Gulf Thyroid Eye Disease Advisory Board Program – Advisors Pre-Read Material

May 24th, 2024

AMGEN
Rare Disease

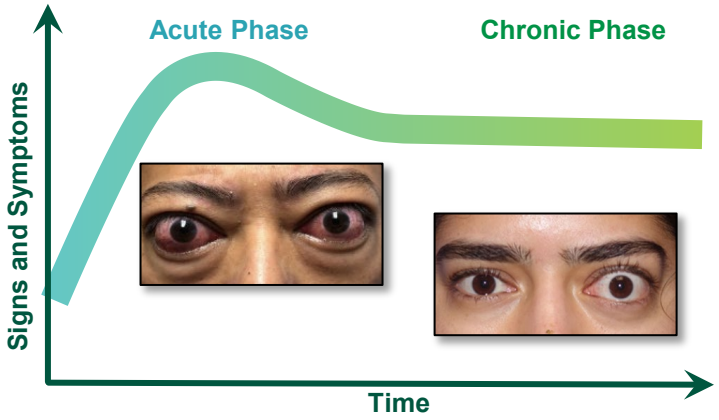
Thyroid Eye Disease Overview

Rare Disease

TED Overview

TED Is a Serious, Debilitating, and Potentially Vision-threatening Autoimmune Eye Disease[1]

- Generally thought to follow a defined disease course[1]
  - An active phase with inflammatory signs and symptoms progressing over time
  - A chronic phase in which inflammatory signs and symptoms stabilize and clinical manifestations reach a plateau above normal



Left image from Douglas RS, et al. *N Engl J Med*. 2020.[11]
Right image courtesy of Raymond Douglas, MD, PhD.

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

- **Up to 30-40% of patients with Graves' disease (GD) will develop TED[4,5]**
- **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]**

1. Wang Y, et al. *Ther Clin Risk Manag*. 2019;15:1305-1318. 2. Lazarus JH. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):273-279. 3. Perros P, et al. *Orphanet J Rare Dis*. 2017;12(1):72. 4. Prummel MF, et al. *JAMA*. 1993;269(4):479-482. 5. Perros P, et al. *Clin Endocrinol (Oxf)*. 1993;38(4):367-372. 6. Bartalena L, et al. *N Engl J Med*. 1998;338(2):73-78. 7. Khong JJ, et al. *J Clin Endocrinol Metab*. 2016;101(7):2711-2720. 8. Perros P, et al. *Nat Rev Endocrinol*. 2009;5(6):312-318. 9. Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-352.

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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]

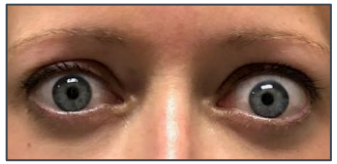
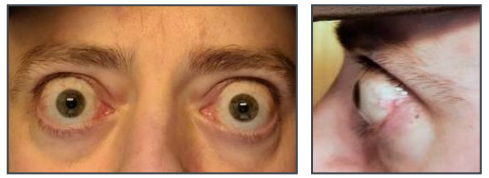


Figure adapted from Briceño CA, et al. *Int Ophthalmol Clin.* 2013; 53(3):93-101.

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

Orbital Fat[2-3]

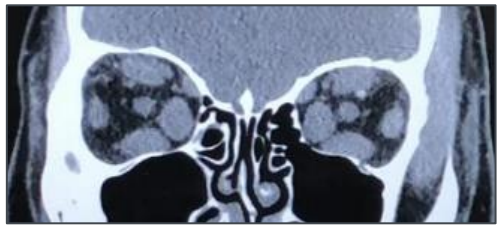


- **Proptosis 60%[8]**
- Pain
- Disfigurement
- Exposure keratopathy
- Vision loss

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 CB et al. *Eur J Endocrinol.* 2002;146(6):751-757.

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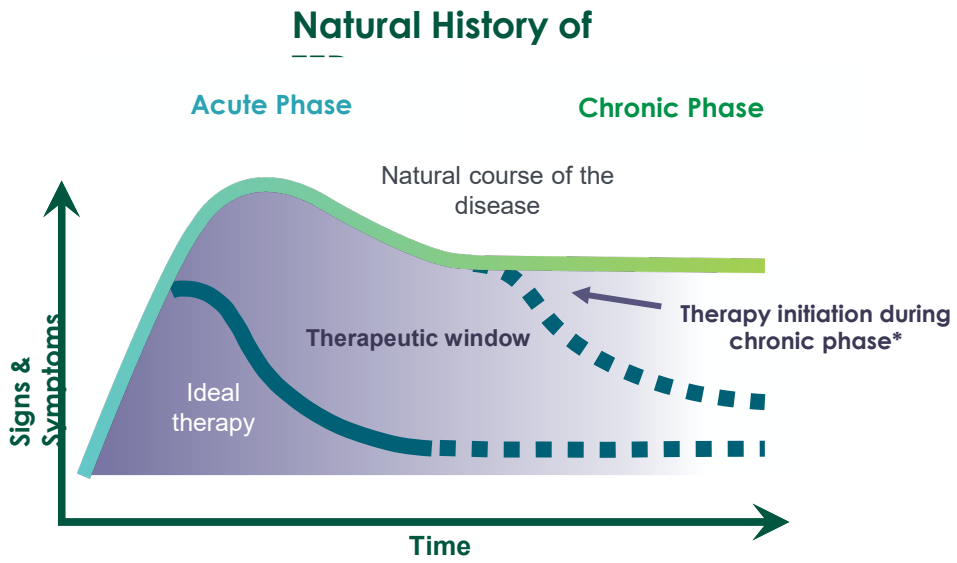
Understanding of the Natural Course of TED is Evolving

IGF-1R may Drive the Pathophysiology of TED throughout the Course of Disease[1-4]



Acute Phase
- Signs and symptoms worsen over time[1]

Chronic Phase
- Clinical manifestations reach a plateau above normal and patient may require intervention[1]

Therapeutic Window
- Initiating therapy early has been shown to be effective, but the therapeutic window may continue beyond the acute phase into the chronic phase[4,5]

Timing of Medical Intervention
- Early intervention is considered ideal to reduce signs and symptoms and minimize disease impact,[6] but there may be a broader window for treatment

*This is a theoretical model based on potential patient response when therapy is initiated during the chronic phase of TED.[4]

1. Wang Y, et al. *Ther Clin Risk Manag*. 2019;15:1305-1318. 2. Pritchard J, et al. *J Immunol*. 2003;170:6348-6354. 3. Smith TJ, et al. *J Clin Endocrinol Metab*. 2004;89:5076-5080. 4. Ozzello DJ, et al. *Am J Ophthalmol Case Rep*. 2020;19:100744. 5. Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-352. 6. Dolman PJ. *Ophthalmic Plast Reconstr Surg*. 2018;34(4S suppl 1):S34-S40.

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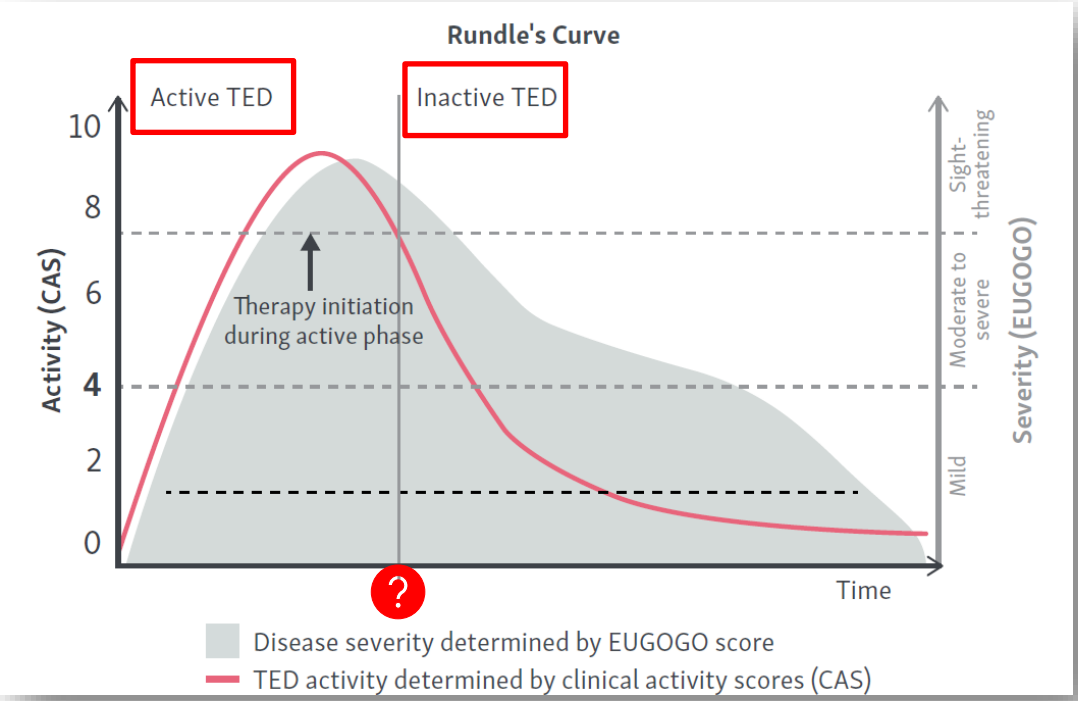
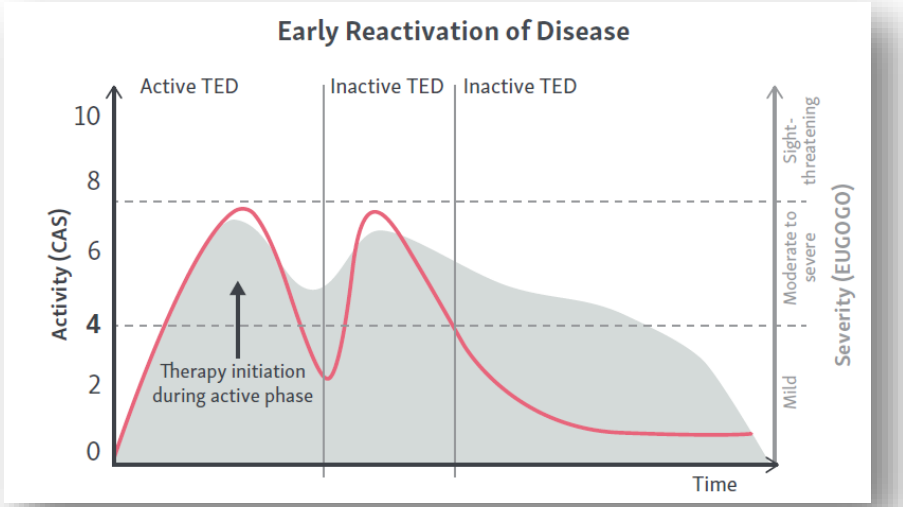
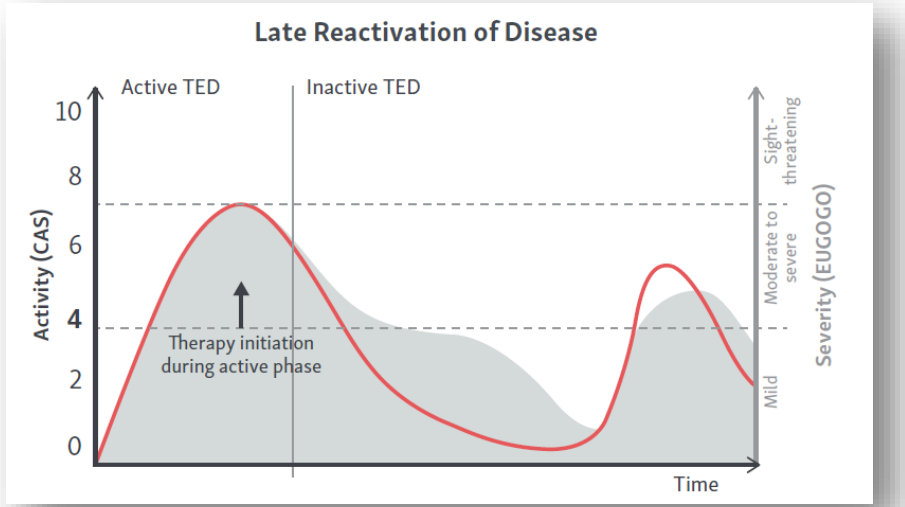
The Natural Course of TED







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.

*Content was adapted with permission from: Campi L, Fuggazola L. How can we prevent disease relapse in Graves' orbitopathy after immunosuppressive treatment? *Expert Rev Endocrinol Metab*. 2022;17(4):269-274

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Evaluation and Identification of TED

Clinical Assessment[1]	Laboratory Tests[2]	Imaging[3]
• CAS • Severity measures • Exophthalmometry • Diplopia • Ocular motility • Corneal involvement • Optic nerve involvement	• TSI • TSH • FT3 • FT4 • TPO • TRAb	• Orbital CT without contrast *Or* • Orbital MRI fat saturation with and without contrast

CAS, clinical activity score; CT, computed tomography; MRI, magnetic resonance imaging; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase antibodies; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

1. Bartalena L, et al. *Eur Thyroid J.* 2016;5(1):9-26. 2. Ross DS, et al. *Thyroid*. 2016;26(10):1343-1421. 3. Siakallis LC, et al. *Ophthalmic Plast Reconstr Surg.* 2018;34(4S Suppl 1):S41-S51.

Diagnosis of Thyroid Eye Disease

Clinical Activity Score (CAS)

1. Spontaneous orbital pain
2. Gaze evoked orbital pain
3. Eyelid swelling that is considered to be due to active GO
4. Eyelid erythema
5. Conjunctival redness that is considered to be due to active GO
6. Chemosis
7. Inflammation of caruncle OR plica

Diplopia Score

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

Upper Limits of Normal (Proptosis)

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)

Proptosis Measured By Exophthalmometer

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

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American Thyroid Association TED Severity Grades

Grade*	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

*Mild TED: 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 dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.
†Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

Ross DS, et al. *Thyroid.* 2016; 26(10):1343-1421.

European Group of Graves' Orbitopathy Classification of TED Severity

Mild

- Only a mild impact on daily life
- Insufficient signs/symptoms to justify immunosuppressive drugs or surgical treatment
- One or more of the following
  - Minor lid retraction (<2mm)
  - Mild soft tissue involvement
  - Proptosis (bulging of the eye out of the eye socket) <3mm above normal for race and gender
  - Transient or no diplopia (double vision)
  - Dry eye symptoms responsive to lubricants/ointments

Moderate-To-Severe

- Non sight-threatening, has sufficient impact on daily life to justify immunosuppression or surgical intervention
- Two or more of the following
  - Lid retraction ≥2mm
  - Moderate or severe soft tissue involvement
  - Proptosis ≥3 above normal for race and gender
  - Transient or constant diplopia

Sight-Threatening

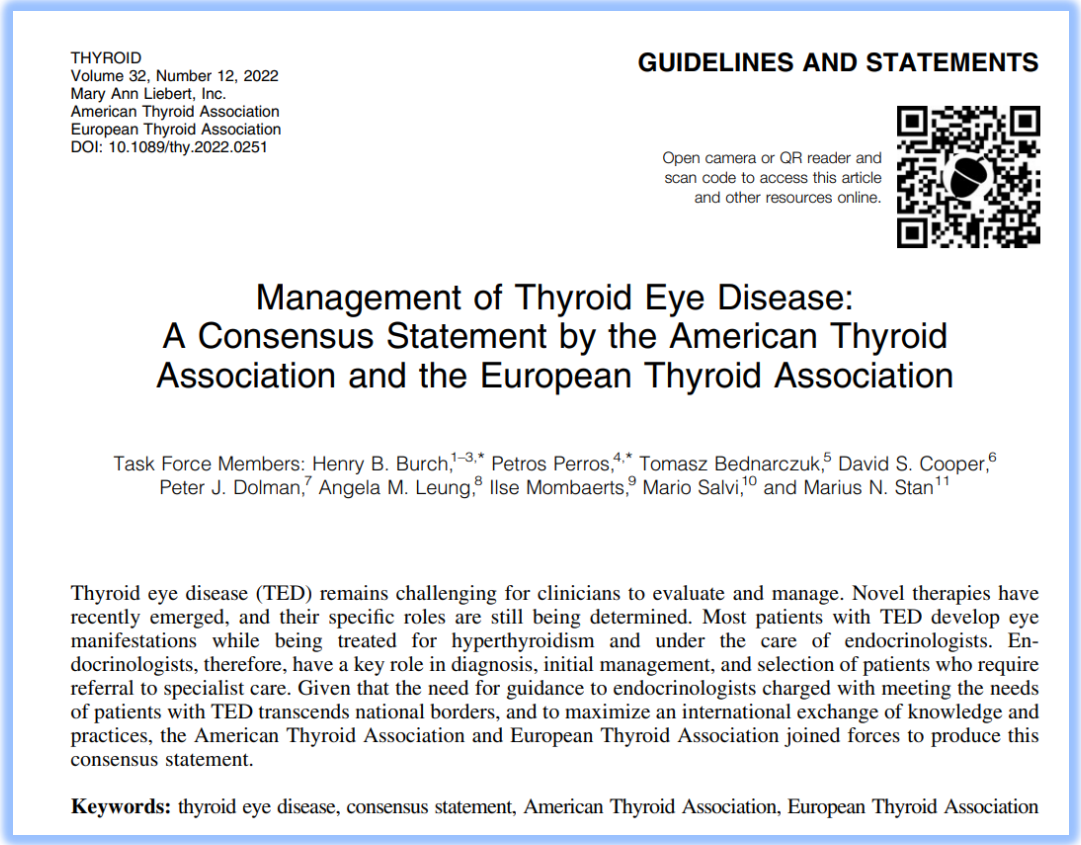
- Patients with TED with optic neuropathy and/or corneal breakdown
  - Warrants immediate intervention

Bartalena L, et al. *Eur Thyroid J*. 2016;5(1):9-26.

