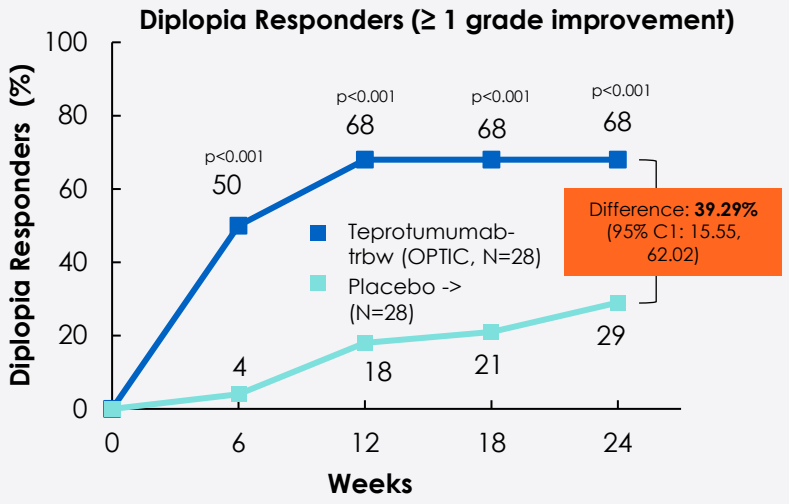


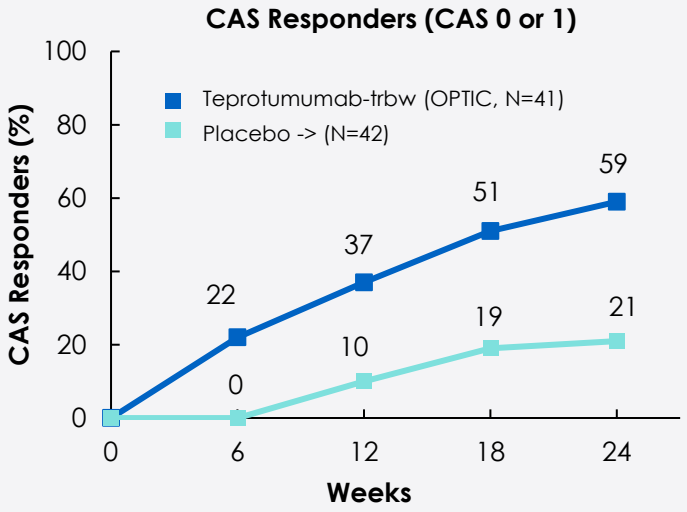
Primary endpoint at Week 24

Percentage of participants with ≥2mm reduction in proptosis

Off-Treatment Follow-up Period

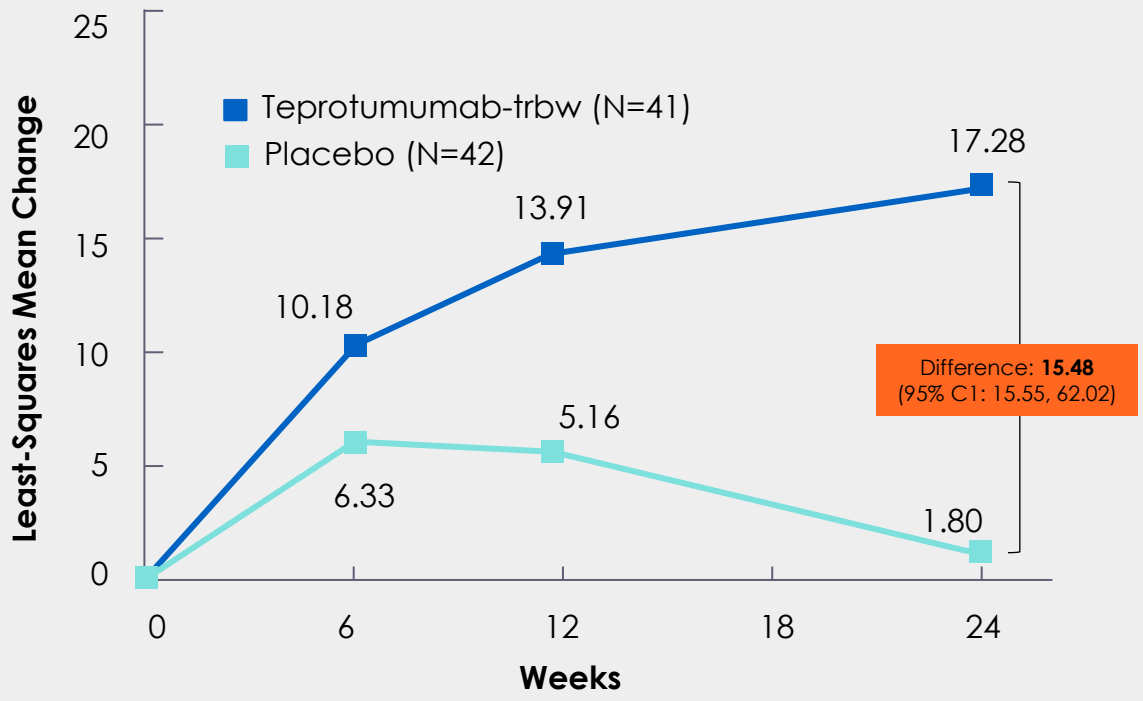






Douglas RS, et al. *N Engl J Med*. 2020;382(4):341–352.

GO-QoL Improvements Overall



Adapted from: Douglas RS, et al. *N Engl J Med.* 2020; 382(4|:341-352.

Drivers of decreased QoL:

- TED activity[1-4] and ocular pain[1,5]
- Disease severity[2-4,6,7]:
  - Proptosis[4,8-10] and asymmetric proptosis (≥2 mm difference between eyes)[4]
  - Diplopia[1,3-5,11]
  - Blurred vision[1]

MMRM ANCOVA model with an unstructured covariance matrix, including the following terms: baseline score, tobacco use status (non-user, user), treatment group, visit, and visit-by-treatment and visit-by-baseline-score interactions; least square mean +/- standard error.

1. Kahaly GJ, et al. *Clin Endocrinol (Oxf).* 2005;63:395-402. 2. Choi YJ, et al. *Eye (Long).* 2012;26:544-551. 3. Lin IC, et al. *J Formo Mdl Assoc.* 2015;114:1047-1054. 4. Villagelin D, et al. *Front Endocrinol (Lousanne).* 2019; 10:192. 5. Kahaly GJ, et al. *Thyroid.* 2002;12:237-239. 6. Park JJ, et al. *Br J Ophthalmol.* 2004;88:75-78. 7. Delfino LC, et al. *Arch Endocrinol Metab.* 2017;61:374-381. 8. Bartalena L, et al. *Endocr Rev.* 2000;21:168-199. 9. Gerding MN, et al. *Thyroid.* 1997;7:885-889. 10. Tehrani M, et al. *Eur J Ophthalmol.* 2004;14:193-199. 11. Bradley EA, et al. *Ophthalmology.* 2006;113:1450-1454.

Warnings, Precautions, and Special Populations

Infusion-related Reactions

- Teprotumumab-trbw may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with teprotumumab-trbw

Exacerbation of Preexisting Inflammatory Bowel Disease

- Teprotumumab-trbw may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of teprotumumab-trbw

Hyperglycemia

- Hyperglycemia or increased blood glucose may occur in patients treated with teprotumumab-trbw. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary
- Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with teprotumumab-trbw. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving teprotumumab-trbw

TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.

Warnings, Precautions, and Special Populations

Hearing Impairment Including Hearing Loss

- Teprotumumab-trbw may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with teprotumumab-trbw and consider the benefit-risk of treatment with patients

Special Populations

- Teprotumumab-trbw should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment, and for 6 months following the last dose of teprotumumab-trbw

TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.

Adverse Reactions

Adverse Events Occurring in 5% or More of Patients Treated With Teprotumumab-trbw and Greater Incidence than Placebo (Phase 2 & Phase 3 studies)

