New Integrated Data and Follow-up Outcomes From Two TEPEZZA® (teprotumumab-trbw) Pivotal Trials Published in The Lancet Diabetes & Endocrinology

April 16, 2021

-- TEPEZZA significantly improved the clinical course of Thyroid Eye Disease (TED) in all patient subgroups, including those with more severe disease at baseline --

-- For patients in the follow-up period with data available at 51 weeks after the last dose of TEPEZZA, 67 percent had a proptosis response, 69 percent had a diplopia response and 83 percent had an ophthalmic composite outcome response --

DUBLIN--(BUSINESS WIRE)--Apr. 16, 2021-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that new pooled data from the TEPEZZA® (teprotumumab-trbw) Phase 2 and Phase 3 clinical trials are now published in *The Lancet Diabetes & Endocrinology*. The data further reinforce that TEPEZZA significantly improves proptosis (eye bulging) and diplopia (double vision) for TED patients in different subgroups, with most maintaining a long-term response. TEPEZZA – the first and only medicine approved by the U.S. Food and Drug Administration (FDA) for TED – is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor-1 receptor (IGF-1R).

“This integrated analysis comprises one of the largest controlled study populations reported to date in people living with Thyroid Eye Disease, which allowed us to evaluate a variety of patient subgroups, including those whose symptoms were considered more severe,” said George Kahaly, M.D., Ph.D., professor of medicine and endocrinology and metabolism, Johannes Gutenberg University Medical Center and primary author of the paper. “Of most importance, the data clearly show that TEPEZZA mitigates varying levels of disease severity, including proptosis and diplopia, which are the most progressive and difficult findings to treat, and that improvements continue for the long term.”

In this report, treatment study outcomes and follow-up off-treatment data were integrated from two 24-week multicenter, double-masked, placebo-controlled clinical trials where patients were randomized to receive TEPEZZA (n=84) or placebo (n=87) once every three weeks for a total of eight infusions. The final treatment study visit was at Week 24, which was three weeks after the final infusion. Responses were also evaluated at seven weeks and 51 weeks after the final dose of TEPEZZA. Responses were analyzed for proptosis and diplopia, as well as a post-hoc analysis of a combined outcome measure: the “ophthalmic composite outcome.” The composite outcome is calculated as the percentage of patients with clinical improvement in one eye in at least two of the following: 1) proptosis, 2) diplopia, 3) eyelid swelling, 4) lid aperture, 5) globe motility, and 6) Clinical Activity Score, without deterioration of at least two of these outcomes in either eye.

New Study Findings

- There was no evidence for acute disease rebound (increase in percentage of patients no longer meeting proptosis, diplopia or ophthalmic composite outcome) seven weeks after the last dose of TEPEZZA.
- Proptosis (87 percent; 62/71), diplopia (66 percent; 38/58) and ophthalmic composite outcome (92 percent; 66/72) responses were observed seven weeks after the last dose of TEPEZZA.
- A post-hoc analysis of the composite ophthalmic outcome indicated that 81 percent (68/84) of TEPEZZA patients versus 44 percent (38/87) of placebo patients were responders at Week 24.
- Proptosis (67 percent; 38/57), diplopia (69 percent; 33/48) and composite outcome response (83 percent; 48/58) were observed 51 weeks after the last dose of TEPEZZA for those who had long-term off-treatment data available.

