Orbital Imaging in Teprotumumab-Treated Patients With Thyroid Eye Disease (TED)

Indication[1]

Teprotumumab is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor indicated for the treatment of TED regardless of activity or duration.

Background

TED is a lifelong, underdiagnosed, debilitating, and potentially vision-threatening autoimmune disease with a significant impact on functional, psychological, and psychosocial well-being and substantial economic burden.[2-7]

TED is the most common extrathyroidal manifestation of Graves' disease, affecting up to 40% of patients; however, these conditions are pathophysiologically distinct, and treatment of thyroid function does not improve TED.[8-13] TED can be a progressive disease with flare-ups over many years and is associated with orbital inflammation that affects the conjunctiva, eyelid, and extraocular muscles and orbital fat.[14,15]

Mechanism of Action[1]

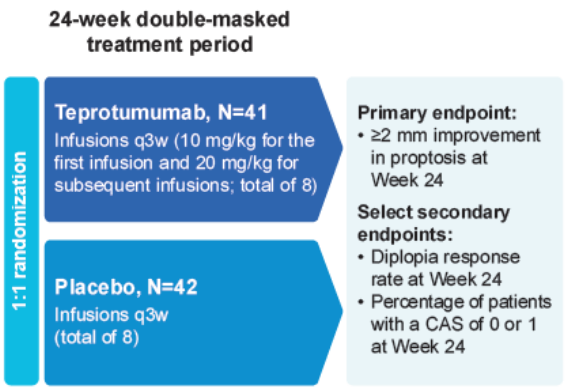
Teprotumumab binds to IGF-1R and blocks its activation and signaling. The precise mechanism by which teprotumumab exerts a therapeutic effect in patients with TED has not been fully characterized.

Phase 3 OPTIC Trial[16,17]

Moderate-to-severe TED with clinical activity score (CAS) ≥4 and short duration (≤9 months)

Figure 1: Study design[16]

Randomized, double-masked, placebo-controlled, phase 3 multicenter trial. Patients received 8 infusions of teprotumumab* or placebo, one every 3 weeks over 24 weeks.



*Teprotumumab-trbw is referred to as teprotumumab throughout this document.

Results

Efficacy outcome data[16]

	Teprotumumab (N=41)	Placebo (N=42)	p-value
Primary outcome			
Proptosis response rate at Week 24[a], % (n/N)	83 (34/41)	10 (4/42)	p<0.001
Other outcome			
Proptosis least-squares mean change from baseline at Week 24[b], mm	−3.3	−0.5	p<0.001
Key secondary outcomes			
Diplopia response rate at Week 24[c], % (n/N)	68 (19/28)	29 (8/28)	p=0.001
CAS of 0 or 1 at Week 24[d], % (n/N)	59 (24/41)	21 (9/42)	p<0.001

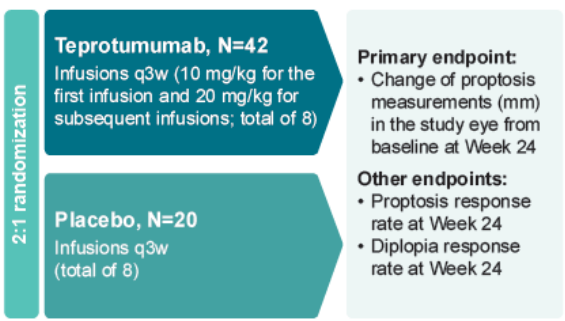
[a]Proptosis response was defined as a ≥2 mm reduction in proptosis from baseline in the study eye without deterioration in the non-study eye (≥2 mm increase in proptosis).
[b]Teprotumumab, n=40; placebo, n=40.
[c]Diplopia was evaluated on a 4-point scale in which scores ranged from 0 (no diplopia) to 3 (constant diplopia). A diplopia response was defined as a reduction in diplopia of ≥1 grade at Week 24.
[d]CAS based on 7 components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component is scored as present or absent (score of 1 or 0, respectively), and the CAS is the sum of the scores (range, 0-7) with higher scores indicating greater level of inflammation.