Thyroid Eye Disease treatment landscape

Rare Disease

ATA ETA Consensus Statement – Publications in US and EU Journals



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European Thyroid Association
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GUIDELINES AND STATEMENTS

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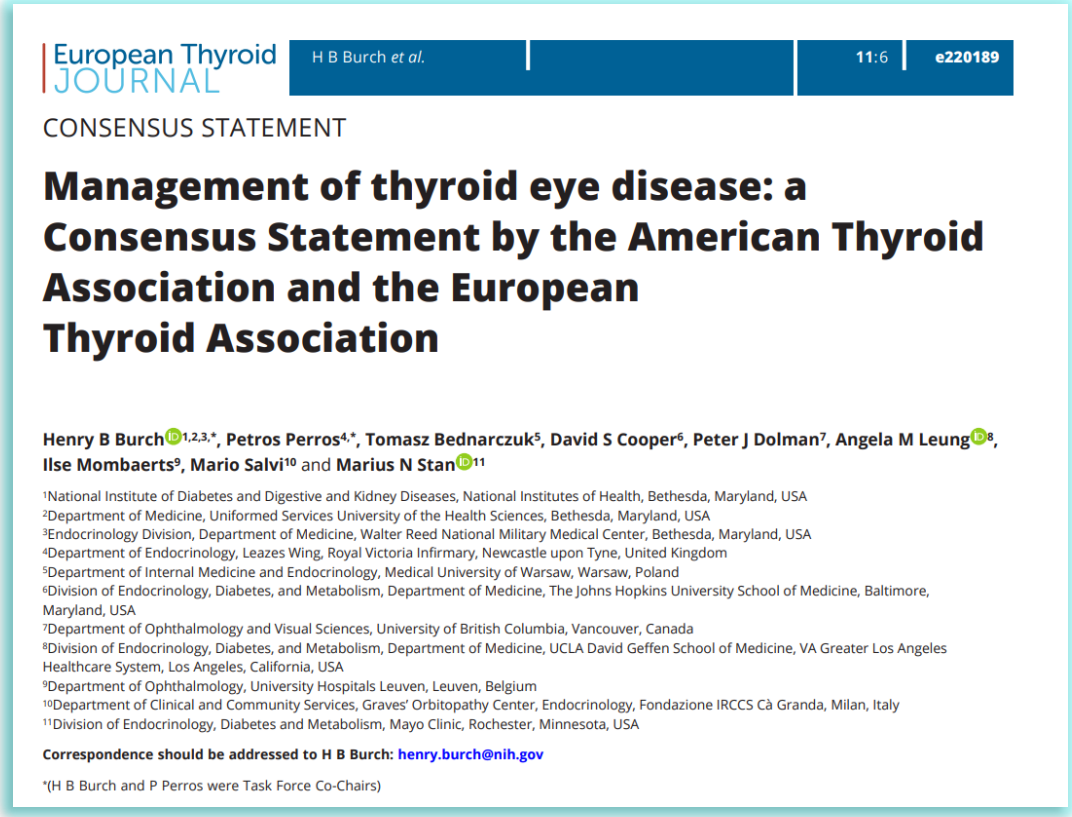
Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association

Task Force Members: Henry B. Burch,[1–3,*] Petros Perros,[4,*] Tomasz Bednarczuk,[5] David S. Cooper,[6] Peter J. Dolman,[7] Angela M. Leung,[8] Ilse Mombaerts,[9] Mario Salvi,[10] and Marius N. Stan[11]

Thyroid eye disease (TED) remains challenging for clinicians to evaluate and manage. Novel therapies have recently emerged, and their specific roles are still being determined. Most patients with TED develop eye manifestations while being treated for hyperthyroidism and under the care of endocrinologists. Endocrinologists, therefore, have a key role in diagnosis, initial management, and selection of patients who require referral to specialist care. Given that the need for guidance to endocrinologists charged with meeting the needs of patients with TED transcends national borders, and to maximize an international exchange of knowledge and practices, the American Thyroid Association and European Thyroid Association joined forces to produce this consensus statement.

Keywords: thyroid eye disease, consensus statement, American Thyroid Association, European Thyroid Association



European Thyroid JOURNAL | H B Burch *et al.* | 11:6 | e220189

CONSENSUS STATEMENT

Management of thyroid eye disease: a Consensus Statement by the American Thyroid Association and the European Thyroid Association

Henry B Burch[1,2,3,*], Petros Perros[4,*], Tomasz Bednarczuk[5], David S Cooper[6], Peter J Dolman[7], Angela M Leung[8], Ilse Mombaerts[9], Mario Salvi[10] and Marius N Stan[11]

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[6]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[7]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, Canada
[8]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, UCLA David Geffen School of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, California, USA
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[10]Department of Clinical and Community Services, Graves' Orbitopathy Center, Endocrinology, Fondazione IRCCS Cà Granda, Milan, Italy
[11]Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Rochester, Minnesota, USA

Correspondence should be addressed to H B Burch: henry.burch@nih.gov

*(H B Burch and P Perros were Task Force Co-Chairs)

1. Burch HB, et al. *Thyroid*. 2022 Dec 8.;32(12):1439-1470. Burch HB, et al. *Eur Thyroid J*. 2022 Dec 8;11(6):e220189.

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Thyroid Eye Disease

- Diagnose GD (measure TRAb)
- Restore stable euthyroidism[1]
- Urge smoking cessation
- Local measures
- Refer to TED Specialty Care[2]

Assessment of TED severity | **Assessment of TED activity** | **Assessment of QoL**

TREATMENT PLAN

Based on disease activity, severity, duration, trend across time, impact on daily living, treatment goals, patient age and comorbidities[3], patient preference, and availability of therapies and cost

MILD TED[4]

Treatment goals	Active phase / progressive disease			Inactive phase / stable disease
	Medical therapy		Surgical interventions and other	Surgical interventions and other
	Preferred therapy	Acceptable therapy		
Improvement in QoL / promote TED remission or prevention of progression	• Watchful monitoring • Selenium[6]	• OGC[5]	-	• Corrective surgical procedures (including orbital decompression, correction of eyelid retraction, blepharoplasties)

MODERATE –TO-SEVERE TED

Treatment goals	Active phase / progressive disease				Inactive phase / stable disease
	Medical and radiation therapy			Surgical interventions and other	Surgical interventions and other
	Preferred therapy (where available)	Acceptable therapy	May be considered		
Disease inactivation / reduction of ST involvement	• IVGC[7]	• RT ± IVGC/OGC • TEP	• RTX[10] • TCZ[11] • Watchful monitoring[12]		• Orbital decompression ("congestive" TED)[13] • Blepharoplasty
Disease inactivation and diplopia	• TEP	• RT ± IVGC/OGC			
Reduction of proptosis	• TEP				• Orbital decompression
Eye motility improvement	• IVGC[8] • RT ± IVGC/OGC • TEP[9]			• Selective ocular occlusion • Adhesive prisms	• Strabismus surgery • Permanent prisms
Reduction of lid aperture				• Botulinum toxin injection • Subconjunctival levator GC • Tarsorrhaphy	• Eyelid correction

Teprotumumab is recommended as **preferred** for patients with active, moderate-to-severe TED with proptosis and/or diplopia, as well as for eye motility improvement.

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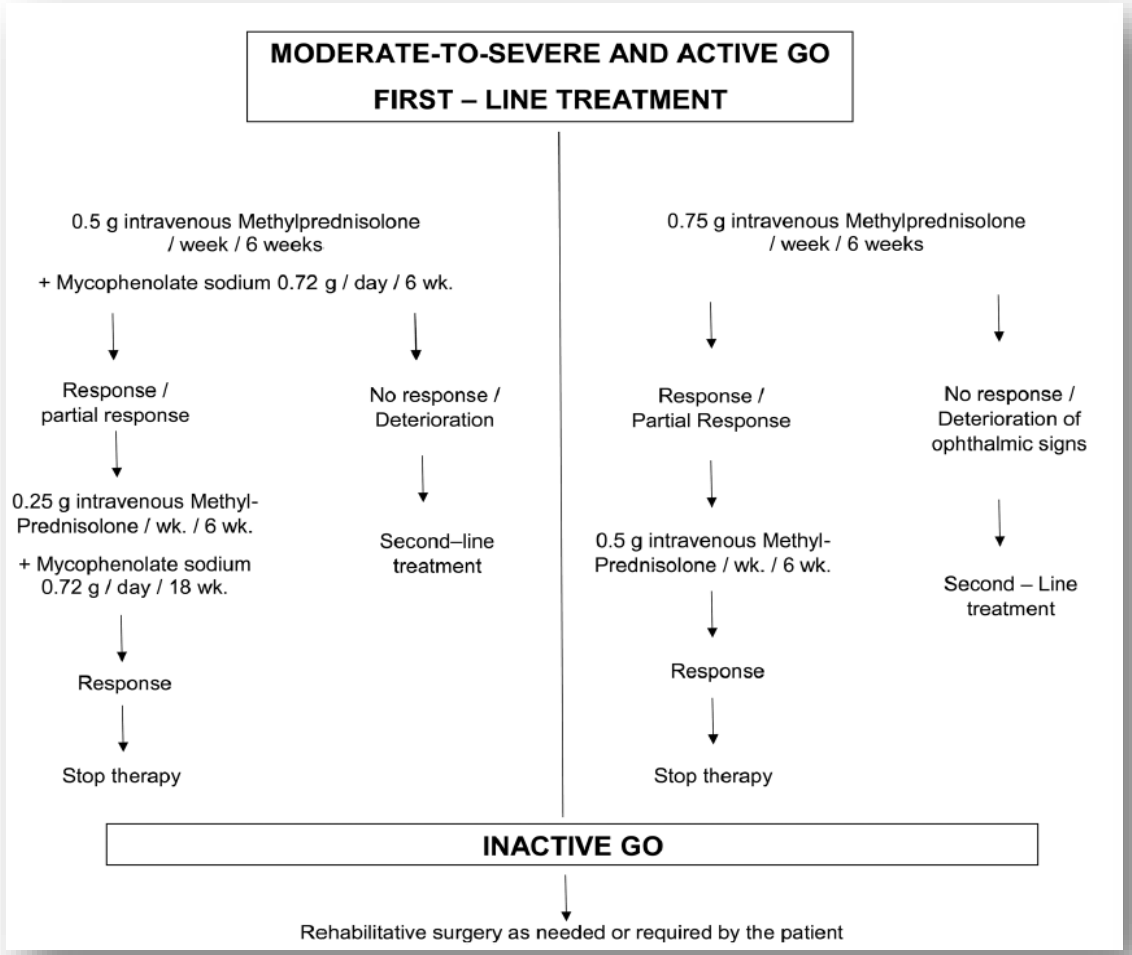
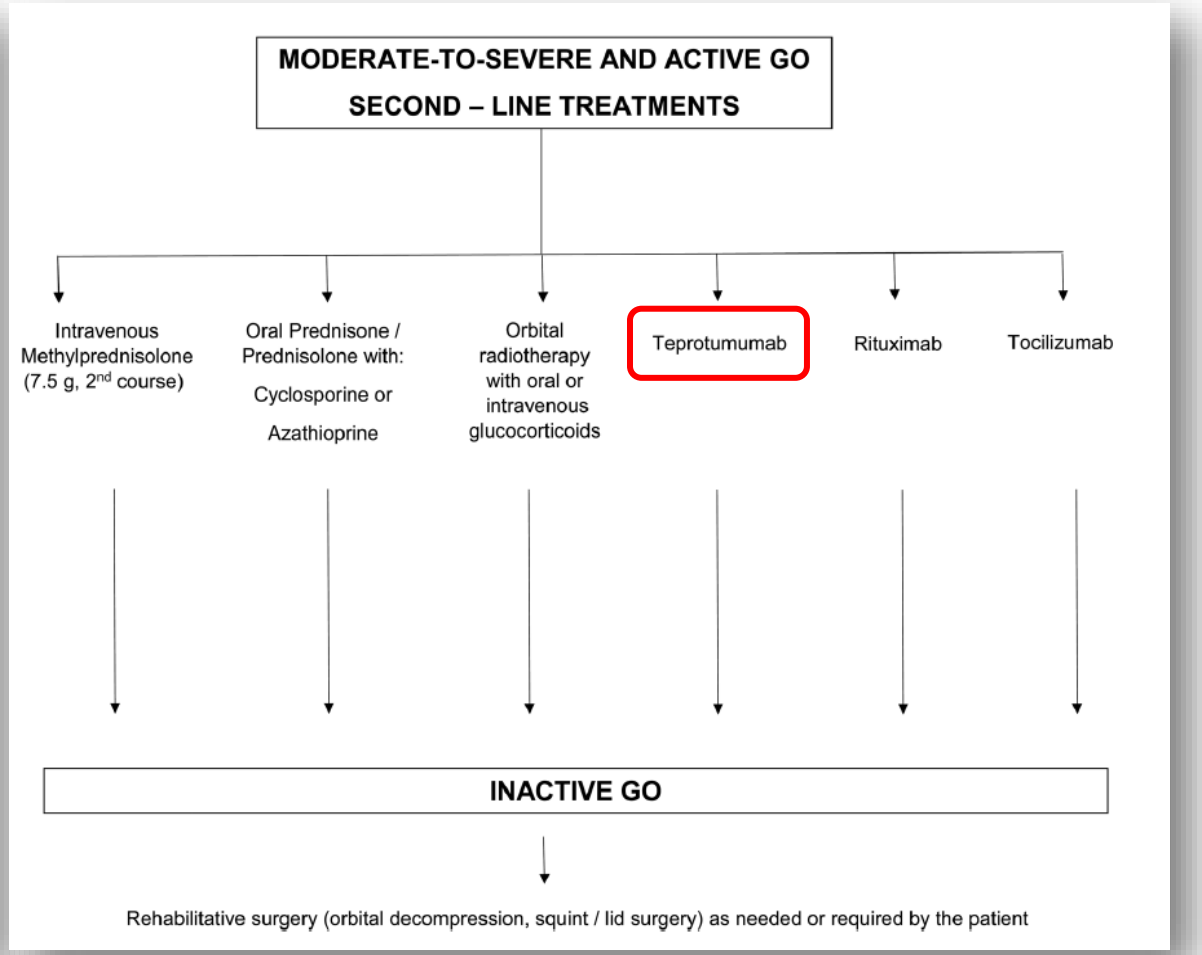
SIGHT THREATENING TED			
Diagnosis	Active phase / progressive disease		
	Medical and radiation therapy		Surgical interventions and other
	Preferred therapy	Acceptable therapy	
Compressive optic neuropathy	• IVGC[15]	• RT ± IVGC	• Orbital decompression
Stretch optic neuropathy[13] Subluxation[13]			• Orbital decompression • Lid retraction correction (for subluxation)
Corneal compromise[14]			• Lubricants and topical antibiotics • Bandaging • Tarsorrhaphy

Overview of the management of TED. An individualized approach to the management of TED, based on disease activity, severity, duration, trend across time, impact of the disease on daily living, treatment goals, patient age, and comorbidities, as well as the availability and relative costs of therapies, must be advised. Wherever possible, the Task Force members ranked therapeutic approaches as either 'preferred', 'acceptable', or 'may be considered' (see Section 2.1 for definitions). [1]See Fig. 1. [2]Except for the mildest cases improving with local measures. [3]See Table 8. [4]In most patients with mild TED, a 'watchful monitoring' strategy is sufficient (it includes simple measures, see Section 5.1 and Fig. 1). Selected cases (with a significant decrease in QOL) may be treated as moderate-to-severe TED. [5]In patients with symptomatic inflammatory soft tissue involvement or if radioactive iodine is used (oral glucocorticoids prophylaxis). [6]Particularly in countries that are selenium insufficient. [7]Standard treatment—IVGC (cumulative dose 4.5 g). [8]In selected patients, a higher cumulative dose of methylprednisolone (7.5 g) may be considered. [9]In patients with prominent soft tissue involvement and diplopia. [10]In patients with a short duration of TED (< 9 months). [11]In patients who are intolerant or resistant to IVGC. [12]In selected patients with moderate-to-severe TED, a 'watchful monitoring' strategy may be acceptable. [13]See Section 7.3.2, and Supplementary Figure S2a,b. [14]If there is coexistent active disease, then medical treatment as for moderate-to-severe disease is indicated in parallel with surgical treatment. [15]High doses of IVGC (500–1000 mg of methylprednisolone) for 3 consecutive days or on alternate days during the first week. IVGC, intravenous glucocorticoid.