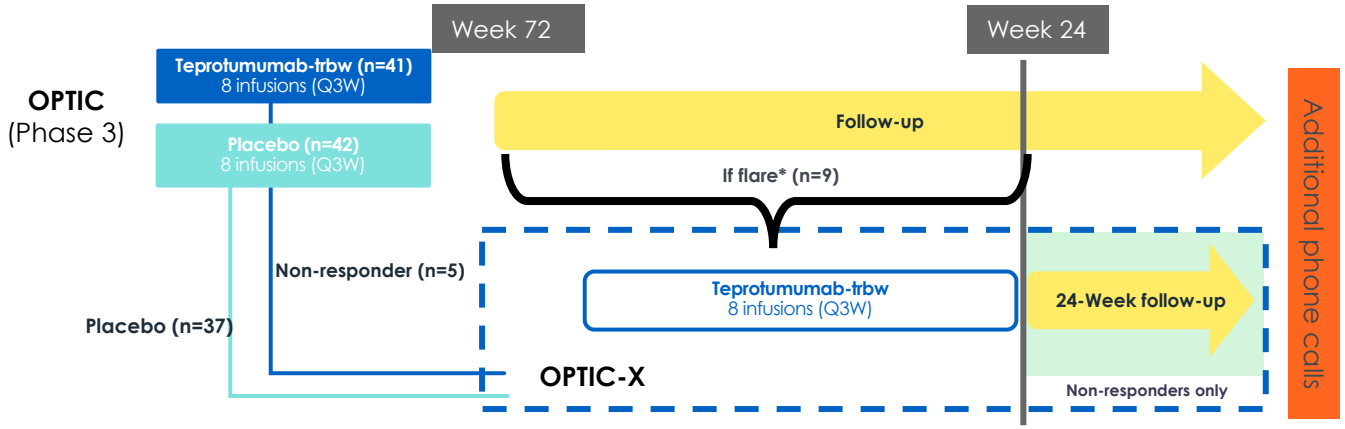
Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder[d]	4 (5%)	0

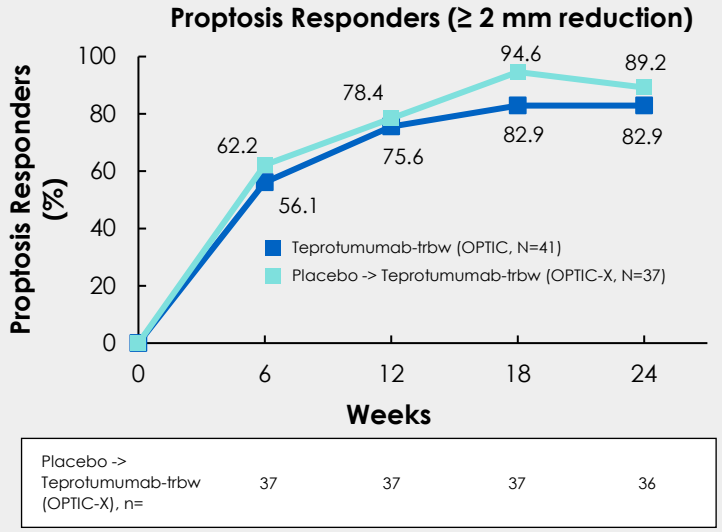
a) Fatigue includes asthenia
b) Hyperglycemia includes blood glucose increase
c) Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)
d) Nail disorder (includes nail discoloration, nail disorder and onychoclasis)

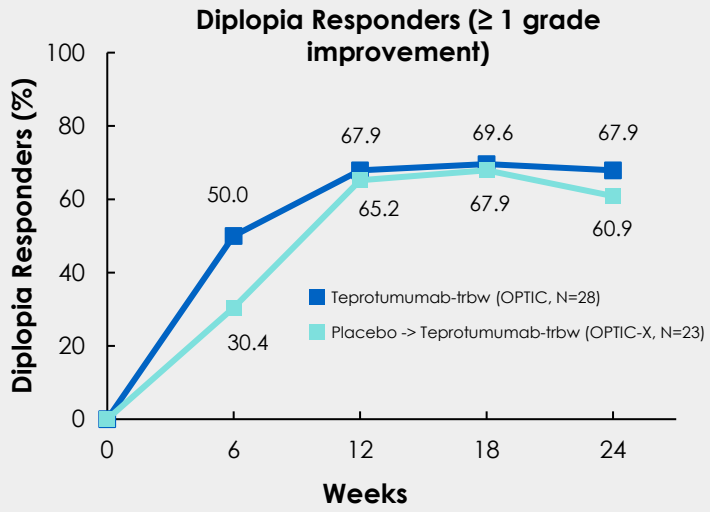
TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.