Efficacy in Difficult-to-Treat Patients at Week 24

- In a post-hoc analysis, TEPEZZA-treated patients with more severe disease (those with ≥3 mm of proptosis and/or inconstant or constant diplopia) and those with less severe disease at baseline both experienced significant improvements in proptosis and diplopia.
    - In patients with more severe disease, those treated with TEPEZZA had a proptosis response of 79 percent (50/63) compared to 17 percent (11/65) of those who received placebo (P<0.0001), and a diplopia response of 68 percent (38/56) compared to 31 percent of those who received placebo (15/49) (P<0.0001).
    - In patients with less severe disease, those treated with TEPEZZA had a proptosis response of 71 percent (15/21) compared to 9 percent in those who received placebo (2/22) P<0.0001, and a diplopia response of 80 percent (8/10) compared to 30 percent in placebo (3/10) (P=0.015).
- In post-hoc analyses, patients who received TEPEZZA in both the lower baseline CAS subgroup (4 or 5) and the higher CAS subgroup (6 or 7) demonstrated statistically significant improvements compared with placebo in proptosis and diplopia. Overall response and CAS of 0 or 1 response also improved.
- Post-hoc analysis from the Phase 3 study demonstrates that in patients treated with teprotumumab, those with higher (≥10 IU/L) or lower (<10 IU/L) serum thyrotropin-binding inhibitory immunoglobulin (TBII) baseline levels both had a proptosis

response (mean reduction of -3.65 mm and -3.01 mm, respectively) with no treatment difference between the two groups (p=0.43). In patients with higher baseline TBII, 71 percent (10/14) of patients who received TEPEZZA experienced an improvement in diplopia compared to 23 percent (3/13) of patients who received placebo (p=0.0046).

Adherence and Safety

- Nearly 91 percent of patients in the TEPEZZA treatment group (76/84) and the placebo treatment group (79/87) completed the randomized, double-masked treatment period.
- There were no new safety concerns identified in the follow-up period or as part of the pooled analysis that had not been identified in the 24-week treatment period. Of those patients who experienced adverse events, most were mild to moderate (grade 1 or 2) in intensity during the follow-up period. There were no serious adverse events related to TEPEZZA treatment during the follow-up period, as assessed by trial investigators.
- No anti-drug antibodies were reported that impacted safety or efficacy.
- Of the most commonly reported adverse events with TEPEZZA, muscle spasm (18 percent, 95 percent CI 7.3–28.7), hearing loss (10 percent) and hyperglycemia (8 percent, 95 percent CI 1.7–15.0) had the greatest risk difference from placebo. Hearing impairment events were all classified as nonserious and all patients continued in the study without event worsening or discontinuing treatment.

“These comprehensive data enlighten our understanding of how TEPEZZA improves Thyroid Eye Disease symptoms in both the short- and longer-term,” said Saba Sile, M.D., study author and executive director, clinical development, ophthalmology, Horizon. “We will apply these learnings as we continue to study TEPEZZA in the broader Thyroid Eye Disease population and report findings in a larger, more diverse patient population in the future.”

About Thyroid Eye Disease (TED)

TED is a serious, progressive and vision-threatening rare autoimmune disease.[1] TED often occurs in people living with hyperthyroidism or Graves’ disease, but it is a distinct disease that is caused by autoantibodies activating an IGF-1R-mediated signaling complex on cells within the retro-orbital space.[2,3] This leads to a cascade of negative effects, which may cause long-term damage. As TED progresses, the serious damage it can cause includes proptosis (eye bulging), strabismus (misalignment of the eyes) and diplopia (double vision) – and in some cases can lead to blindness.[4,5]

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 ≥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 the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory 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 and follow us on Twitter, LinkedIn, Instagram and Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to the potential benefits of TEPEZZA; Horizon’s plans to further study TEPEZZA and business and other statements that are not historical facts. These forward-looking statements are based on Horizon’s current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ

materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks related to clinical trials, including the fact that prior results may not predict future clinical trial outcomes; Horizon's ability in increase adoption of TEPEZZA; impacts of the COVID-19 pandemic and actions taken to slow its spread, including impacts on supplies of Horizon's medicines and potential delays in clinical trials; the availability of coverage and adequate reimbursement and pricing from government and third-party payers; risks relating to Horizon's ability to successfully implement its business strategies; risks in the ability to recruit, train and retain qualified personnel; competition, including potential generic competition; the ability to protect intellectual property and defend patents; regulatory obligations and oversight, including any changes in the legal and regulatory environment in which Horizon operates and those risks detailed from time-to-time under the caption "Risk Factors" and elsewhere in Horizon's filings and reports with the SEC. Horizon undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information.

References

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