New Data on the Pharmacokinetic Profile of TEPEZZA™ (teprotumumab-trbw) Reinforce the Labeled Dosing Regimen, Indicating a Positive, Consistent Response to Therapy

May 14, 2020

-- Additional Horizon data accepted as a poster presentation at ENDO 2020 summarize the first U.S.-based assessment of the GO-QOL questionnaire and demonstrate the significant burden of Thyroid Eye Disease on patient quality of life --

DUBLIN--(BUSINESS WIRE)--May 14, 2020-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced new data that provide important insights into the mechanisms of TEPEZZA™ (teprotumumab-trbw), illustrating its pharmacokinetic (PK) profile and supporting the dosing regimen established in the labeling for the treatment of Thyroid Eye Disease (TED). A separate abstract summarizes the first U.S.-based validation of the Graves' Ophthalmopathy Quality of Life (GO-QOL) questionnaire. Both studies were accepted as poster presentations at ENDO 2020, the Endocrine Society's annual meeting. They were also published in a special supplement of the *Journal of the Endocrine Society*. 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).

A population PK analysis was performed on data from the teprotumumab Phase 1 oncology clinical trial (n=60) and the Phase 2 and 3 TED clinical trials (N=83), evaluating the exposure-response relationship for key efficacy endpoints (proptosis response rate, percent of patients with a clinical activity score value of 0 or 1, and diplopia responder rate), as well as selected safety variables (hyperglycemia and muscle spasms).

The analysis found that in TED patients, TEPEZZA had a long elimination half-life, low systemic clearance and low volume of distribution, consistent with other monoclonal antibodies. There was no meaningful exposure-response relationship at the selected dose regimen for both efficacy and safety endpoints. There also were no significant differences in PK response based on patient demographics, including baseline age, gender, race, weight, smoking status, renal impairment (mild/moderate) or hepatic function (total bilirubin, aspartate and alanine aminotransferases).

“The TEPEZZA clinical development program evaluated the efficacy and safety of an initial infusion of 10 mg/kg followed by seven infusions of 20 mg/kg once every three weeks,” said Elizabeth H.Z. Thompson, Ph.D., group vice president, development and external search, research and development, Horizon. “This PK analysis provides further evidence that the dosing used in the clinical trials, which is now part of the product labeling, is appropriate and also consistent across various patient types.”

A separate abstract summarizes the first U.S.-based validation of the GO-QOL questionnaire. In the Phase 2 and Phase 3 TEPEZZA clinical trials, the GO-QOL questionnaire was used to evaluate QOL changes in patients who received TEPEZZA compared with placebo. The GO-QOL questionnaire includes eight questions each on visual functioning and appearance-related impacts. Though widely used and validated in Europe, the questionnaire has not previously been validated in the United States. For this evaluation, 13 eligible TED patients completed the questionnaire and then underwent a separate cognitive QOL-related interview. Qualitative interviews indicated that patients found the GO-QOL content relevant and complete.

The most commonly reported visual functioning impacts included the following:

- Difficulty driving (92 percent)
- Difficulty using electronic screens, such as televisions, smart phones and computers (77 percent)
- Difficulty moving around outdoors, due to things like light sensitivity, uneven surfaces and depth perception (69 percent)
- Difficulty doing hobbies (69 percent)

Frequently reported emotional and psychological impacts included the following:

- Change in appearance (92 percent)
- Depression and anxiety (77 percent)
- Frustration and anger (69 percent)
- Negative reactions from others, social impacts and isolation, and lack of self-confidence and embarrassment (each 62 percent)

“Part of Horizon’s goal in introducing novel therapies is to meaningfully improve the state of care for the community, and we believe the assessment of the GO-QOL questionnaire for U.S. patients will help physicians quantify the true burden of this disease as they make treatment decisions for their patients,” said Thompson. “Taken together, these studies offer further insights into TEPEZZA and TED – supporting the important role TEPEZZA plays in helping physicians address the devastating effects of this challenging disease.”

About Thyroid Eye Disease

TED is a serious, progressive and vision-threatening rare autoimmune disease.[1] TED often occurs in people living with hyperthyroidism or Graves’ disease; however, 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, irreversible 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 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 and follow us on Twitter, LinkedIn, Instagram and Facebook.

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.

References

1. Barrio-Barrio J, et al. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. Journal of Ophthalmopathy. 2015;2015:1-16.
2. Weightman DR, et al. Autoantibodies to IGF-1 Binding Sites in Thyroid Associated Ophthalmopathy. *Autoimmunity*. 1993; 16(4): 251–257.
3. Pritchard J, et al. Immunoglobulin Activation of T Cell Chemoattractant Expression in Fibroblasts from Patients with Graves’ Disease Is Mediated Through the Insulin-Like Growth Factor 1 Receptor Pathway. J Immunol. 2003;170:6348-6354.
4. Ross DS, et al. The 2016 European Thyroid Association /European Group on Graves' Orbitopathy Guidelines for the Management of Graves ' Orbitopathy. Eur Thyroid J. 2016;5(1):9-26.
5. McKeag D, et al. Clinical features of dysthyroid optic neuropathy: a European Group on Graves ' Orbitopathy (EUGOGO) survey. Br J Ophthalmol. 2007;91:455-458.

View source version on businesswire.com: https://www.businesswire.com/news/home/20200514005255/en/

Contacts:
Tina Ventura
Senior Vice President, Investor Relations

Investor-relations@horizontherapeutics.com

Ruth Venning
Executive Director, Investor Relations
Investor-relations@horizontherapeutics.com

U.S. Media Contacts:
Matt Flesch
Vice President, Communications and Patient Advocacy
media@horizontherapeutics.com

Rachel Vann
Associate Director, Product Communications
media@horizontherapeutics.com

Ireland Media Contact:
Gordon MRM
Ray Gordon
ray@gordonmrm.ie

Source: Horizon Therapeutics plc