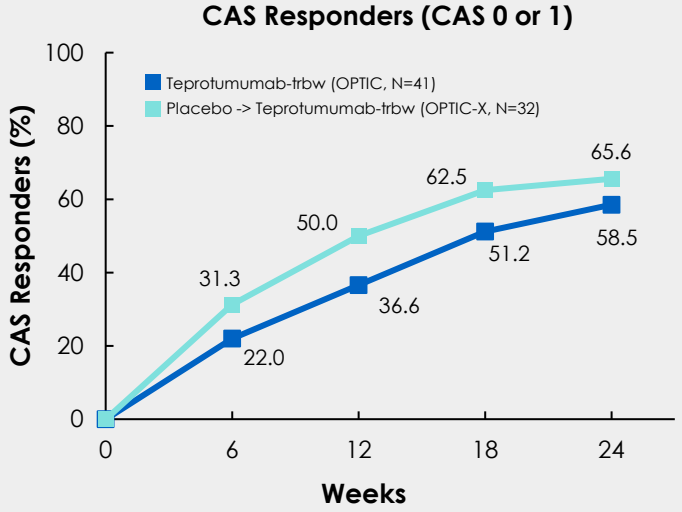
OPTIC-X Study

Treatment of Graves Orbitopathy to Reduce Proptosis with Teprotumumab-trbw Infusions in an Open-Label Clinical Extension Study









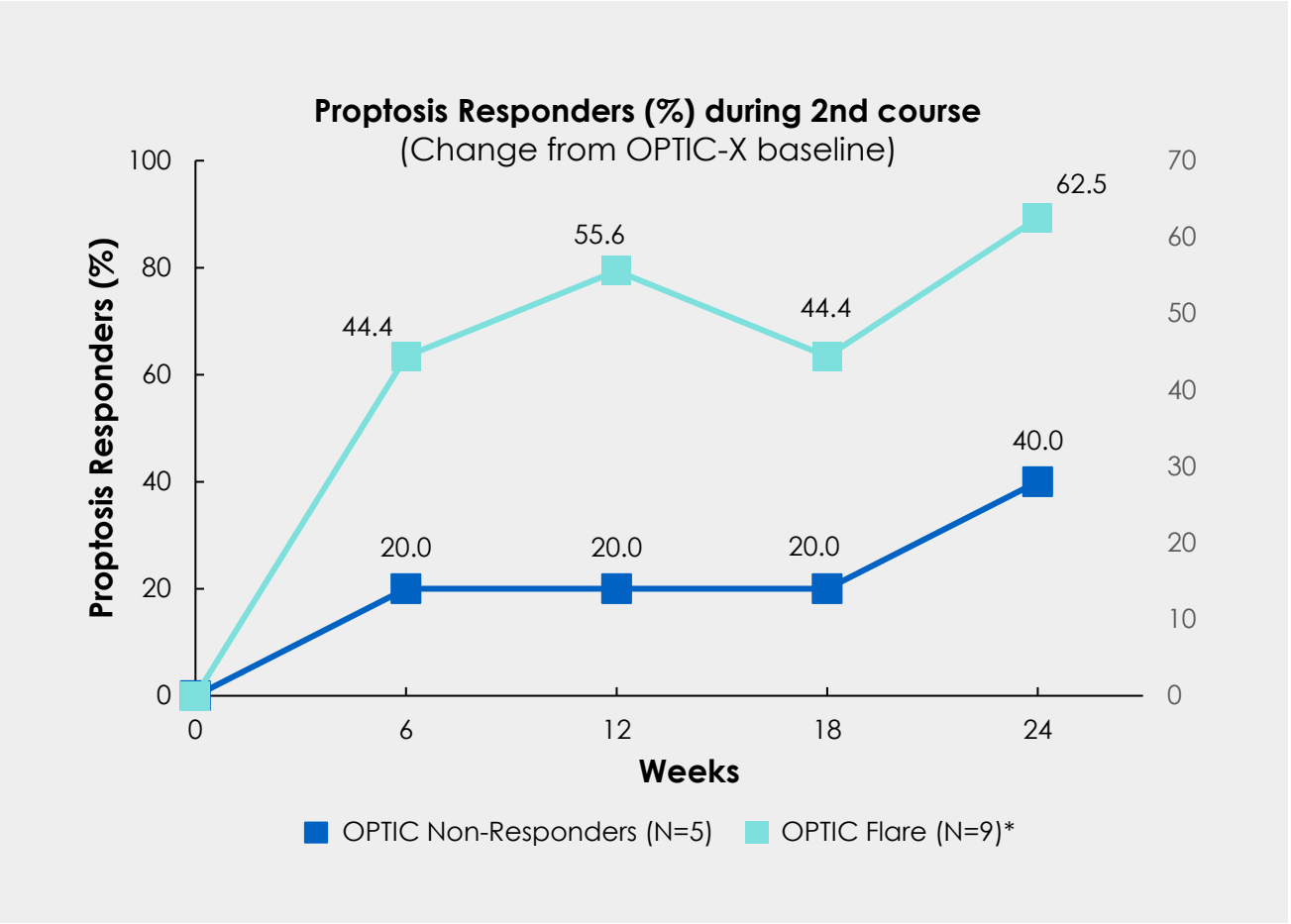
*Flare: Increase in proptosis of ≥2 mm in the study eye since Week 24, OR Increase in CAS ≥2 points since Week 24 with an absolute CAS of ≥ 4 in the study eye following the Week 24 Visit, AND Presence of symptoms (e.g. new onset of double vision).

