



The New England Journal of Medicine Publishes Comprehensive Data from Phase 3 Clinical Trial (OPTIC) of TEPEZZA™ (teprotumumab-trbw) for Thyroid Eye Disease

January 22, 2020

-- Phase 3 trial achieved its primary endpoint and all secondary endpoints with marked improvement in key indicators of disease --

DUBLIN--(BUSINESS WIRE)--Jan. 22, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that *The New England Journal of Medicine* has published [comprehensive results](#) of the Phase 3 OPTIC clinical trial evaluating TEPEZZA™ (teprotumumab-trbw) for Thyroid Eye Disease (TED). OPTIC is part of the largest clinical program in TED and demonstrates that TEPEZZA provides significant improvements in proptosis (eye bulging) and diplopia (double vision) compared to placebo.

TEPEZZA is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor-1 receptor (IGF-1R) that is administered to patients once every three weeks for a total of eight infusions. TEPEZZA was approved by the U.S. Food and Drug Administration (FDA) on January 21, 2020 – making it the first and only medicine approved for the treatment of TED. The medicine received Priority Review, Orphan Drug, Fast Track and Breakthrough Therapy designations from the FDA.

“Thyroid Eye Disease is a rare, devastating autoimmune disease that is not adequately treated, leaving patients to struggle for years until they become candidates for surgeries that are not only complex, but often don’t fully restore vision or appearance,” said Raymond Douglas, M.D., Ph.D., director of the Orbital and Thyroid Eye Disease Program, Cedars-Sinai Medical Center and co-principal investigator of the OPTIC trial. “In this clinical trial, we saw statistically significant improvements across critical symptoms – including proptosis and diplopia – at the first patient assessment at six weeks of treatment, and those improvements continued over the 24-week treatment period. TEPEZZA, which was just recently approved by the FDA, has the potential to significantly change the treatment paradigm in a disease where patients have historically had to watch and wait in pain as symptoms progress and put them at risk for serious vision impairment.”

OPTIC compared the efficacy and safety of TEPEZZA to placebo administered by infusion once every three weeks for a total of eight infusions. As previously reported, the trial met its primary endpoint and all secondary endpoints.

Key trial findings published in *The New England Journal of Medicine* include the following¹:

- **Proptosis:** At Week 24, more patients receiving TEPEZZA (83%) versus placebo (10%) had a ≥ 2 mm reduction of proptosis in the study eye, without deterioration in the fellow eye ($p < 0.001$). Mean change in proptosis with TEPEZZA was -3.32 mm at Week 24, which is similar to the results attained on average with orbital decompression surgery. All patients who received TEPEZZA had some reduction in proptosis at Week 24, regardless of the initial severity of proptosis, which ranged from 16 mm to 31 mm in the trial. The number needed-to-treat (NNT) was 1.36 (NNT is the number of patients needed to treat in order to achieve response in one additional patient).
- **Muscle and Fat Volume:** Orbital imaging was performed at one trial site, as a part of the site’s standard practice, and showed that the reduction in proptosis was associated with a reduction in extraocular muscle volume, orbital fat volume or both. All six patients in the TEPEZZA group had significantly decreased extraocular muscle volume in the study eye, with an average percentage decrease of 35%. Orbital fat volume in the study eye had an average percentage decrease of 17%. Orbital fat volume was reduced by 44% in one patient and by 40% in another.
- **Diplopia:** At Week 24, 68% of patients receiving TEPEZZA had an improvement from baseline of at least one grade in diplopia, compared to 29% of patients receiving placebo ($p = 0.001$). This endpoint measured the percentage of patients who reported at least some diplopia at baseline in the study eye and who had a reduction of ≥ 1 grade with no corresponding deterioration (≥ 1 grade worsening) in the fellow eye at Week 24.
- **Quality of Life (QoL):** At Week 24, patients receiving TEPEZZA had a mean change of 17 on the Graves’ Ophthalmopathy Quality of Life (GO-QoL) scale compared with a change of 2 for patients receiving placebo ($p < 0.001$). These scores indicate a statistically and clinically meaningful improvement over placebo in these QoL measures. The GO-QoL scale consists of two subscales to evaluate the quality of life of TED (Graves’ Ophthalmology) patients, including impact on visual function and self-assessment of appearance. A change of 6 points is considered clinically significant.²
- **Clinical Activity Score (CAS):** At Week 24, more patients achieved a CAS value of 0 or 1 with TEPEZZA treatment (59% vs 21% of placebo participants) ($p < 0.001$). CAS is a scale used to assess the disease activity of TED, and measures the degree of inflammation, including pain, swelling and redness. The CAS scale ranges from 0 to 7, with a score of 0 representing no swelling or activity.³
- **Overall Responder Rate:** At Week 24, patients treated with TEPEZZA had an overall responder rate of 78% compared with 7% in the placebo group ($p < 0.001$). Overall responder rate is the percent of participants with a ≥ 2 -point reduction in CAS and a ≥ 2 mm reduction in proptosis from baseline, without deterioration in the fellow eye.