2021 EUGOGO Guidelines Defines Steroids as 1st Line Treatment and Biologics, Including Teprotumumab, are in 2nd Line





Source: EUGOGO Guidelines

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Expected treatment effects: Drugs

	<25%	25-50%		51-75%	>75%	
Drug	**Composite outcome**	**CAS**	**Proptosis ↓ 2mm**	**Diplopia ↓ 1 class**	**Disease relapse(weeks)**	
IVGC *(Zang 2011 JCEM, Salvi 2015 JCEM, Kahlay 2018 Lancet, Campi, 2021 Frontiers Endo)*	**23-53%**	**45-83%**	**0-46%**	**0-60%**	**21-40% (after 12 weeks)**	
MMF *(Kahaly 2018 Lancet)*	**63%**	**80%**	**n.n.**	**n.n**	**8% week 12 11% week 24**	
RTX (Salvi 2015 JCEM)	**60%**	**100%**	**30%**	**20%**	**0% week 40**	4 Mo
RTX *(Stan 2015 JCEM)*	**8%**	**31%**	**No change**	**No change**	**0% week 40**	12 Mo
TCZ *(Peres-Moreiras AJO 2018)*	**73%**	**93%**	**27%**	**7%**	**No data**	
TEP *(Douglas 2020 NEJM)*	**78%**	**59%**	**83%**	**68%**	**29% week 51 Real life: 15-20%**	
Placebo *(Douglas 2020 NEJM)*	**7-22%**	**29-59%**	**10%**	**29%**		
IVGC + Irradiation	**64%**	**76,4%**	**13%**	**26%**	**Worsening CAS 1,4% Proptosis 6% Motility 21% Diplopia 21%**	

Salvi 2023 ETA consensus, Burch et al. 2023 Thyroid

Slide: courtesy of Prof Anja Eckstein, 2023, modified

Reference: Eckstein A et al. Current Therapeutic Approaches… Klin Monatsbl Augenheilkd 2024; 241: 48–67

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Teprotumumab Clinical Evidence in Thyroid Eye Disease

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The role of IGF1-R in TED Pathogenesis and Teprotumumab MOA

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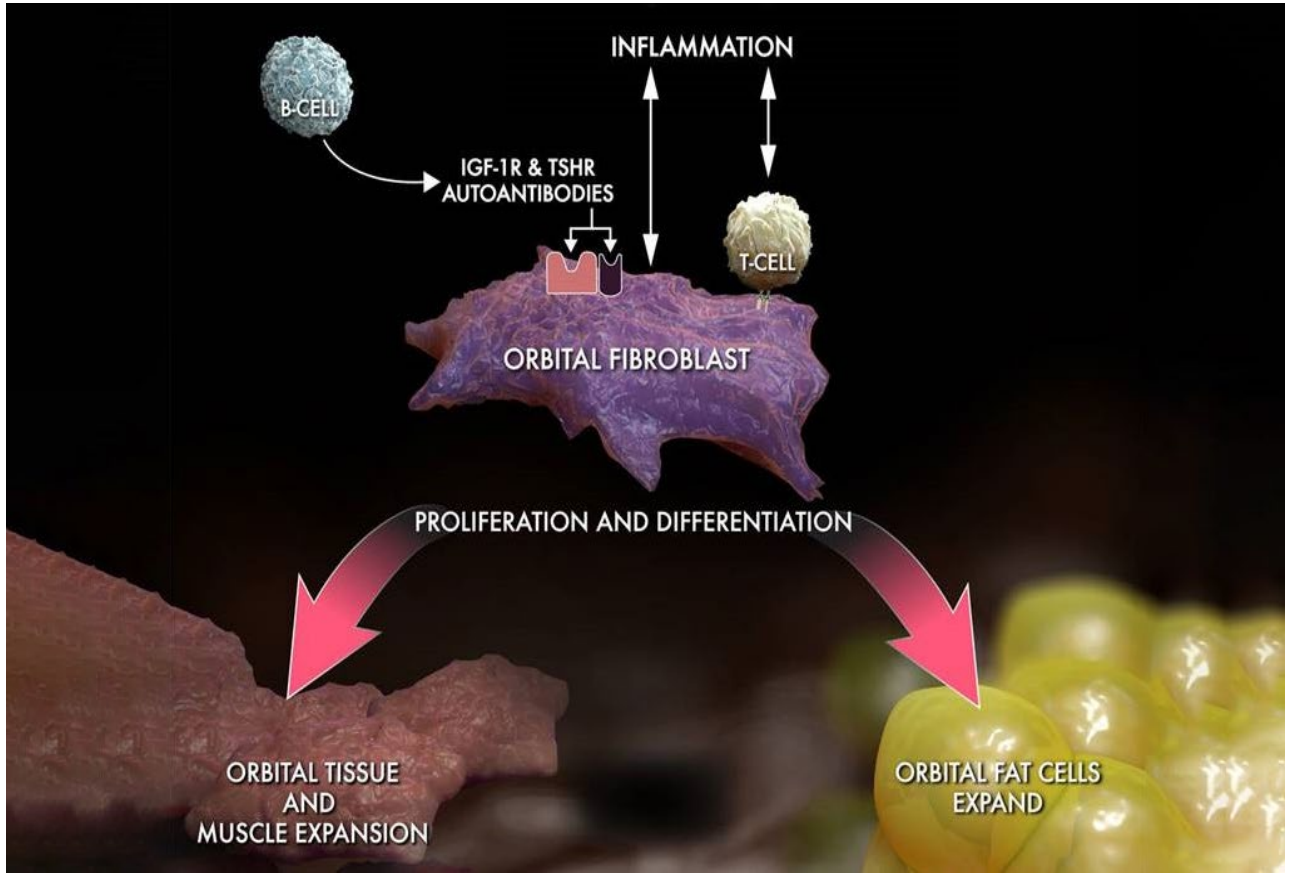
Pathology of TED

- 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]



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

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.

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Teprotumumab-trbw Overview

Teprotumumab-trbw	• Fully human monoclonal antibody against IGF-1R[1]
Mechanism of Action (MOA)	• IGF-1R inhibitor[1]
Administration	• 1 infusion q3w across 21 weeks (8 total infusions)[1] • First infusion of 10 mg/kg followed by 7 infusions of 20 mg/kg[1] • First two infusions administered over 90 min and 60 min for each subsequent infusion, if tolerated well[2]
FDA Designations	• Orphan drug, fast track, and breakthrough therapy designations[3] • Approved January 21, 2020[4]

FDA, Food And Drug Administration; IGF-1R, Insulin-like Growth Factor-1 Receptor; Q3w, Every Three Weeks; TSHR, Thyroid-stimulating Hormone 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. 2. Data On File: Clinical Study Protocol For Teprotumumab-trbw (HZN-001). Protocol Number: HZNP-TEP-301. Version 3.0, Incorporating German Amendment 1.1 And Amendment 2. April 16, 2018. 3. Horizon Pharma. Events & Presentations. Http://Ir.Horizon-pharma.Com/Static-files/Ea9e5fb6-45d0-498a-8001-6949540eef4f. Accessed November 15, 2018. 4. TEPEZZA (Teprotumumab-trbw) [Prescribing Information] Horizon.

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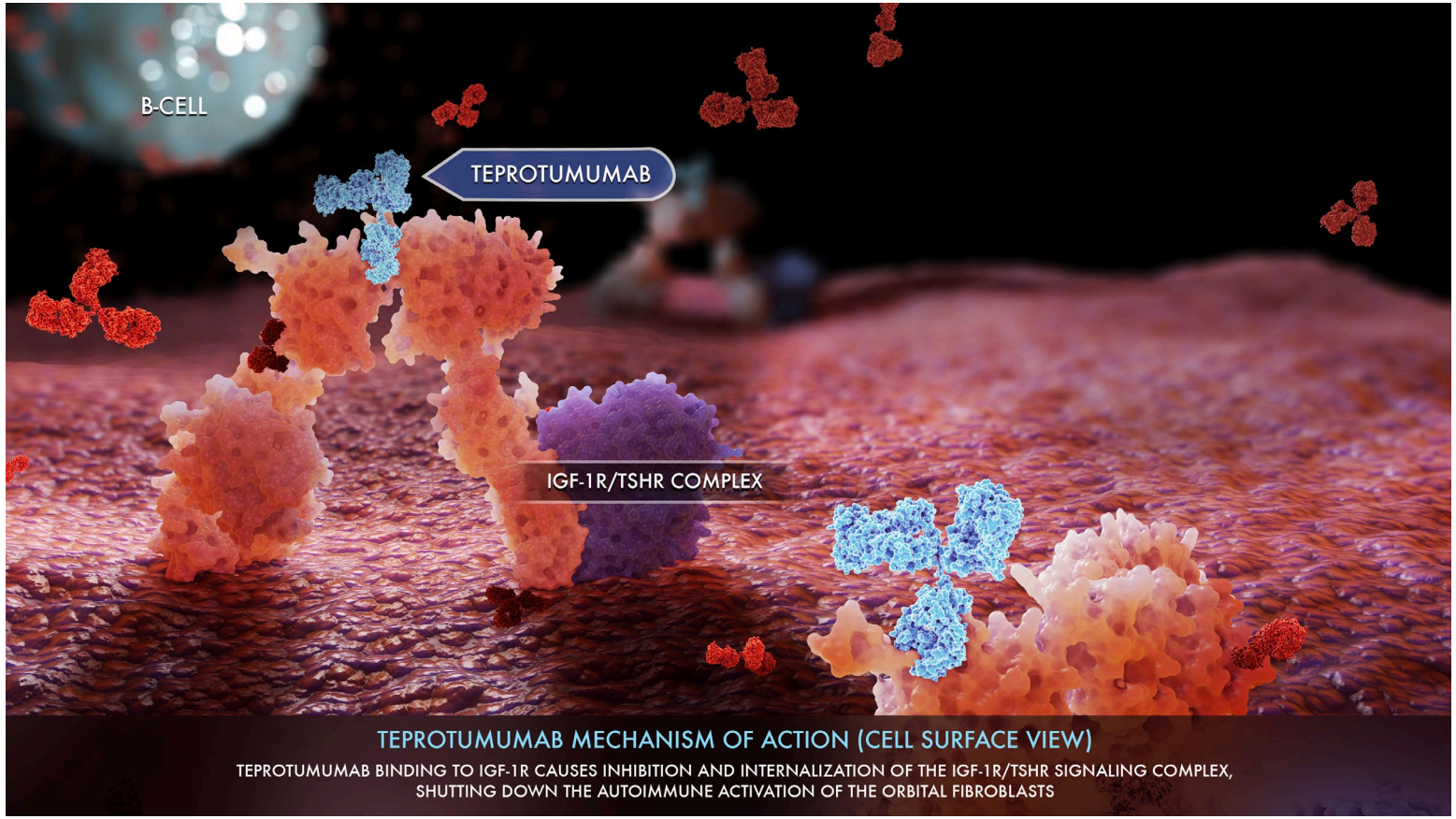
Teprotumumab-trbw Targets Underlying Pathophysiology of TED



- Teprotumumab-trbw inhibits IGF-1R on orbital fibroblasts, blocking autoantibody activation of the IGF-1R/TSHR signaling complex and reducing the inflammation, tissue expansion, and remodeling that cause the signs and symptoms of TED[1-5]

1. Pritchard J, et al. J Immunol. 2003;170(12):6348-6354. 2. Tsui S, et al. J Immunol. 2008;181(6):4397-4405. 3. Krieger CC, et al. J Clin Endocrinol Metab. 2016;101(6):2340-2347. 4. Chen H, et al. J Clin Endocrinol Metab. 2014;99(9):E1635-1640. 5. Data on file: Investigator's brochure for teprotumumab (HZN-001) human anti-IGF-1 receptor antibody for ophthalmic indications including thyroid eye disease. Edition 7.0. Effective Date: 07 July 2017.

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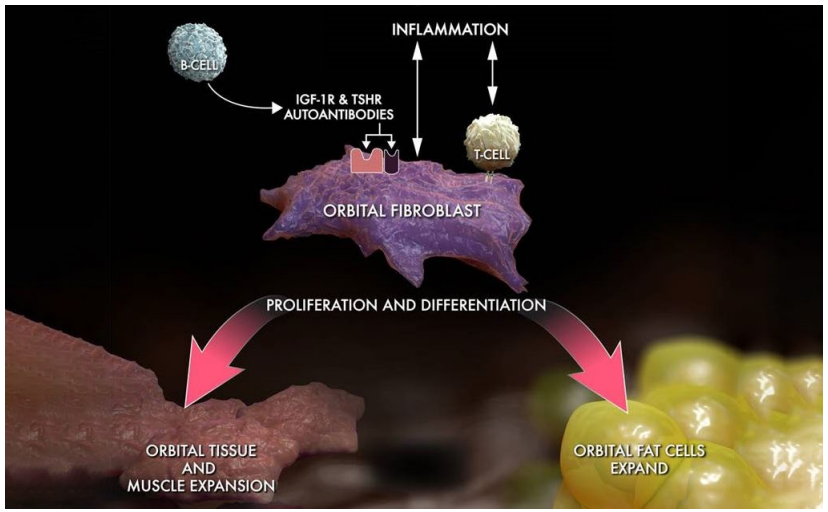
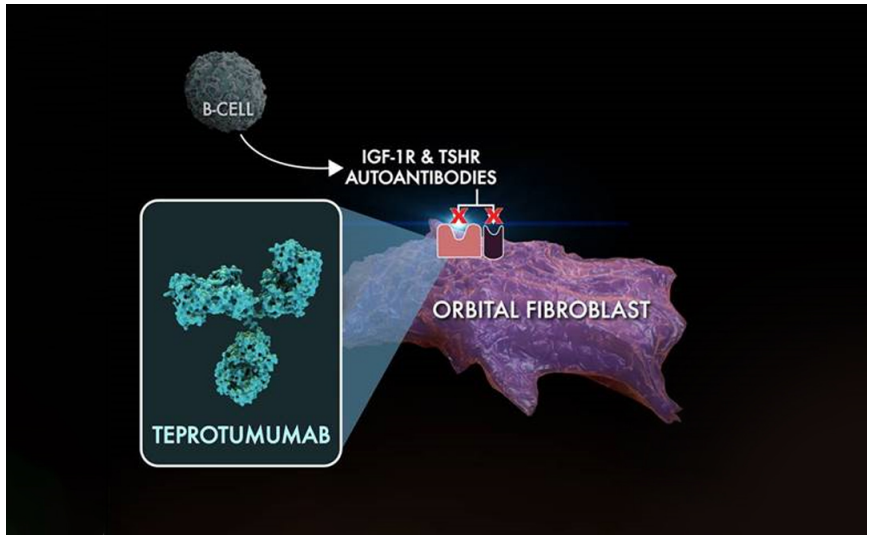
Mechanism of Action of Teprotumumab-trbw for TED



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]



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 precent 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.