Douglas RS, et al. *Ophthalmology*. 2022;129(4):438-449.

Proptosis Response with Retreatment

Teprotumumab-trbw Non-Responders and Flares from OPTIC Trial

- Of the OPTIC teprotumumab-trbw **non-responders**, 40% (2 of 5 of these patients) became responders when retreated
- Of the OPTIC teprotumumab-trbw **responders who flared**, 62.5% (5 of 8 patients)* became responders when retreated



*Only 8 patients contributing to data at week 24 as one patient had a significantly delayed visit due to COVID; excluded from week 24 analysis per SAP. This patient experienced a 5-mm reduction in proptosis and 4-point reduction at final assessment. Three patients not experiencing > 2 mm improvement in proptosis had reductions of 3 mm, 3 mm and 4 mm, respectively.

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Safety during OPTIC-X Treatment Period

	2nd Course (OPTIC Teprotumumab-trbw) N=14 (9 flares, 5 non-responders) n (%)	1st Course (OPTIC Placebo) N=37 n (%)
Any Serious Adverse Events	1 (7.1)	0 (0)
Cerebral Hemorrhage[a]	1 (7.1)	0 (0)
Any Adverse Event	11 (78.6)	32 (86.5)
Adverse Events in > 10% of Patients		
Muscle Spasm	4 (28.6)	18 (48.6)
Arthralgia	2 (14.3)	0 (0)
Back Pain	2 (14.3)	0 (0)
Nasal Dryness	2 (14.3)	0 (0)
Alopecia	2 (14.3)	4 (10.8)
Dry Skin	2 (14.3)	4 (10.8)
Hearing Impairment	2 (14.3)[b]	4 (10.8)[c]
Diarrhea	1 (7.1)	5 (13.5)
Fatigue	0 (0)	4 (10.8)
Dysgeusia	0 (0)	4 (10.8)
Any Adverse Events of Special Interest[d] > 10% of Patients	1 (7.1)	5 (13.5)
Potential Infusion-Related Reaction	1 (7.1)[e]	3 (8.1)[f]
Anaphylactic Reaction	0 (0)	0 (0)
Hyperglycemia	0 (0)	3 (8.1)[g]

OPTIC placebo patients

- All AEs were mild to moderate, and no patients experienced serious AEs

OPTIC teprotumumab-trbw non-responders or flares:

- One patient experienced a serious, life-threatening (grade 4) AE following third infusion
- All other AEs were mild or moderate and none led to study discontinuation

a. Patient experienced an intracerebral and subarachnoid hemorrhage and underwent neurosurgery for hematoma evacuation. Reporting investigator and his hospital consultants suggested event may be related to underlying medical condition and not study medication
b. Hearing impairment reported in 2 patients and persisted at the end of study: 1 patient experienced mild autophony (intermittent echoing) in the left ear and the other experienced mild hypoacusis. Both reported hearing impairment events earlier in OPTIC which resolved during that study.
c. Hearing impairment was reported in four patients as mild AEs: two with hypoacusis that resolved, one with tinnitus that resolved within 8 months, 1 patient with tinnitus that continued at last visit accompanied by muscle spasms (lower leg) of moderate severity that led to discontinuation after sixth infusion (considered treatment-related).
d. Diarrhea, hearing Impairment and muscle spasm AEs of special interest are included in the section AEs in > 10% of patient.
e. Infusion reaction was characterized as eye pain during the first infusion and asthenia during the second but did not discontinue study.
f. Three had infusion reactions characterized as dysgeusia during multiple infusions in one patient, generalized pruritis during second infusion in another, and post-infusion hypertension in a third patient. All completed the course of therapy.
g. Three experienced hyperglycemia: two developed new onset T2DM which persisted at end of study (baseline HbA1c was indicative of pre-diabetes in both). One patient experienced increased blood glucose concentration that resolved without medication.