Phase 4 Trial[18]

TED with CAS ≤1 and longer duration (2 to 10 years)

Figure 2: Study design[18]

Randomized, double-masked, placebo-controlled, phase 4 multicenter trial. Patients received 8 infusions of teprotumumab or placebo, one every 3 weeks over 24 weeks.



Results

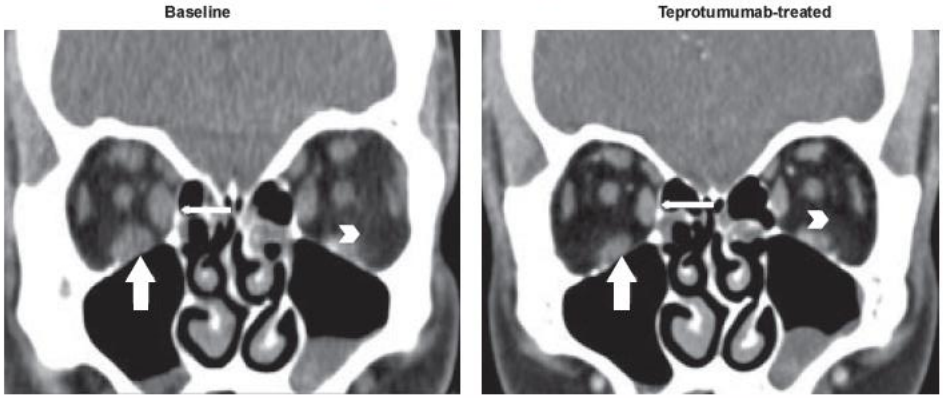
Efficacy outcome data[18]

	Teprotumumab (N=42)	Placebo (N=20)	p-value
Primary outcome			
Proptosis mean change from baseline at Week 24[a], mm	−2.41	−0.92	p=0.0004
Other outcomes			
Proptosis response rate at Week 24[b], % (n/N)	62 (26/42)	25 (5/20)	p=0.0134
Diplopia response rate at Week 24[c], % (n/N)	43 (6/14)	50 (2/4)	NS[d]

[a]Intent-to-treat analysis (pre-specified primary analysis method).
[b]Proptosis response was defined as a ≥2 mm reduction in proptosis from baseline in the study eye without deterioration in the non-study eye (≥2 mm increase in proptosis).
[c]Diplopia was evaluated on a 4-point scale in which scores ranged from 0 (no diplopia) to 3 (constant diplopia). A diplopia response was defined as a reduction in diplopia of ≥1 grade at Week 24.
[d]Not significant; the study was not powered to detect differences in diplopia.

Phase 3 OPTIC Trial[16,17]

Figure 3: Non-contrast coronal computed tomography (CT) images in a teprotumumab-treated patient with TED[17]



Non-contrast coronal CT images demonstrate reductions in size of the inferior rectus (thick white arrow) and medial rectus (thin white arrow) as well as improved inflammation of the orbital fat (white arrowhead) after teprotumumab treatment.

Total muscle reduction: 43%
Total fat reduction: −12%

Proptosis reduction (study eye): 3 mm
Gorman diplopia score improvement from 1 to 0

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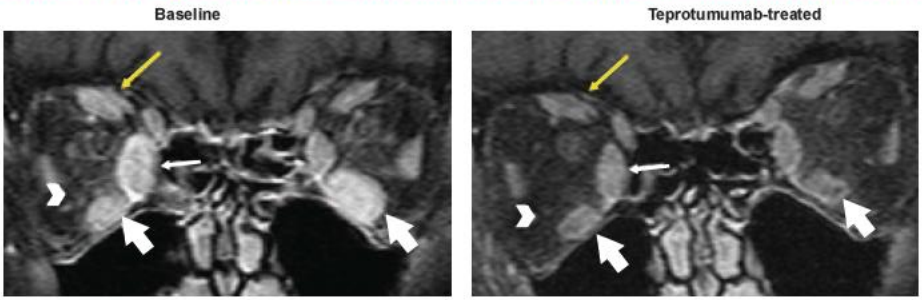
Figure 4: Coronal T1 post-gadolinium fat saturation images in a teprotumumab-treated patient with TED[17]



Coronal T1 post-gadolinium fat saturation images demonstrate reductions in size and inflammation of the inferior rectus (thick white arrow), medial rectus (thin white arrow), and superior rectus muscles (thin yellow arrow) as well as improved inflammation of the orbital fat (white arrowhead) after teprotumumab treatment.