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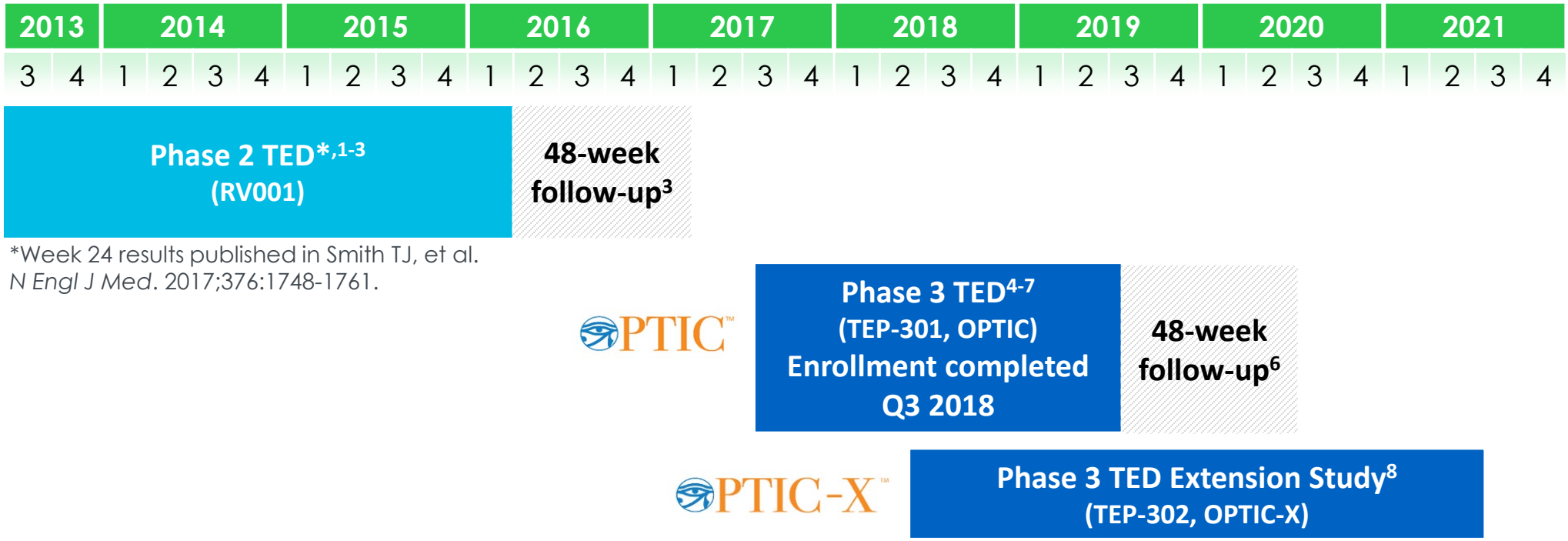
Phase 3 (OPTIC)

AMGEN

Rare Disease

Efficacy and Safety of Teprotumumab-trbw Was Studied in Robust, Well-Designed Clinical Trials



OPTIC, treatment of Graves' orbitopathy (thyroid eye disease) to reduce proptosis with teprotumumab infusions in a randomized, placebo-controlled, clinical study; OPTIC-X, Treatment of Graves' orbitopathy to reduce proptosis with teprotumumab infusions in an open-label clinical extension study; TED, thyroid eye disease.

1. Smith TJ, et al. N Engl J Med. 2017;376(18):1748-1761. 2. Horizon Pharma USA, Inc. Teprotumumab (RV 001) treatment in patients with active thyroid eye disease. https://www.clinicaltrials.gov/ct2/show/NCT01868997. Accessed November 27, 2018. 3. Data on file: Statistical analysis plan. A multicenter, double-masked, placebo-controlled, efficacy and safety study of RV001, an insulin-like growth factor-1 receptor (IGF-1R) antagonist antibody (fully human), administered every 3 weeks (q3w) by intravenous (IV) infusion in patients suffering from active thyroid eye disease (TED). Final, Version 2.0. October 5, 2015. 4. Douglas RS, et al. N Engl J Med. 2020;382(4):341–352. 5. Horizon Pharma USA, Inc. Treatment of Graves' orbitopathy (thyroid eye disease) to reduce proptosis with teprotumumab infusions in a randomized, placebo-controlled, clinical study (OPTIC). https://www.clinicaltrials.gov/ct2/show/NCT03298867. Accessed November 15, 2018. 6. Horizon Pharma plc completes enrollment of confirmatory Phase 3 trial of teprotumumab ahead of schedule [news release]. Dublin, Ireland: Horizon Pharma; September 4, 2018. http://ir.horizon-pharma.com/news-releases/news-release-details/horizon-pharma-plc-completes-enrollment-confirmatory-phase-3. Accessed January 2, 2019. 7. Data on file: Clinical study protocol for teprotumumab (HZN-001). Protocol Number: HZNP-TEP-301. Version 3.0, incorporating German Amendment 1.1 and Amendment 2. April 16, 2018. 8. Horizon Pharma USA, Inc. Treatment of Graves' orbitopathy to reduce proptosis with teprotumumab infusions in an open-label clinical extension study (OPTIC-X). https://www.clinicaltrials.gov/ct2/show/NCT03461211. Accessed November 27, 2018.

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Phase 3 Results Published in NEJM 2020

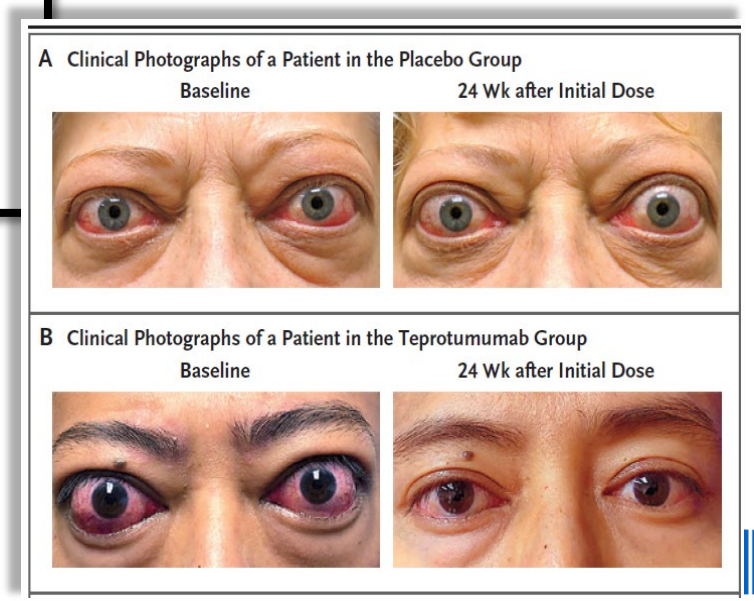
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teprotumumab for the Treatment of Active Thyroid Eye Disease

R.S. Douglas, G.J. Kahaly, A. Patel, S. Sile, E.H.Z. Thompson, R. Perdok, J.C. Fleming, B.T. Fowler, C. Marcocci, M. Marinò, A. Antonelli, R. Dailey, G.J. Harris, A. Eckstein, J. Schiffman, R. Tang, C. Nelson, M. Salvi, S. Wester, J.W. Sherman, T. Vescio, R.J. Holt, and T.J. Smith

OPTIC Study Published in NEJM



Douglas, et al. New Engl J Med 2020;382(4):341-352.

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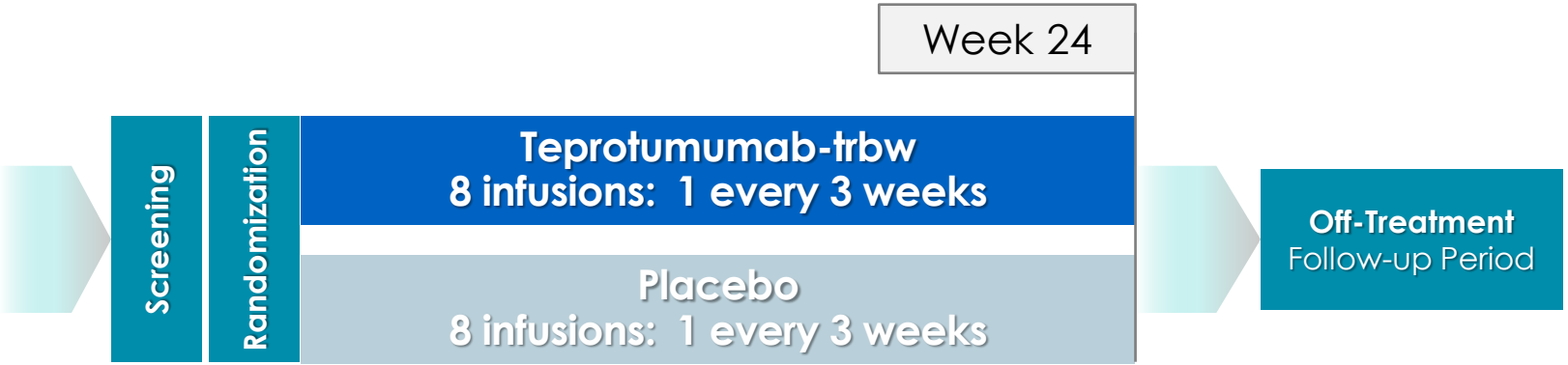
Trial Design: 24-Week Randomized, Double-Masked, Placebo-Controlled Trial of teprotumumab-trbw

Patient Criteria

- TED
- 18–80 years
- <9 months since TED onset with no prior treatment
- CAS ≥4
- FT4 and FT3 <50% above or below normal limits
- Negative serum pregnancy test at screening and negative urine pregnancy tests at all protocol-specified timepoints



Primary endpoint at Week 24

Percentage of participants with ≥2 mm reduction in proptosis

CAS, Clinical Activity Score (a 7-point scale that measures change in orbital inflammation and pain; a score of ≥3 indicates active TED); FT3, free triiodothyronine; FT4, free thyroxine

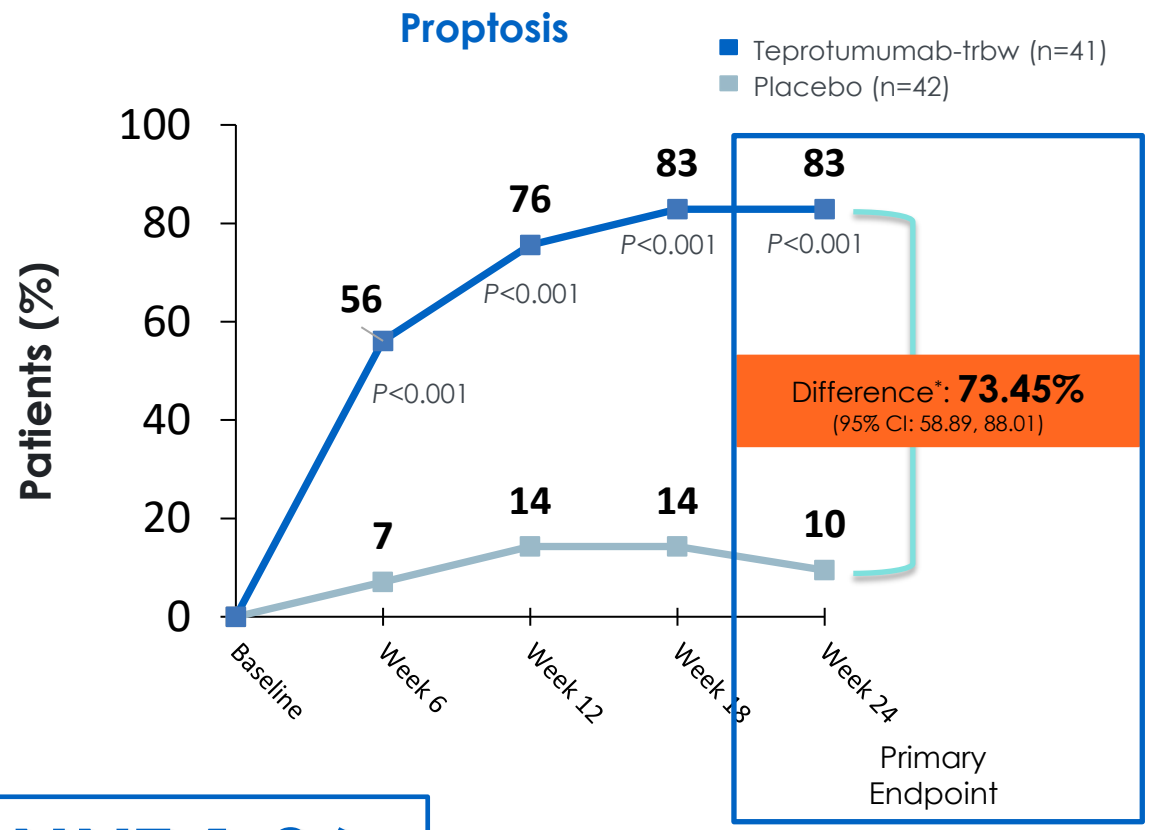
Douglas RS, et al. N Engl J Med. 2020;382(4):341–352.