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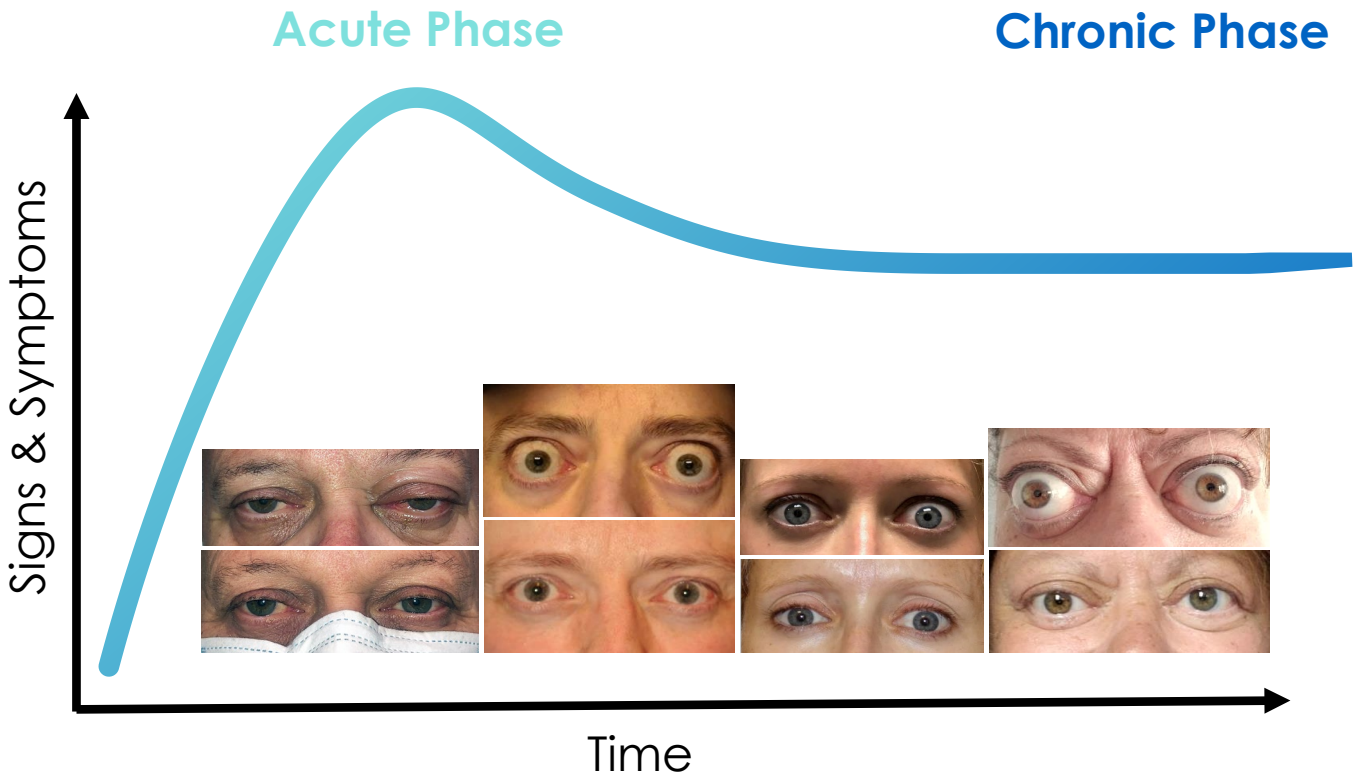
Evolving TED Disease State Understanding



"This treatment has the potential to alter the course of the disease, potentially sparing patients from needing multiple invasive surgeries by providing an alternative, nonsurgical treatment option."