Total muscle reduction: 37%
Total fat reduction: 33%

Proptosis reduction (study eye): 5 mm
Gorman diplopia score improvement from 3 to 0

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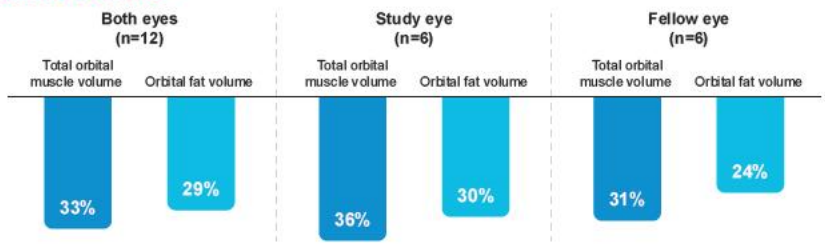
Imaging results[17]

- Orbital imaging [CT/magnetic resonance imaging (MRI)] was performed to assess volumetric and inflammatory changes of the orbital soft tissues before and after teprotumumab treatment (n=6).

Figure 5: Average percentage reduction from baseline in total orbital soft tissue volumes[17]



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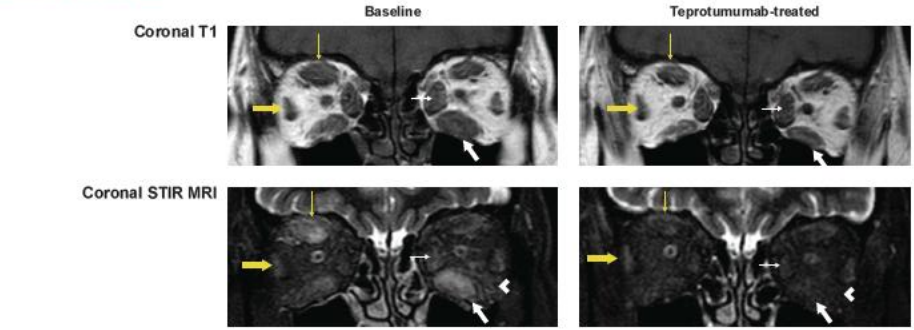
Phase 4 Trial[18]

Figure 6: Coronal T1 and short tau inversion recovery (STIR) MRI images of a teprotumumab-treated patient with TED[19]



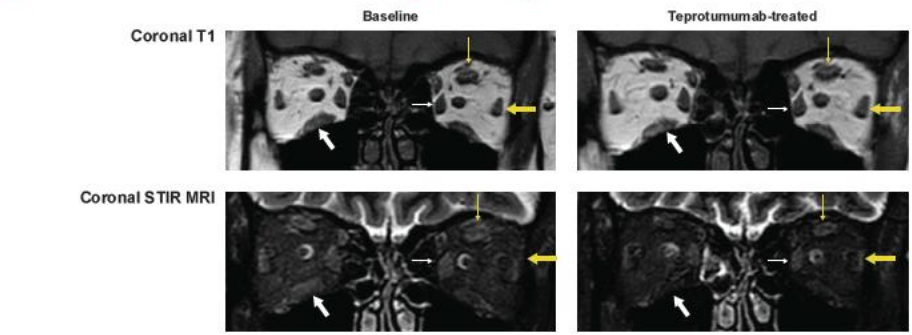
Patient is a 64-year-old female with TED duration of 7.2 years.

Coronal T1 (top) and coronal STIR MRI (bottom) images demonstrate reductions in size and inflammation of the inferior rectus (thick white arrow), medial rectus (thin white arrow), superior rectus (thin yellow arrow) and lateral rectus (thick yellow arrow) as well as improved inflammation of the orbital fat (white arrowhead) after teprotumumab treatment.