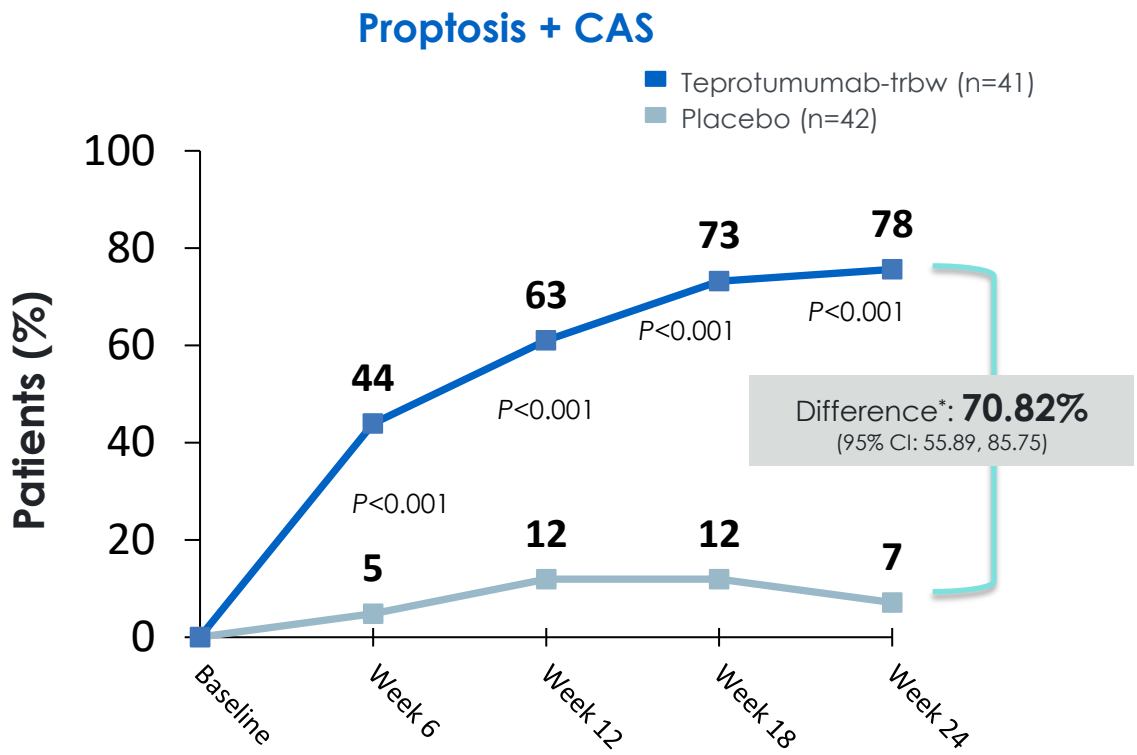
Baseline Characteristics

Patient Demographics	Placebo (n=42)	Teprotumumab-trbw (n=41)
Age (y), mean (SD)	48.9 (12.96)	51.6 (12.63)
Gender, %		
Male	26.2%	29.3%
Female	73.8%	70.7%
Race, %		
White	88.1%	85.4%
Black	4.8%	9.8%
Asian	2.4%	4.9%
Other	4.8%	0%
Years since diagnosis of Graves' disease, median (range)	0.905 (0.09–14.81)	1.04 (0.26–28.24)
Months since diagnosis of TED, median (range)	6.830 (1.05–10.33)	6.32 (0.92–9.67)
Smoking status, %		
Nonsmoker	81.0%	78.0%
Smoker	19.0%	22.0%

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

Greater Proportion of Teprotumumab-trbw Patients were Proptosis or Proptosis + CAS Responders



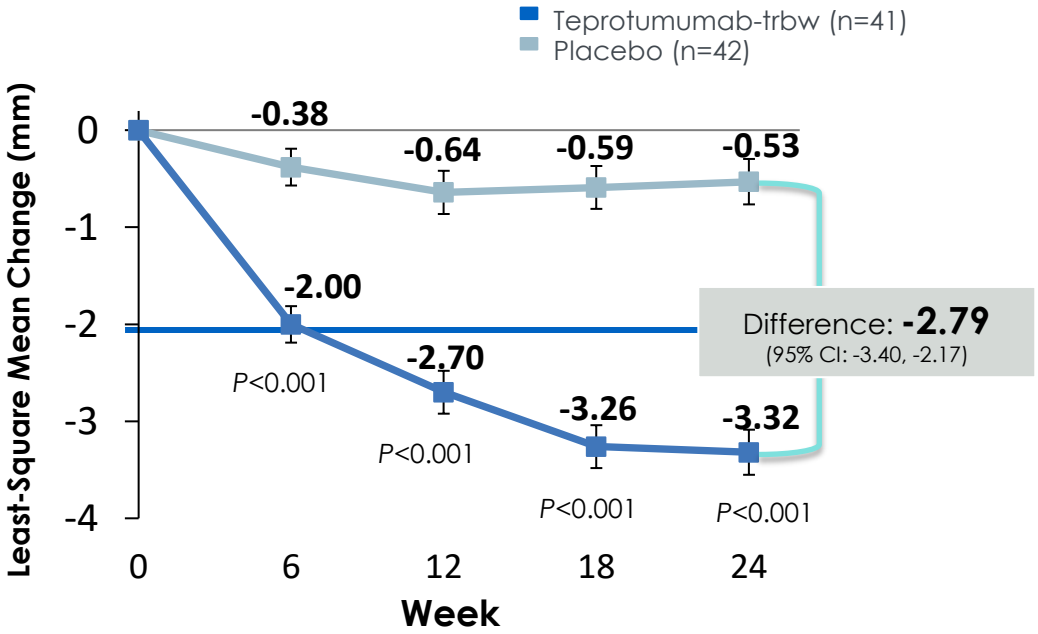


NNT 1.36

CI, confidence interval. *Stratified Difference in Response Rates. Estimates from the 2 strata (tobacco user, tobacco non-user) are combined with Cochran-Mantel-Haenszel weights.
Adapted from: Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-352.

Greater Reduction in Proptosis by Visit with Teprotumumab-trbw

Change From Baseline in Proptosis by Visit

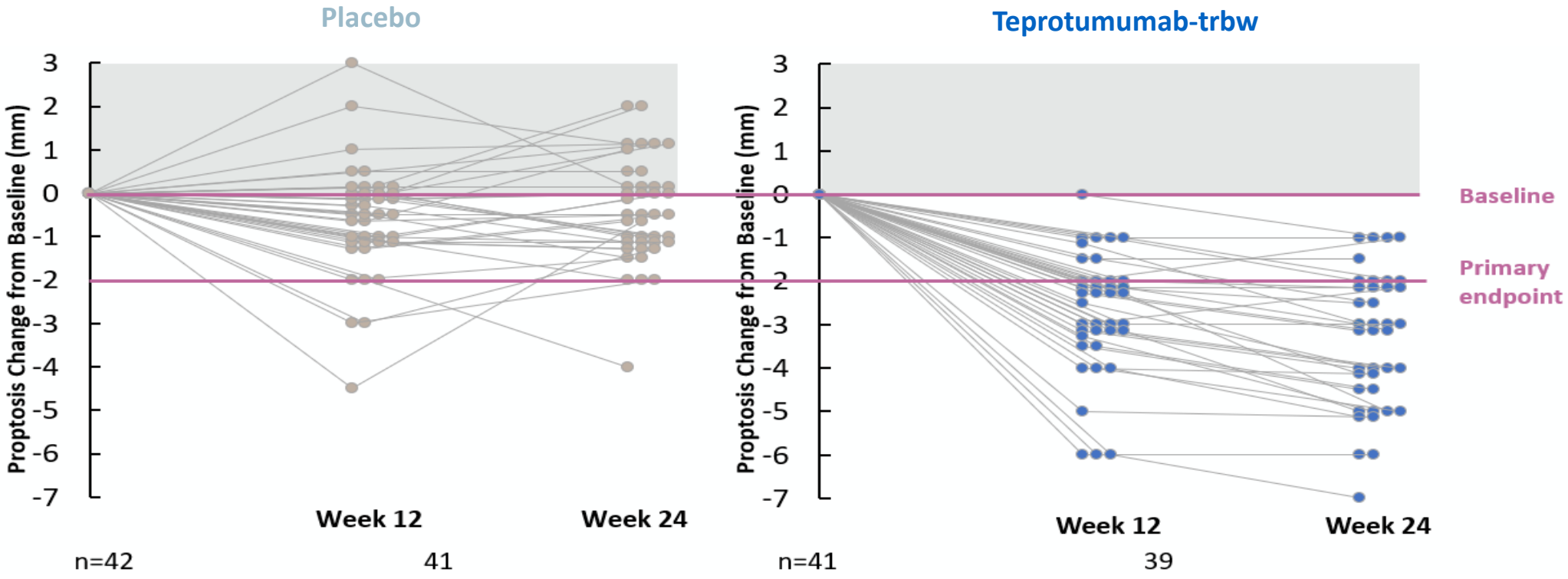


Overall Average Proptosis Reduction Over the Treatment Period

Proptosis (mm)	Baseline*	Change from Baseline†	*P* value
Placebo (n=42)	23.2 ± 3.2	−0.54 ± 0.19	<0.001
Teprotumumab-trbw (n=41)	22.6 ± 3.3	−2.82 ± 0.19	

*Mean ± standard deviation. †Change from baseline in proptosis as a continuous variable is based on Mixed-Model Repeated-Measures (MMRM) analysis of covariance (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.
Adapted from: Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-352.

Individual Patient Plots Indicate Nearly All Teprotumumab-trbw Patients Experienced Proptosis Reduction

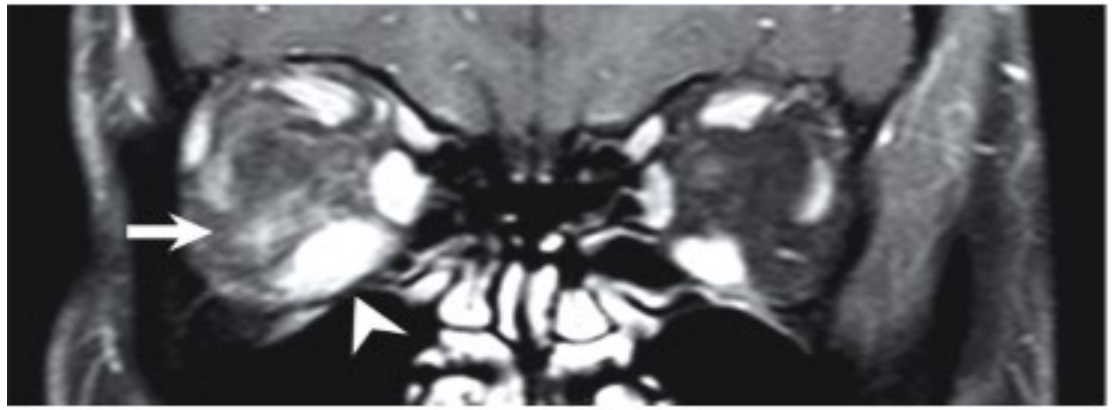


Note: Excludes 2 teprotumumab-trbw patients who did not complete the course of therapy.
Douglas RS, et al. [supplemental appendix]. *N Engl J Med*. 2020;382(4):341-352.

Teprotumumab-trbw Decreased Proptosis and Reduced Orbital Swelling

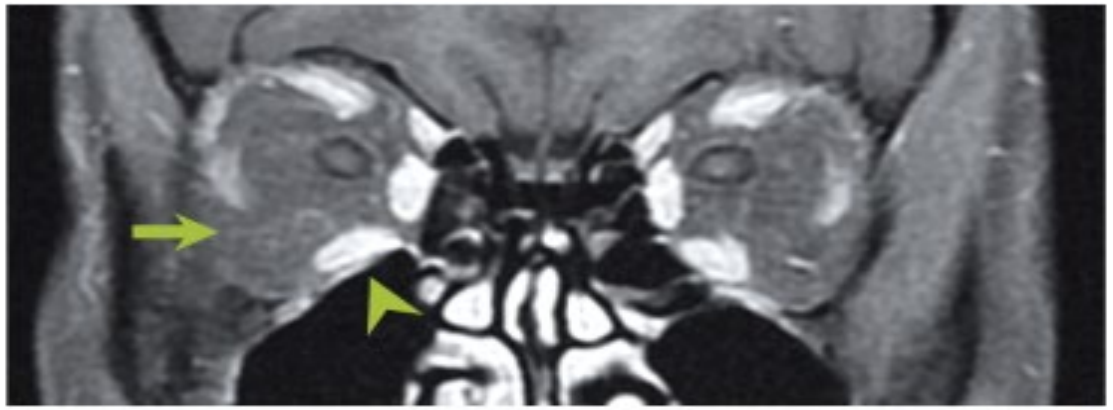
Coronal, Contrast-enhanced, Fat-saturated, T1-weighted MRI

Baseline



- Marked enhancement (inflammation/ edema) of the inferior rectus muscle (white arrowhead) and orbital fat (white arrow)
- Patient had proptosis measurement of 23 mm, inflammatory signs and symptoms of TED, and Gorman diplopia score of 3

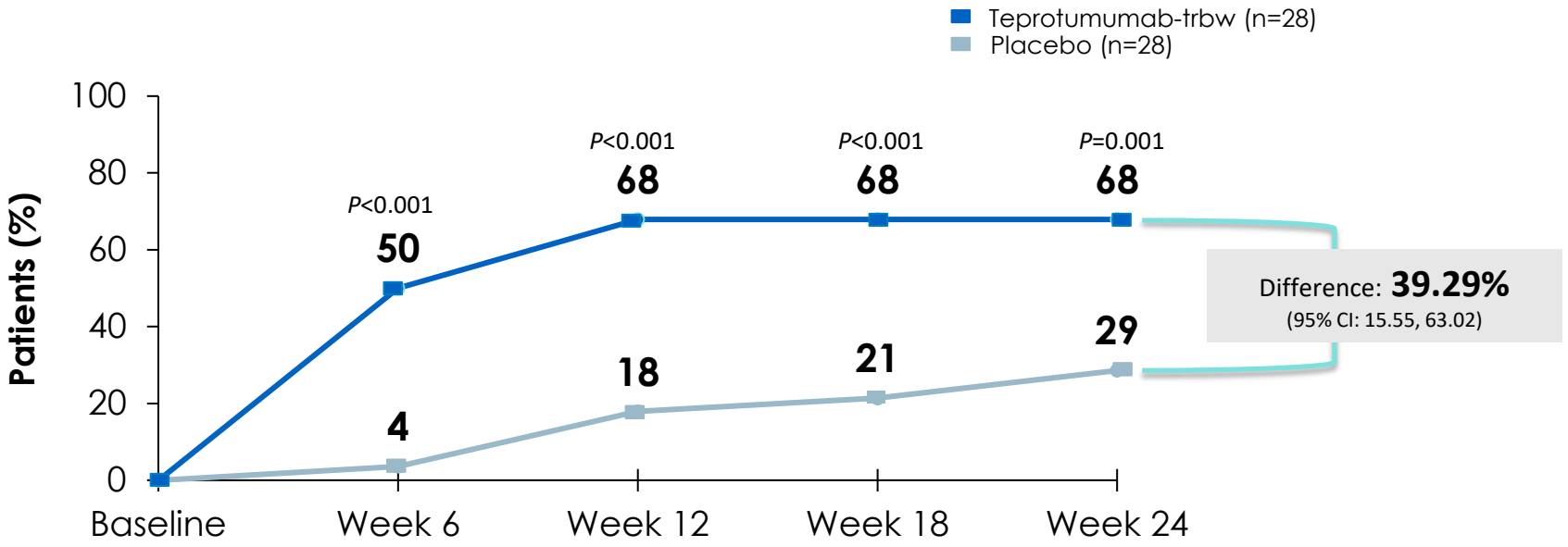
Week 24

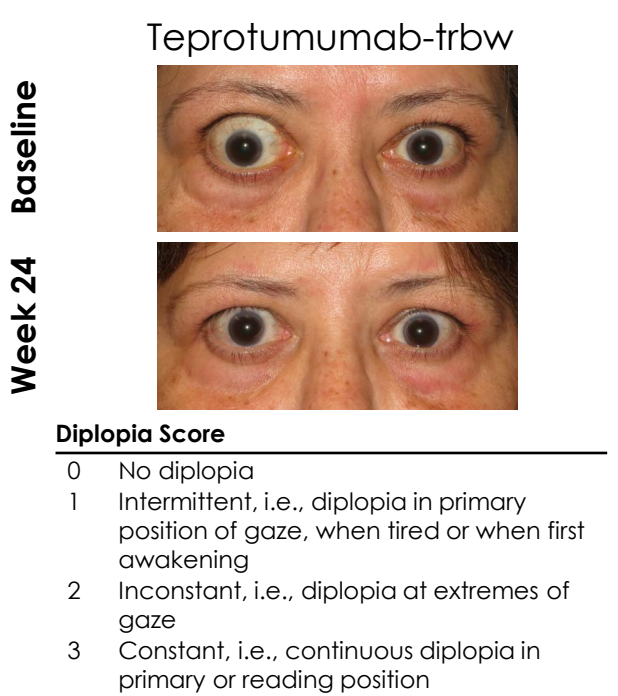


- Orbital fat enhancement resolved (green arrow), inferior rectus muscle (green arrowhead) size decreased by 49%, and medial rectus muscle volume decreased by 41%
- At 24, patient had proptosis measurement of 18 mm, no signs or symptoms of TED, and Gorman diplopia score of 0

MRI, magnetic resonance imaging
Douglas RS, et al. *N Engl J Med*. 2020;382(4):341-352.

