TEPEZZA®
teprotumumab-trbw

First and Only FDA-Approved Medicine for Thyroid Eye Disease

TEPEZZA® (teprotumumab-trbw) is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor-1 receptor (IGF-1R).[1] It is the first and only medicine approved by the U.S. Food and Drug Administration (FDA) for the treatment of Thyroid Eye Disease (TED).

TEPEZZA is a biologic that is administered to patients once every three weeks for a total of eight infusions.[1]

TED is a serious, progressive and potentially vision-threatening rare autoimmune disease that is associated with proptosis (eye bulging), diplopia (double vision), blurred vision, pain, inflammation and facial disfigurement.[2,3]

Clinical Development Program

The FDA approval of TEPEZZA is supported by a robust body of clinical evidence, including statistically significant, positive results from the **Phase 2 clinical study**; as well as the Phase 3 confirmatory clinical study, **OPTIC**, and an open-label extension study called OPTIC-X, designed to better understand whether certain patients may benefit from retreatment or longer treatment (more than six months) with TEPEZZA.

OPTIC™

OPTIC: Treatment of Graves' **O**rbitopathy (Thyroid Eye Disease) to Reduce **P**roptosis with **T**eprotumumab **I**nfusions in a Randomized, Placebo-Controlled, **C**linical Study

Phase 3 Confirmatory Study (**NCT03298867**)

Trial Design[4]

OPTIC, a double-masked, randomized, multicenter, placebo-controlled trial, investigated the efficacy, tolerability and safety of TEPEZZA in patients with active TED. Patients were assigned to receive TEPEZZA or placebo administered intravenously (10 mg/kg for their first infusion followed by 20 mg/kg for the remaining 7 infusions) once every 3 weeks for a total of 8 infusions. Eighty-three subjects enrolled in OPTIC. At Week 24 of OPTIC, proptosis responders entered into a 48-week off-treatment follow-up period, without receiving additional TED treatment, including TEPEZZA.

Inclusion Criteria[4]

See clinical trial **site** for full inclusion criteria.

- Age 18–80 years
- TED diagnosis ≤ 9 months since the onset of symptoms
- Previous steroid use was limited to low doses with no use at least 4 weeks prior to study entry

Results[4]

OPTIC met its primary endpoint, with significantly more patients achieving a reduction in proptosis – a major cause of morbidity in TED – with TEPEZZA compared to placebo. The study also showed significant differences versus placebo in all secondary endpoints, demonstrating potential benefits to important measures of the patient experience with this disfiguring disease.

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Endpoint	Results
Primary Endpoint	
Responder rate of ≥ 2 mm reduction of proptosis in the study eye (without deterioration in the fellow eye) at Week 24.	In the intent-to-treat population, 34/41 (82.9%) patients receiving TEPEZZA and 4/42 (9.5%) patients receiving placebo were proptosis responders at Week 24 (p<0.001).
Key Secondary Endpoints	
Average change in proptosis throughout 24 weeks of treatment (average of the improvements seen at weeks 6, 12, 18 and 24).	Throughout the 24-week treatment period, patients treated with TEPEZZA had an average proptosis reduction of 2.82 mm compared with 0.54 mm for those who received placebo (p<0.001). After the full course of therapy, there was a 3.32 mm reduction from baseline for the TEPEZZA group vs 0.53 mm reduction for placebo at Week 24 (p<0.001).
Overall responder rate at Week 24: percent of participants with ≥2-point reduction in Clinical Activity Score (CAS) and ≥2 mm reduction in proptosis from baseline, provided there is no corresponding deterioration (≥2-point/mm increase) in CAS or proptosis in the fellow eye. *CAS is a 7-point scale that quantifies the pain, redness and swelling of various eye tissues. A score of 0 represents no swelling or activity, and a change in score of 2 points is considered to be clinically relevant.*	Patients treated with TEPEZZA had an overall responder rate of 78% compared with 7.1% in the placebo group at Week 24 (p<0.001). Overall response rate to TEPEZZA was significantly different than placebo from baseline at all study time points: Week 6 (43.9% vs. 4.8%), Week 12 (63.4% vs. 11.9%), Week 18 (73.2% vs 11.9%), and Week 24 (78.0% vs. 7.1%).
Percentage of participants with a CAS value of 0 or 1 at Week 24 in the study eye.	At Week 24, more patients achieved a CAS value of 0 or 1 with TEPEZZA treatment (58.5% vs 21.4% of placebo participants) (p<0.001).
Percentage of patients with a change from baseline of at least 1 grade in diplopia (double vision). *This endpoint measured the percentage of patients who reported at least some diplopia at baseline and who had a reduction of ≥ 1 grade at Week 24.*	At Week 24, 67.9% of patients receiving TEPEZZA had a change from baseline of at least 1 grade in diplopia, compared to 28.6% of patients receiving placebo (p=0.001).

48-Week Off-Treatment Follow-Up Period:

- The majority of TEPEZZA patients who were proptosis responders at Week 24 in OPTIC maintained their proptosis response at Week 72 (19/34; 56%) without receiving additional TED treatment
- Of the 15 patients who did not qualify as maintaining a proptosis response, eight patients were at least 2 mm better than baseline at the time of their last assessment in the OPTIC 48-week off-treatment follow-up period. The 15 patients include four who prematurely

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discontinued the study, two who had worsened slightly but not enough to qualify as relapsed for OPTIC-X, and nine who met the OPTIC-X criteria for relapse prior to Week 72 of the off-treatment follow-up period (all nine entered OPTIC-X for retreatment).

Safety

The safety profile of TEPEZZA in the double-masked treatment period of OPTIC was similar to that seen in the previously-conducted Phase 2 study with no new safety observations.