Total muscle reduction: 25%
Total fat reduction: 46%

Proptosis reduction (study eye): 3 mm
No baseline diplopia

Figure 7: Coronal T1 and STIR MRI images of a teprotumumab-treated TED patient[19]



Patient is a 55 year-old female with TED duration of 3.9 years.

Coronal T1 (top) and coronal STIR MRI (bottom) images demonstrate reductions in size and inflammation of the inferior rectus (thick white arrow) and medial rectus (thin white arrow) and reductions in size of the superior rectus (thin yellow arrow) and lateral rectus (thick yellow arrow) after teprotumumab treatment.

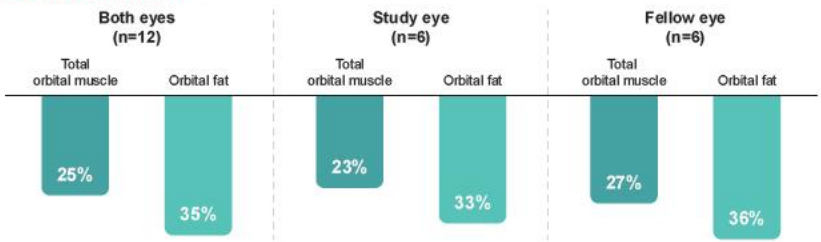
Total muscle reduction: 21%
Total fat reduction: 51%

Proptosis reduction (study eye): 2.5 mm
No baseline diplopia

Imaging results[18,19]

Orbital imaging (MRI) was performed to assess volumetric changes of the orbital soft tissues before and after teprotumumab treatment (n=6).

Figure 8: Average percentage reduction from baseline in total orbital soft tissue volumes[18,19]



Adapted from reference 18

Key Takeaways

- TED leads to soft tissue remodeling of the orbital muscles and fat, including enlargement and inflammation/edema.[14]
- TED is a heterogeneous disease with varying degrees of orbital soft tissue enlargement and inflammation/edema. Orbital soft tissue remodeling persists regardless of disease duration or activity.[10, 14]
- Teprotumumab reduces orbital muscle and fat inflammation/ edema and enlargement regardless of disease duration or activity. This improvement is seen in both the study eye and the non-study fellow eye showing the systemic impact of teprotumumab.[1,17]
- Teprotumumab improves proptosis and diplopia likely in part by reducing orbital soft tissue volumes including orbital muscle and fat.[16-18]

References

1. Teprotumumab prescribing information approved by ANVISA on February 10, 2025. 2. Lazarus JH. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):273-279. 3. Terwee C, et al. *Eur J Endocrinol*. 2002;146(6):751-757. 4. Estcourt S, et al. *Eur J Endocrinol*. 2009;161(3):483-487. 5. Dosiou C, Kossler AL. *J Endocr Soc*. 2021;5(5):bvab034. 6. Kahaly GJ, et al. *Clin Endocrinol (Oxf)*. 2005;63:395-402. 7. Ponto KA, et al. *J Clin Endocrinol Metab*. 2013;98(1):145-152. 8. Bartalena L, et al. *Eur Thyroid J*. 2016;5(1):9-26. 9. Chin YH, et al. *Clin Endocrinol (Oxf)*. 2020;93(4):363-374. 10. Smith TJ, et al. *N Engl J Med*. 2016;375(16):1552-1565. 11. Perros P, et al. *Orphanet J Rare Dis*. 2017;12(1):72. 12. Hegedüs L, et al. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):313-324. 13. Douglas RS, et al. *J Neuroophthalmol*. 2021;41(4):461-468. 14. Wang Y, et al. *Ther Clin Risk Manag*. 2019;15:1305-1318. 15. Burch HB, et al. *Thyroid*. 2022;32(12):1439-1470. 16. Douglas RD, et al. *N Engl J Med*. 2020;382(4):341-352. 17. Jain AP, et al. *Br J Ophthalmol*. 2022;106(2):165-171. 18. Douglas RS, et al. *J Clin Endocrinol Metab*. 2024;109(1):25-35. 19. Data on file, Amgen. May 2024.