Gorman Diplopia Score Improved through Week 24 Responder= ≥1 Grade Improvement in Patients with Diplopia





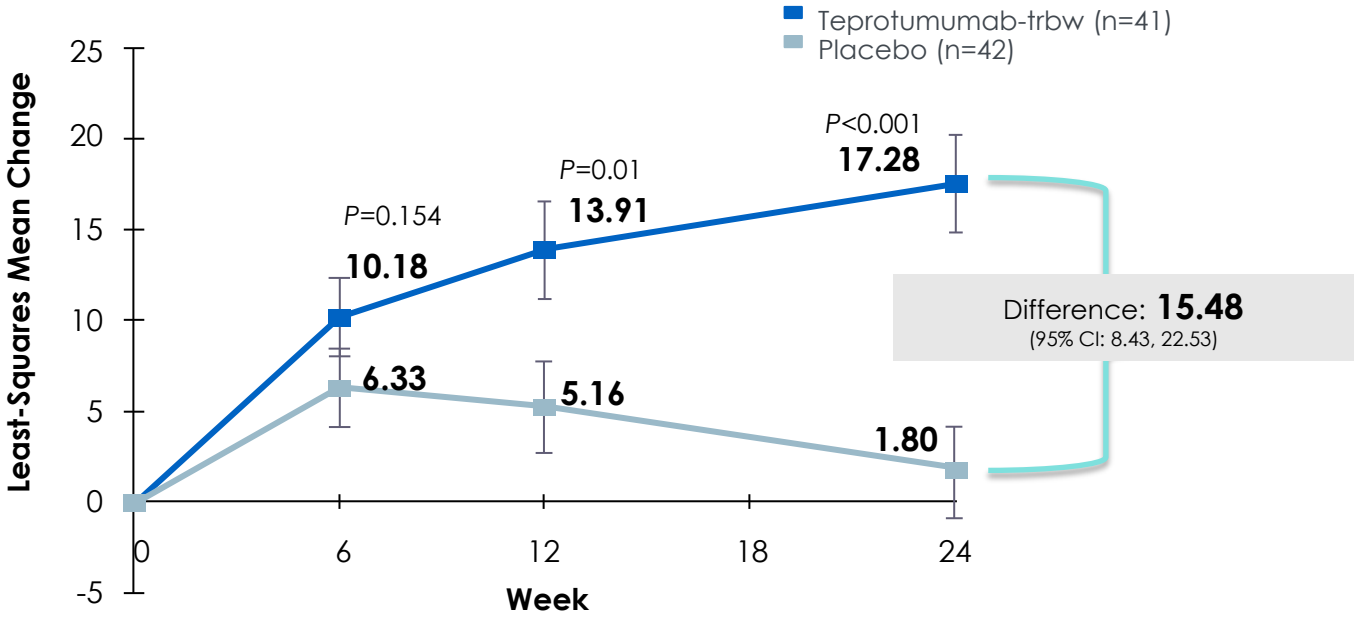
Diplopia Score

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

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

GO-QOL Improvements – Overall

Change from Baseline in GO-QOL Overall Score



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 (≥3 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 (Lond). 2012;26:544-551. 3. Lin IC, et al. J Formo Mdl Assoc. 2015;114:1047-1054. 4. Villagelin D, et al. Front Endocrinol (Lausanne). 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.

All Endpoints Met Statistical Significance

	Placebo (n=42)	Teprotumumab-trbw (n=41)	*P* value
Proptosis response rate at Week 24	10%	83%	<0.001
Overall response rate at Week 24*	7%	78%	<0.001
CAS 0 or 1 at Week 24	21%	59%	<0.001
Mean proptosis change through Week 24	-0.54 mm	-2.82 mm	<0.001 (95% CI: -2.77, -1.80)
• **Change from baseline in proptosis at Week 24**	• -0.53 mm	• -3.32 mm	• <0.001
Diplopia responder rate at Week 24	29%	68%	0.001
Mean GO-QOL change through Week 24	4.43	13.79	<0.001 (95% CI: 4.08, 14.64)

*≥2 points or greater improvement in CAS; ≥2 mm or greater improvement in proptosis

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

Safety Overview

- Safety profile similar to Phase 2 with no new safety observations
- Dropout rate was low (<5%) and balanced across arms
- No deaths
- Vast majority of treatment-emergent adverse events were mild-to-moderate in intensity and no non-serious events led to discontinuation

	Placebo (n=42)	Teprotumumab-trbw (n=41)
TEAEs	29 (69.0%)	35 (85.4%)
SAEs	1 (2.4%)*	2 (4.9%)†

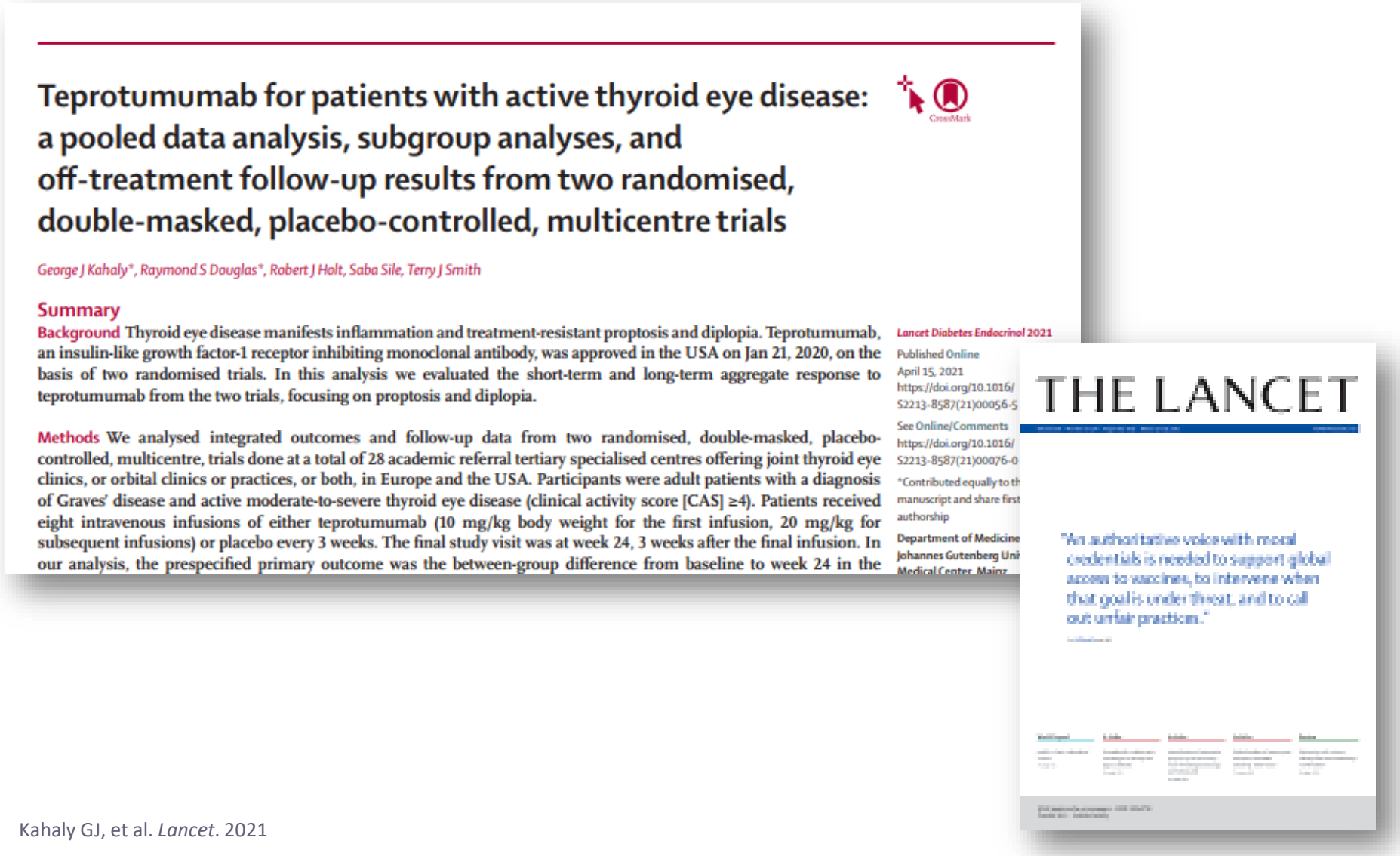
*Placebo: visual field defect requiring orbital decompression surgery (patient discontinued study).
†Teprotumumab-trbw: pneumothorax (considered not related to study drug; patient had history of throat cancer with radiation treatment), infusion reaction (patient discontinued study).

Note: Table represents number of subjects with TEAEs and SAEs. TEAE, treatment-emergent adverse event; SAE, serious adverse event.

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

Teprotumumab for the Treatment of Thyroid Eye Disease

Pooled Data Analysis, Subgroup Analysis, Off-Treatment Follow-up Results



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

George J Kahaly*, Raymond S Douglas*, Robert J Holt, Saba Sile, Terry J Smith

Summary

Background Thyroid eye disease manifests inflammation and treatment-resistant proptosis and diplopia. Teprotumumab, an insulin-like growth factor-1 receptor inhibiting monoclonal antibody, was approved in the USA on Jan 21, 2020, on the basis of two randomised trials. In this analysis we evaluated the short-term and long-term aggregate response to teprotumumab from the two trials, focusing on proptosis and diplopia.

Methods We analysed integrated outcomes and follow-up data from two randomised, double-masked, placebo-controlled, multicentre, trials done at a total of 28 academic referral tertiary specialised centres offering joint thyroid eye clinics, or orbital clinics or practices, or both, in Europe and the USA. Participants were adult patients with a diagnosis of Graves' disease and active moderate-to-severe thyroid eye disease (clinical activity score [CAS] ≥4). Patients received eight intravenous infusions of either teprotumumab (10 mg/kg body weight for the first infusion, 20 mg/kg for subsequent infusions) or placebo every 3 weeks. The final study visit was at week 24, 3 weeks after the final infusion. In our analysis, the prespecified primary outcome was the between-group difference from baseline to week 24 in the

Lancet Diabetes Endocrinol 2021

Published Online April 15, 2021 https://doi.org/10.1016/S2213-8587(21)00056-5

See Online/Comments https://doi.org/10.1016/S2213-8587(21)00076-0

*Contributed equally to th manuscript and share first authorship

Department of Medicine Johannes Gutenberg Uni Medical Center, Mainz

THE LANCET

"An authoritative voice with moral credentials is needed to support global access to vaccines, to intervene when that goal is under threat, and to call out unfair practices."

Kahaly GJ, et al. *Lancet*. 2021

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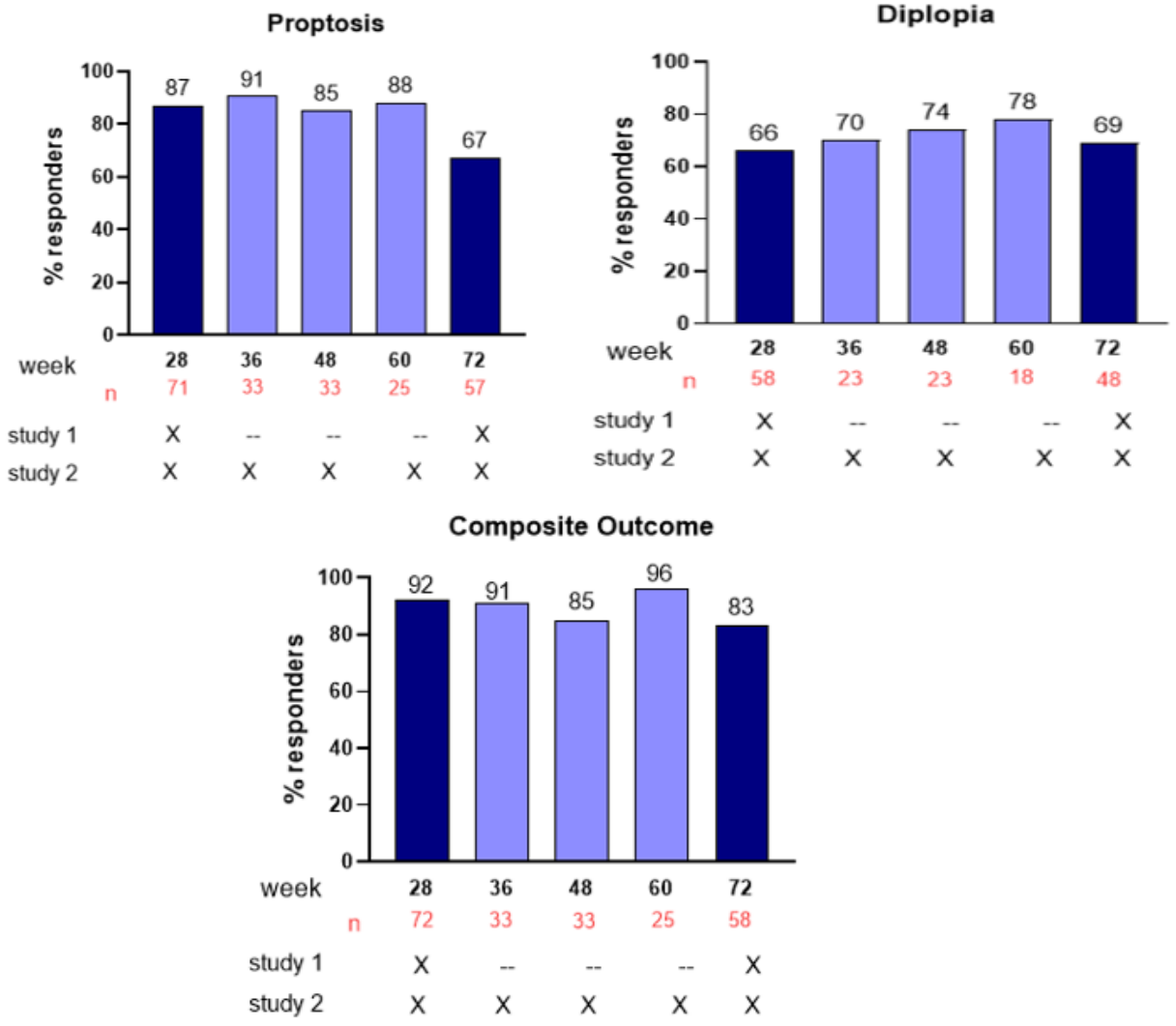
Pooled Analysis:

Week 72 Follow-up: Pooled Observed Data



- At Week 72 after starting the teprotumumab course (≈1 year after finishing treatment):
  - **67% of proptosis responders (n=57) maintained their responder status (≥2-mm improvement) vs pretreatment baseline.[1]**
  - **69% of diplopia responders (n=48) maintained their responder status (≥1-grade improvement) vs pretreatment baseline.[1]**
  - **85% of CAS responders (n=58) maintained their responder status (≥2-point improvement) vs pretreatment baseline.[1]**
  - **Patients receiving teprotumumab (n=57) observed a mean ≈15-point overall change from baseline in GO-QOL.[1]**
- The pooled analysis demonstrated long term sustainability of response to teprotumumab in patients treated in the controlled trials.[1]

*Increase in percentage of patients no longer meeting proptosis, diplopia, or ophthalmic composite outcome **GO-QOL score for Study 2 (phase 3)
Light blue bars indicate time points with only study 2 data available*. Dark bars indicate integrated time points. Diplopia responders are among patients with diplopia at Baseline. In study 2, 14 patients entered OPTIC-X (five non-responders). Change from baseline (Mean, SEM) in Transformed scores for Overall GO-QOL, Visual function and Appearance subscale. In study 2, 14 patients entered OPTIC-X (five non-responders)