- Adverse events (> 10%) included muscle spasm, alopecia, nausea and fatigue
- The dropout rate was low and balanced across placebo and treatment arms
- There were no deaths during the study and a total of three serious adverse events: in the placebo arm, one patient had a visual field defect and required orbital decompression surgery and discontinued the study; in the TEPEZZA arm, one patient had pneumothorax (considered not related to study drug), and another had an infusion reaction that led to discontinuation of study drug
- The vast majority of treatment-emergent adverse events were mild to moderate in intensity and no other adverse events resulted in discontinuation

The OPTIC trial was conducted at leading centers in the U.S., Germany and Italy, with co-principal investigators Raymond Douglas, M.D., Ph.D., Cedars-Sinai Medical Center; and George Kahaly, M.D., Ph.D., Johannes Gutenberg University Medical Center.

OPTIC-X™ **OPTIC-X:** Assessing TEPEZZA retreatment and extended treatment

Open-label Extension Study (**NCT03461211**)

Trial Design

OPTIC-X evaluated the safety and efficacy of TEPEZZA in TED patients who were enrolled in OPTIC and were either proptosis nonresponders at Week 24 of OPTIC, or were proptosis responders at Week 24 but flared during the 48-week off-treatment follow-up period. Nonresponders were defined as patients who did not achieve at least a 2 mm proptosis improvement from baseline at Week 24 of OPTIC. Flare was defined as patients who lost at least 2 mm of their Week 24 proptosis improvement during the 48-week off-treatment follow-up period – even if their proptosis was still substantially better than at baseline of OPTIC – or who had a substantial increase in the number of inflammatory signs or symptoms without worsening proptosis. Patients could qualify as relapsing at any point during the 48-week off-treatment follow-up period of OPTIC.

Results[5]

OPTIC-X demonstrated meaningful reduction in proptosis and supported the efficacy of TEPEZZA in patients who have had TED for a longer period of time (12 mos. average) than those in the OPTIC trial (6 mos. average).

- Eighty-nine percent of patients (33/37) who received placebo during the OPTIC trial and then entered OPTIC-X and received TEPEZZA, achieved the primary endpoint of a 2 mm or more reduction in proptosis at Week 24 (average reduction of -3.5 mm). This is consistent with results from the OPTIC trial, where 83% of TEPEZZA patients (N=41) had a proptosis reduction of 2 mm or more at Week 24 (average reduction of -3.3 mm).
- Sixty-one percent of patients (14/23) who received placebo during the OPTIC trial and

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then entered OPTIC-X and received TEPEZZA were considered diplopia responders (≥1 grade improvement) at Week 24. This is consistent with results from the OPTIC trial, where 68% of patients (19/28) who received TEPEZZA had a change from baseline of at least 1 grade in diplopia at Week 24.

- Of the eight TEPEZZA patients who flared during the OPTIC 48-week off-treatment follow-up period, received a second course of TEPEZZA and had Week 24 data available, more than 60% had a 2 mm or more proptosis improvement from OPTIC-X baseline at Week 24
- Only five patients had not achieved a proptosis response after completing a full course of TEPEZZA in OPTIC. Of these, two achieved a 2 mm or more proptosis reduction in OPTIC-X after an additional course of TEPEZZA. Two did not have Week 24 data and one was a nonresponder.
- There were no new safety concerns, including in patients who received additional TEPEZZA treatment in OPTIC-X

Phase 2 Clinical Study: TEPEZZA treatment in patients with active Thyroid Eye Disease

Pivotal Phase 2 Clinical Study (**NCT01868997**)

Trial Design[6]

The multicenter, double-masked, randomized, placebo-controlled Phase 2 trial was conducted to determine the efficacy and safety of TEPEZZA in patients with active TED. A total of 88 patients were randomly assigned to receive TEPEZZA or placebo administered intravenously (10 mg/kg for their first infusion followed by 20 mg/kg for the remaining 7 infusions) once every 3 weeks for a total of 8 infusions.

Inclusion Criteria[6]

- Age 18-75 years
- TED diagnosis ≤ 9 months since the onset of symptoms
- No prior treatment except for low-dose oral glucocorticoids and not received within 6 weeks of randomization

Results[6]

The Phase 2 clinical trial demonstrated positive findings for the primary composite endpoint, reduction in both proptosis and CAS. These **data** were reported in the *New England Journal of Medicine*.

- At Week 24, 69% of TEPEZZA-treated patients were overall responders in both proptosis and CAS score versus 20% of placebo-treated patients; 71% of TEPEZZA-treated patients had a response in proptosis versus 20% of placebo-treated patients
  - Response was defined as a reduction of 2 points or more in the CAS and a reduction of 2 mm or more in proptosis at Week 24 without corresponding deterioration in the fellow eye[1]
- The treatment was generally well tolerated. The majority of adverse events experienced with TEPEZZA treatment were graded as mild to moderate and were managed in the trials. Adverse events included hyperglycemia, nausea, diarrhea, muscle spasms, hearing impairment and inflammatory bowel disease in a patient with a recent diagnosis of ileitis and colitis. No deaths occurred during the trial.

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INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA 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 TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

For additional information on TEPEZZA, please see Full Prescribing Information at TEPEZZAhcp.com.

References:

1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon.
2. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125.
3. Bahn RS. Graves' ophthalmopathy. *N Engl J Med.* 2010;362(8):726-738.
4. Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352.
5. Douglas R, et al. Long Term Assessment of Proptosis and Diplopia from the OPTIC Trial of Teprotumumab in Thyroid Eye Disease; Oral presentation at American Academy of Ophthalmology, Annual Meeting, November 2020. https//www.aao.org/annual-meeting.
6. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761.

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