- In general, the onset of activity of TEPEZZA was rapid and evident at the first post-baseline assessment at Week 6, with continued improvement over the full 24-week course of treatment.

“TEPEZZA is a biologic specifically designed to inhibit the mechanism of Thyroid Eye Disease – actively reducing tissue expansion and remodeling behind the eye,” said Elizabeth H.Z. Thompson, Ph.D., vice president, clinical development, rare disease, Horizon. “This is important because other therapies used to treat Thyroid Eye Disease have not been shown to improve eye bulging or double vision, which are two of the most common and vision-threatening aspects of the disease. The OPTIC study represents a meaningful step in our evolution to an innovation-focused biopharma company, and its results suggest that TEPEZZA has the potential to change the way the disease is managed.”

The majority of adverse events experienced with TEPEZZA treatment were graded as mild to moderate and were managed in the trial, with few discontinuations. Adverse events (> 10%) included muscle spasm, alopecia, nausea and fatigue. Adverse events of special interest that occurred in 5% of patients or less within 21 days after the last dose included two patients in the TEPEZZA group who experienced hyperglycemia (both cases were mild) and five patients in the TEPEZZA group who experienced hearing impairment (all cases resolved). No deaths occurred. Two serious adverse events occurred in the TEPEZZA group: pneumothorax (probably unrelated to the study drug, as determined by an investigator) and an infusion reaction that led to withdrawal from the trial.

About Thyroid Eye Disease

Thyroid Eye Disease (TED) is a serious, progressive and vision-threatening rare autoimmune disease.⁴ While TED often occurs in people living with hyperthyroidism or Graves' disease, it is a distinct disease that is caused by autoantibodies activating an IGF-1R-mediated signaling complex on cells within the retro-orbital space.^{5,6} This leads to a cascade of negative effects, which may cause long-term, irreversible damage. As TED progresses, it causes serious damage – including proptosis (eye bulging), strabismus (misalignment of the eyes) and diplopia (double vision) – and in some cases can lead to blindness.^{7,8} Historically, patients have had to live with TED until the inflammation subsides, after which they are often left with permanent and vision-impairing consequences.^{4,9}

About TEPEZZA

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 \geq 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](#).

About Horizon

Horizon is focused on researching, developing and commercializing medicines that address critical needs for people impacted by rare and rheumatic diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives. For more information on how we go to incredible lengths to impact lives, please visit www.horizontherapeutics.com, follow us [@HorizonNews](#) on Twitter, like us on [Facebook](#) or explore career opportunities on [LinkedIn](#).

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential benefits of TEPEZZA as a treatment of TED. These forward-looking statements are based on management expectations and assumptions as of the date of this press release, and actual results may differ materially from those in these forward-looking statements as a result of various factors. These factors include whether TEPEZZA is successfully commercialized and adopted by physicians and patients, as well as those described in Horizon's filings with the United States Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in those filings. Forward-looking statements speak only as of the date of this press release and Horizon does not undertake any obligation to update or revise these statements, except as may be required by law.

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Source: Horizon Therapeutics plc

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