Kahaly GJ, et al. *Lancet*. 2021

AMGEN Rare Disease

OPTIC-X Study

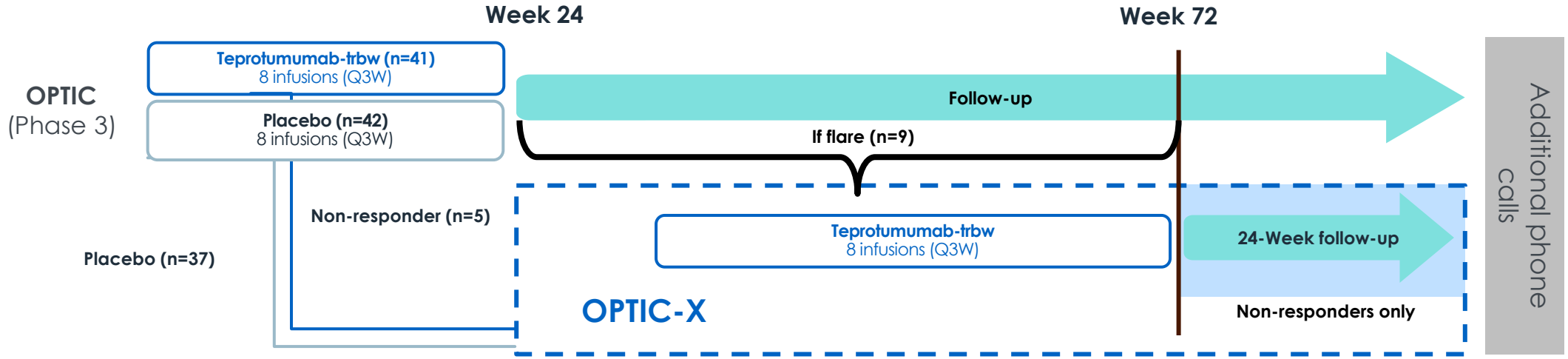
Teprotumumab-trbw Efficacy, Safety and Durability in Longer Duration Thyroid Eye Disease and Retreatment

AMGEN

Rare Disease

OPTIC-X Study Design

Treatment of Graves' **O**rbitopathy to Reduce **P**roptosis with
Teprotumumab-trbw **I**nfusions in an Open-Label **C**linical E**x**tension Study



1. ***Does longer disease duration impact response?***

   Patients in the OPTIC placebo group have longer duration before treatment

2. ***Can non-responders benefit from more treatment?***

   Teprotumumab-trbw **non-responders** can get another course

3. ***Is retreatment helpful?***

   Patients experiencing disease **flare** can get another course

Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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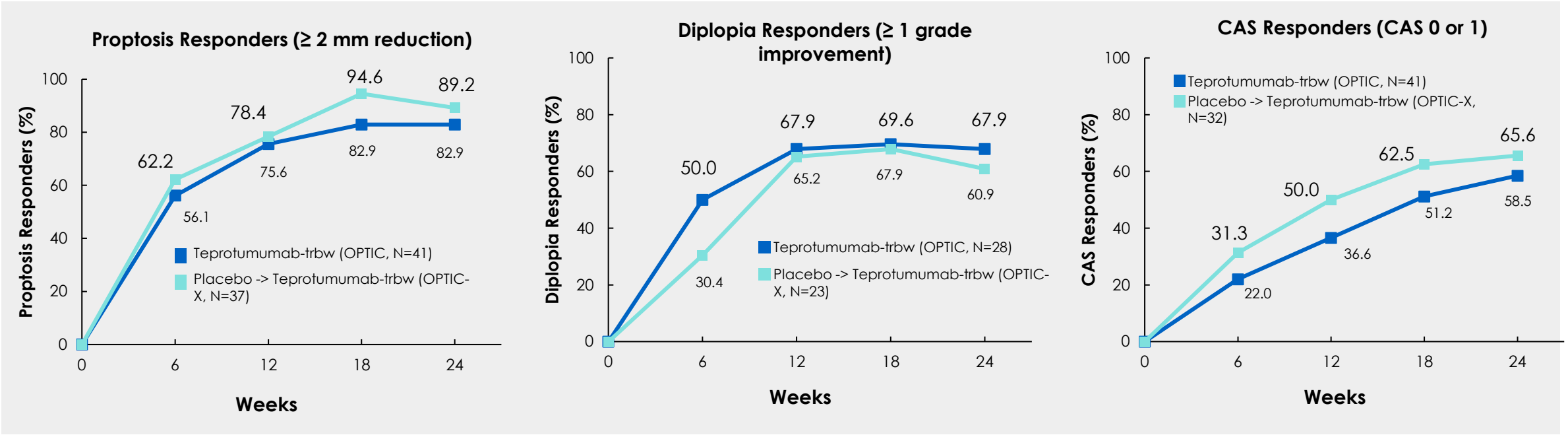
OPTIC-X Patients Had Longer Duration of TED Since Diagnosis than OPTIC Patients

Average of 12 months (up to 16) in OPTIC-X compared to 6 months in OPTIC



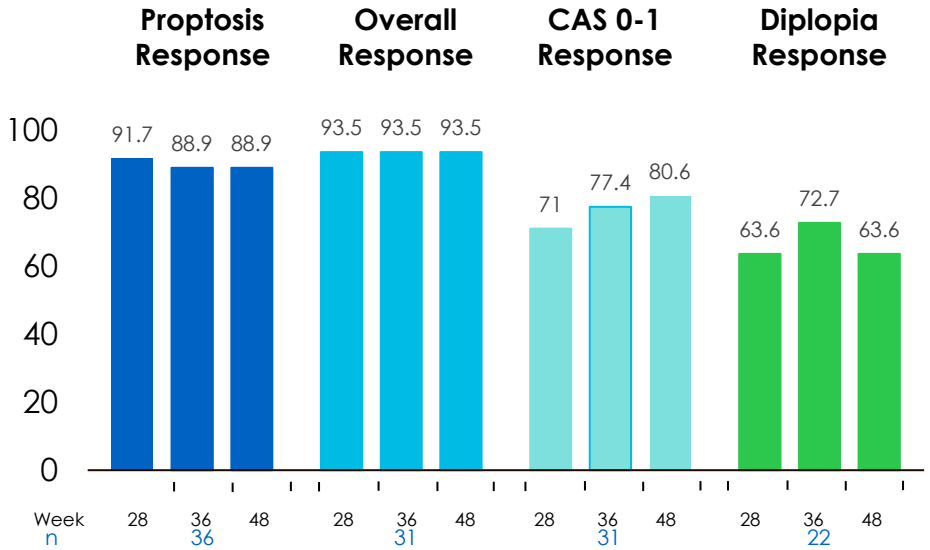
First time treatment in patients with ~1 year average (up to 16 months) since diagnosis of TED leads to proptosis reductions, Diplopia response and CAS score reduction consistent with OPTIC

Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

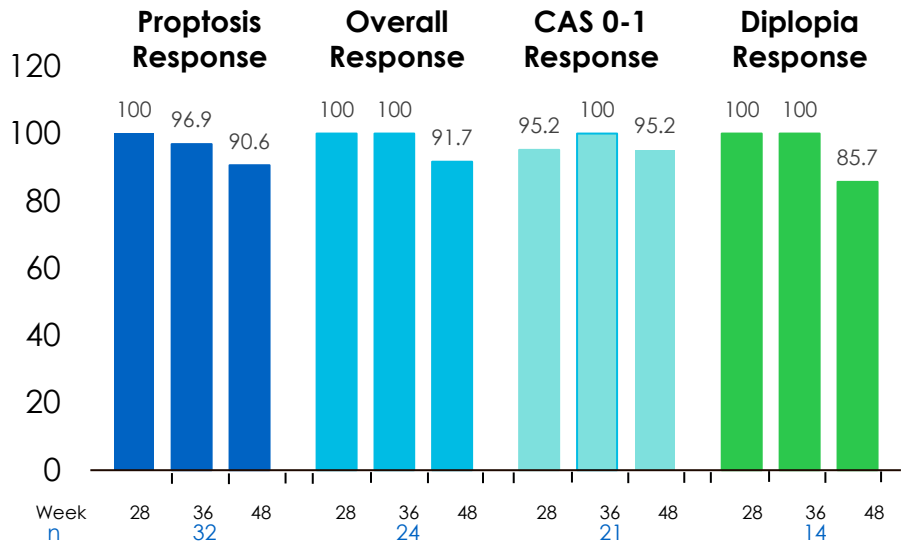
AMGEN Rare Disease

Durability of Response in Patients with Longer Duration of TED (Placebo Non-Responders from OPTIC Trial)

Follow-up Response in All Patients in OPTIC Placebo Group*



Follow-up Response For Week-24 Responders from OPTIC Placebo Group**



- Across the OPTIC-X study follow-up visits, all outcomes were sustained, with greater than 90% reaching overall response criteria at each visit
- In patients with a 24-week response, a large percentage of all outcomes were maintained; greater than 90% maintained proptosis, disease inactivation, and overall responses at each visit

* Percentage of all patients previously on placebo who entered into OPTIC-X who were responders at week 28, 36, and 48

**Percentage of those with week 24 responses remaining responders at week 28, 36, and 48

Douglas R, et al. Oph, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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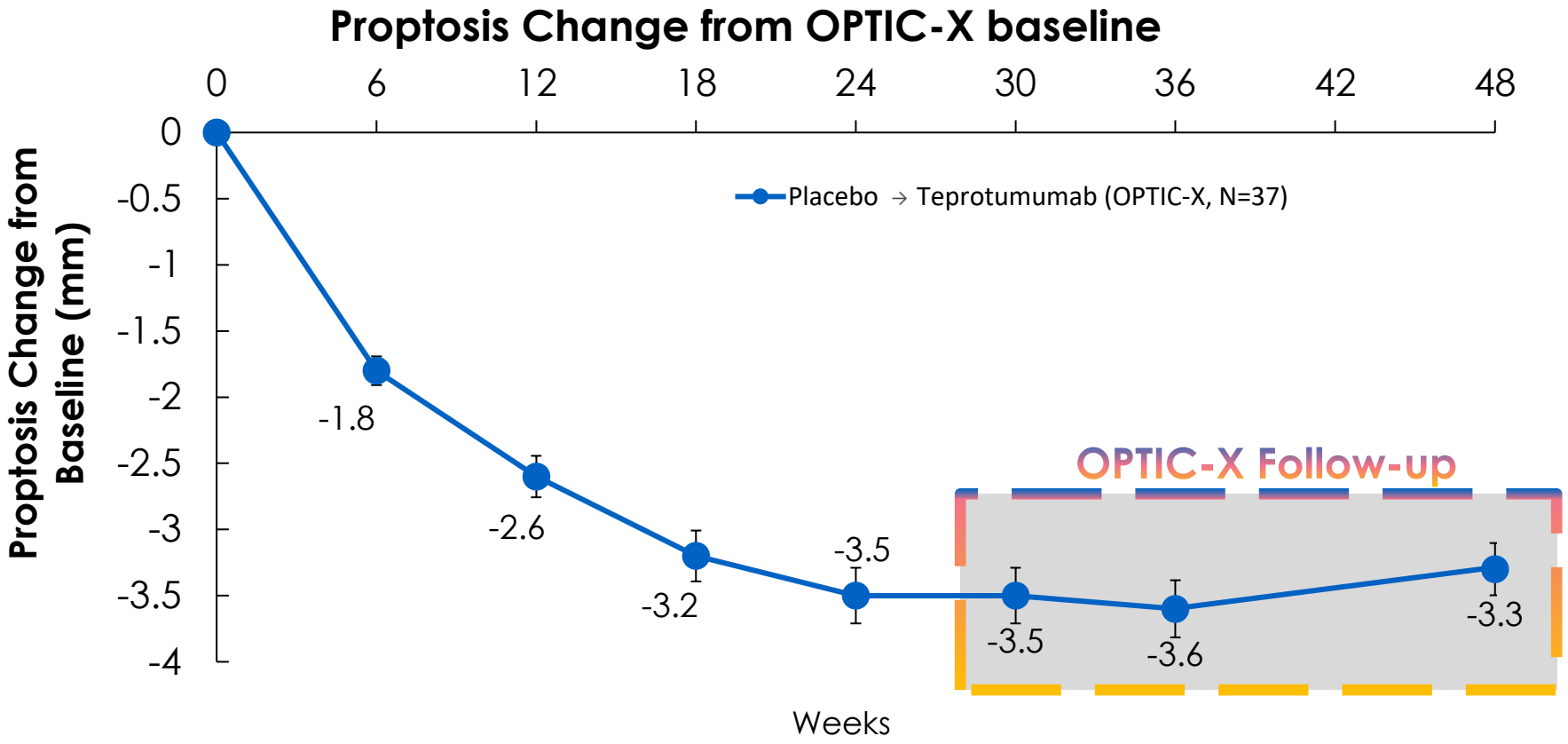
Durability of Response in Patients with Longer Duration of TED (Placebo Non-Responders from OPTIC Trial)

- Proptosis reduction (mm) was sustained across the OPTIC-X study follow-up visits
- In patients with a 24-week response, greater than 90% maintained proptosis response at each visit



Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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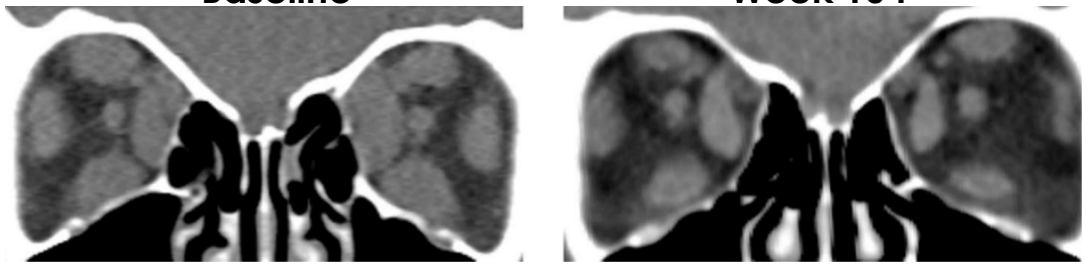
Patient Case from Placebo Non-Responders Group

	OPTIC-X Baseline	Week 24 & 48	Week 104
Proptosis	29 mm OS, 28 mm OD	22 mm OU	Stable
CAS	4 OU	0 OU	
Diplopia	Constant	Complete resolution	

Baseline **Week 104**

Clinical photographs of a patient with TED at baseline and 104 weeks (83 weeks after last infusion).

Baseline **Week 104**



Non-contrast computed tomography orbital images of the same patient at baseline and week 104

Changes in CT imaging from baseline to week 104:

- Right orbit: inferior rectus, superior rectus and superior oblique muscles are decreased in volume
- Left orbit: inferior rectus, medial rectus, superior oblique, and lateral rectus muscles are decreased in volume

Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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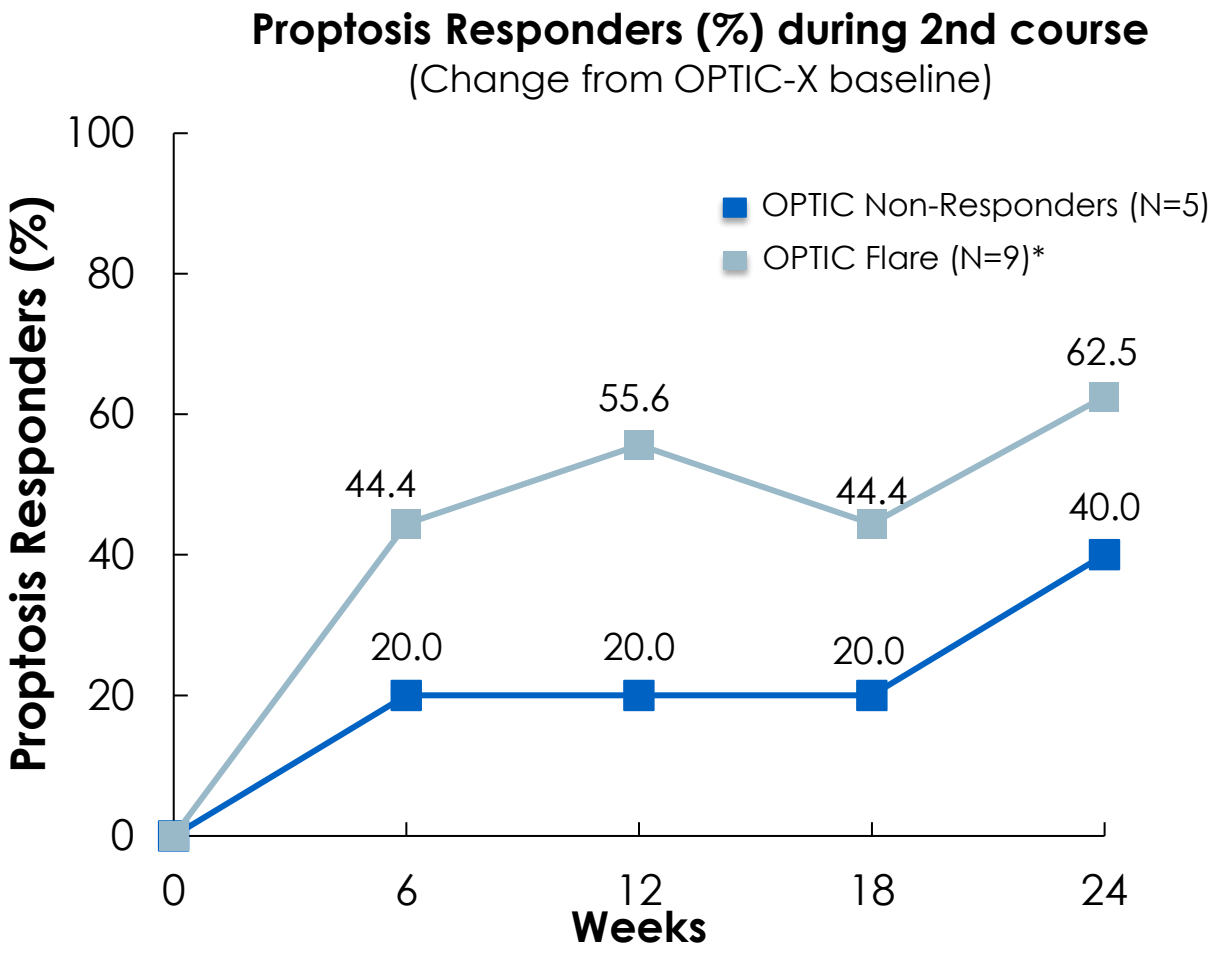
Proptosis Response with Retreatment Teprotumumab-trbw Non-Responders and Flares from OPTIC Trial

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



*Only 8 patients contributing to data at week 24 as 1 patient had a significantly delayed visit due to COVID; excluded from week 24 analysis per SAP. This patient experience a 5mm 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.

Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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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)
Onycholysis	0 (0)	4 (10.8)

- OPTIC placebo patents:
  - All AEs were mild to moderate, and no patients experienced serious AEs
- OPTIC teprotumumab-trbw non-responders or flares:
  - 1 patient experienced a serious, life-threatening (grade 4) AE following 3rd infusion
  - All other AEs were mild or moderate and none led to study discontinuation
- No new safety signals were identified

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 4 patients as mild AEs: 2 with hypoacusis that resolved, 1 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 6th infusion (considered treatment-related).

Douglas R, et al. *Oph*, 2021. doi: https://doi.org/10.1016/j.ophtha.2021.10.017.

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Safety Profile of Teprotumumab

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Teprotumumab Integrated Safety Overview – Phase 2 & Phase 3

- **There was a low rate of discontinuation—89% of Teprotumumab patients and 93% of placebo patients completed 8 infusions[1]**
- **Most adverse reactions were mild or moderate, manageable, and resolved during or after treatment[2,3]**

Adverse Reactions Occurring in ≥5% of Patients Treated With Teprotumumab and Greater Incidence Than Placebo		
Adverse Reactions	**Teprotumumab* (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	10 (12%)	6 (7%)
Hyperglycemia	8 (10%)	1 (1%)
Hearing impairment	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

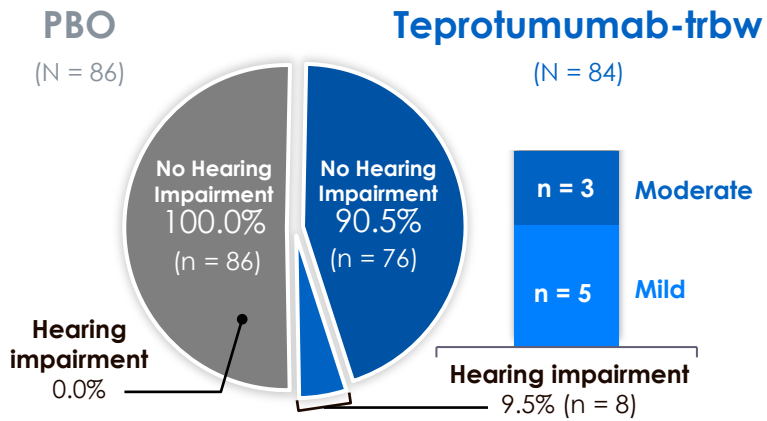
1. Teprotumumab (teprotumumab-trbw) [prescribing information] Horizon. 2. Douglas RS, Kahaly GJ, Patel A, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020;382(4):341-352. 3. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med. 2017;376(18):1748-1761.

Adverse Events in Phase 2/3 Clinical Trials

Teprotumumab-trbw was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with TED[1-3]

Phase 2 N = 88

Phase 3 (OPTIC) N = 83



Hearing impairment was reported in 9.5% (8/84) of patients in the teprotumumab-trbw group compared to no (0/86) patients in the placebo group

- Review of baseline characteristics identified age and female gender as the only potential predisposing factors
- Events were reported as non-serious and mild or moderate in severity
- Patients continued in the study without worsening of the event or discontinuation of treatment

Ongoing post-marketing hearing-related AE rates have been comparable with those in clinical studies[4]

AE, adverse event, IgG1, immunoglobulin G1, IGF-1R, insulin-like growth factor-1 receptor.

1. Smith TJ, et al. *N Engl J Med*. 2017 May 4;376(18):1748-1761. 2. Douglas RS, et al. *N Engl J Med*. 2020 Jan 23;382(4):341-352. 3. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. 4. Cockerham K, et al. Post-marketing surveillance of hearing-related adverse events in patients with TED treated with teprotumumab. Presented at: The North American Neuro-Ophthalmology Society Annual Meeting; February 12-17, 2022. Austin, TX

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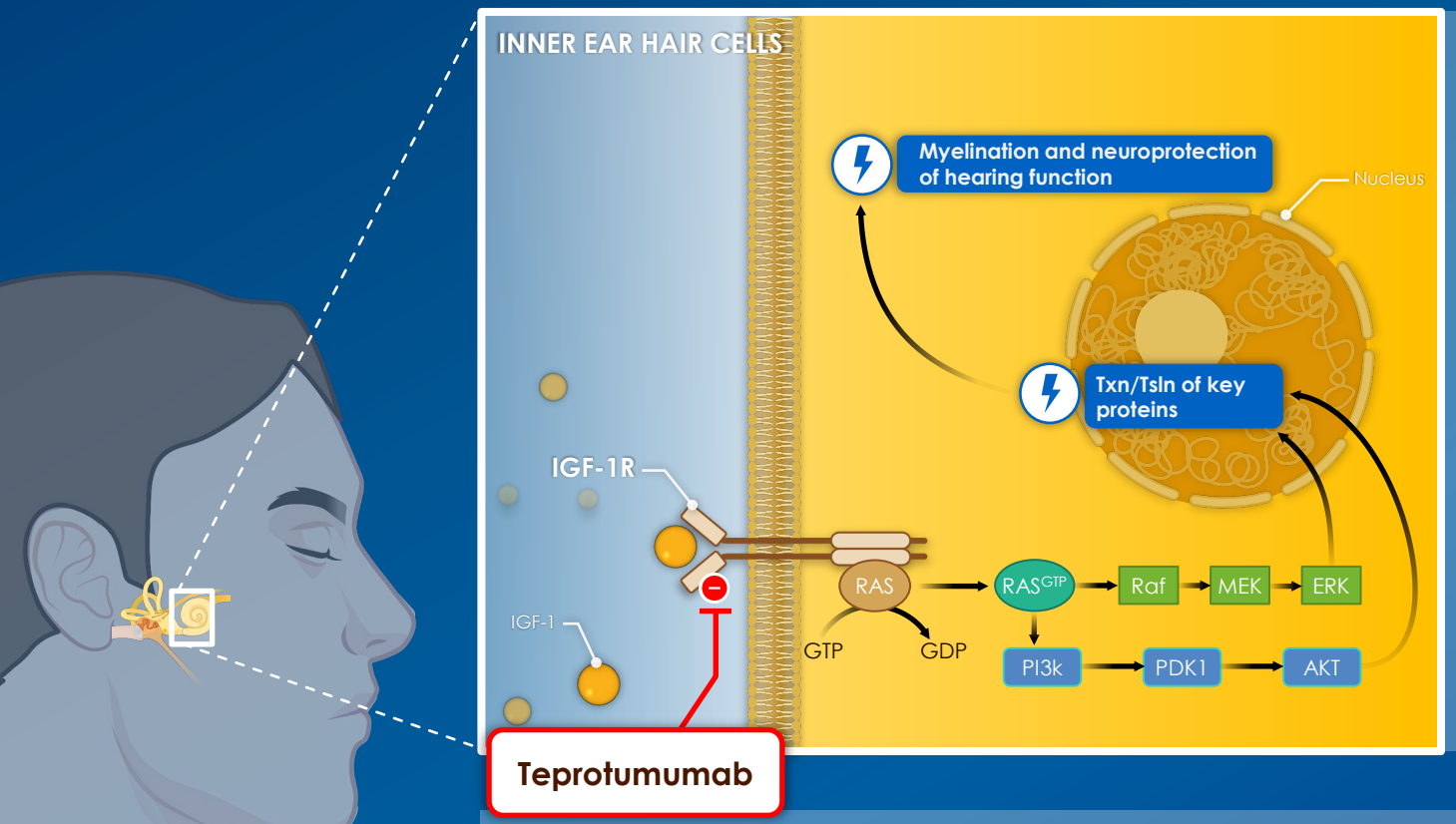
IGF-1/IGF-1R Role in Hearing



In normal mammalian hearing, IGF-1 signaling in the inner ear triggers an intracellular cascade that upregulates key proteins involved in the myelination and neuroprotection of hearing function.[1,2]

IGF-I has been known to protect inner ear hair cells from noise-induced damage, ischemia, and medication toxicity.[3]

In an observational study of 4,390 adults aged ≥ 50 , higher levels of IGF-1 were linked to a lower risk of future hearing impairment among subjects aged 50-60, but not in the older group.[4]

Teprotumumab effectively inhibits IGF-1R on orbital fibroblasts. Therefore, inhibition of IGF-IR is a possible mechanism for teprotumumab-induced hearing impairment; however, more definitive studies are needed.[3]

Limitations of Current Knowledge

- Data on IGF-1's protective role in auditory function relies on models of induced hearing loss and exogenous IGF-1 treatment. IGF-1's specific role in homeostasis is not well described.
- No causal relationship has been established.

AKT, protein kinase B; ERK, extracellular signal-regulated kinases; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IGF-1, insulin growth factor type 1; IGF-1R, insulin growth factor type 1 receptor; PDK1, 3-phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinases; Raf, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; Tsln, translation; Txn, transcription.

1. Rodríguez-de la Rosa L, et al. Front Aging Neurosci. 2017;9:411. 2. Murillo-Cuesta S, et al. Front Mol Neurosci. 2011;4:11. 3. Najjar W, et al. OTO Open. 2022;6(2):2473974X221097097. 4. Lassale C, et al. Scientific Reports. 2017; 7(1): 4212. 4. Smith TH, et al. N Engl J Med. 2016;375:1552-1565.

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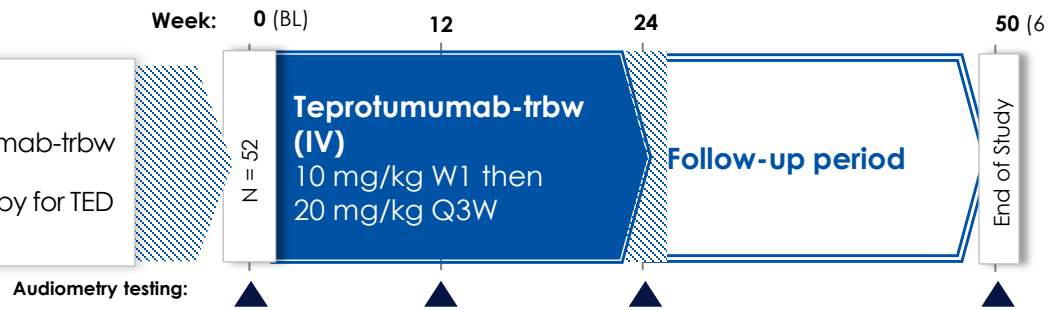
Prospective Studies

Objective:
This study aimed to objectively evaluate the incidence of teprotumumab-induced ototoxicity in patients with TED, using the gold standard of baseline and post treatment audiometry

STUDY DESIGN

Key eligibility criteria:
- Diagnosed with TED
- Received 8 inf of teprotumumab-trbw

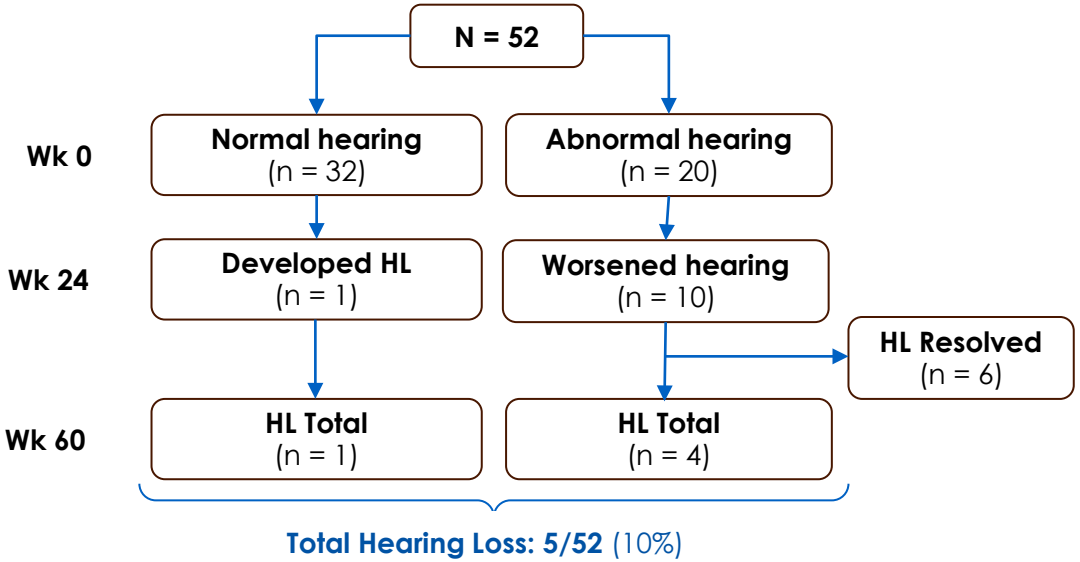
Key exclusion criteria:
- On any other medical therapy for TED or ototoxic medications



Primary Endpoints (Wk 24)

Change in pure tone audiometry

Results



Study Conclusions

Regarding treatment with teprotumumab:

- **Baseline hearing-loss** was a **significant risk factor** for further hearing-loss following teprotumumab-trbw therapy
- **Long-term hearing loss** in TED patients with normal baseline hearing is **rare** (3%)
- **Management of dose and interval between infusions is recommended** for patients with baseline hearing dysfunction

BL, baseline; HL, hearing loss; inf, infusions; IV, intravenous; TED, thyroid eye disease.

1. Douglas RS, et al. Thyroid. 2024 Jan;34(1):134-137. doi: 10.1089/thy.2023.0466. Epub 2023 Dec 27. 2. Ugradar S, et al. Research Square, 2022 Dec. https://doi.org/10.21203/rs.3.rs-2219366/v1.

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Precautions and Monitoring

Teprotumumab-trbw may cause severe hearing impairment[a] including hearing loss, which in some cases may be permanent.

Warnings & Precautions

- Assess patients' hearing before, during, and after treatment with teprotumumab-trbw and consider the benefit-risk of treatment with patients
- It is important to evaluate and discuss the benefits and risks associated with treatment and the burden of TED on the patient's daily activities and emotional well-being
- Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing

[a]Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)
TEPEZZA [teprotumumab-trbw]. Lake Forest, IL: Horizon Therapeutics USA, Inc. 2020

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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.

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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.

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THANK YOU

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