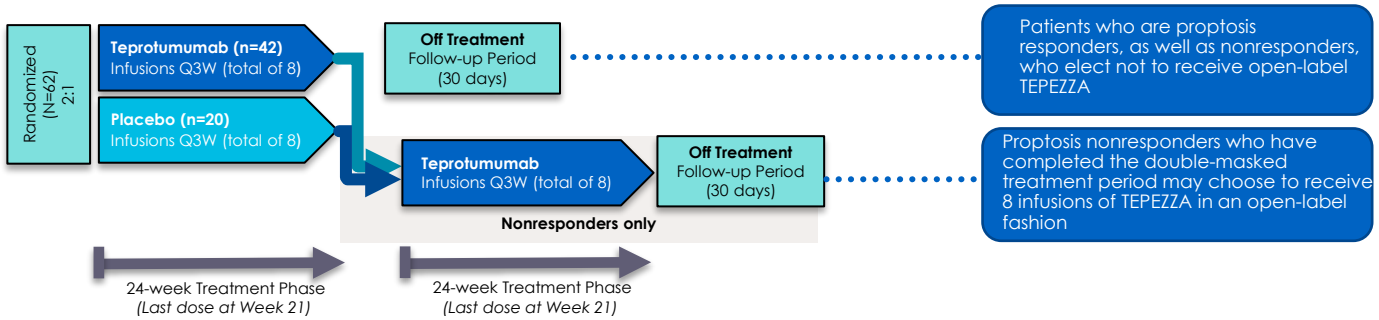
- Wiley Chambers, M.D.,
Deputy Director of the Division of Transplant and Ophthalmology Products in the FDA's Center for Drug Evaluation and Research

Source: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-thyroid-eye-disease

Phase 4: Low Disease Activity/Longer Duration TED

Patient Criteria

- 18-80 years
- **CAS ≤ 1**
- Initial diagnosis of **TED ≥2 years but <10 years** prior to Screening
- FT4 and FT3 <50% above or below normal limits



Primary Efficacy Outcome

- Change from baseline in proptosis (mm) at Week 24

Secondary Efficacy Outcomes (Week 24)

- Proptosis responder rate
- Change from baseline in GO-QOL
- Change from baseline in diplopia

Other Outcomes (Week 24)

- Pharmacokinetics
- Immunogenicity
- Safety and tolerability
- Change from baseline in orbital pain (VAS)
- Change from baseline in muscle and orbital fat volume (MRI)
- Change from baseline in biomarkers

	TEPEZZA (N=42)	Placebo (N=20)	P-value
Reduction in Proptosis – Week 24			
Intent-To-Treat	2.41 mm	0.92 mm	P = 0.0004
Per Protocol	2.44 mm	0.69 mm	P = 0.0006
Proptosis responder rate - Week 24 – (≥2 mm)			
Intent-To-Treat	62%	25.0%	P = 0.0134
Per Protocol	63%	7%	P = 0.0008

- Proptosis was significantly improved with teprotumumab-trbw vs placebo at Week 24
- The proportion of patients with a proptosis response at Week 24 was significantly higher with teprotumumab-trbw vs placebo
- No new safety signals were observed

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Phase 4: Safety

During Double-masked Treatment Period, N (%)	Placebo (N=20)*	TEPEZZA (N=41)
Any adverse events	16 (80.0)	33 (80.5)
Serious adverse events[a]	1 (5.0)	1 (2.4)
Adverse events leading to study drug discontinuation[b]	1 (5.0)	1 (2.4)
Adverse events leading to death	0	0
Adverse events of special interest	**7 (35.0)**	**15 (36.6)**
Infusion reaction	3 (15.0)	2 (4.9)
Hyperglycemia	2 (10.0)	6 (14.6)
Hearing impairment	2 (10.0)	9 (22.0)
New Onset/exacerbation IBD	0	0
Other Adverse Events		
Muscle spasms	2 (10.0)	17 (41.5)
Nausea	1 (5.0)	2 (4.9)
Alopecia	0	2 (4.9)
Diarrhea	4 (20.0)	8 (19.5)
Fatigue	2 (10.0)	9 (22.0)
Dysguesia	1 (5.0)	4 (9.8)
Headache	2 (10.0)	7 (17.1)
Dry skin	0	5 (12.2)
Nail bed disorder	0	2 (4.9)
Eye pain	1 (5.0)	5 (12.2)
Eye pruritus	0	3 (7.3)
HbA1c increased	0	3 (7.3)
Hypertension	0	3 (7.3)

*Includes patient who received one dose of teprotumumab-trbw in error

[a] TEP: left conductive hearing loss in pt with congenital hearing abnormality; PBO: DKA in patient with undiagnosed diabetes mellitus who received teprotumumab for one infusion (first infusion) in error, despite being randomized (assigned) to placebo group [b]TEP: conductive hearing loss (above) occurred in the double-masked period; pt completed the masked period and discontinued in the open-label period; PBO: infusion reaction (dull cardiac-related chest pain, pressure-like, non-radiating, slight difficulty breathing)

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Thank You