Integrated Clinical Trial Analyses Further Substantiate that Teprotumumab Significantly Improves Debilitating Effects of Thyroid Eye Disease, Including Eye Bulging, Double Vision and Quality of Life

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DUBLIN--(BUSINESS WIRE)--Oct. 31, 2019-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced integrated, pooled efficacy data from the Phase 2 and Phase 3 clinical trials of teprotumumab for the treatment of active thyroid eye disease (TED) compared to placebo. The results support prior analyses of significant reductions in inflammation, proptosis (eye bulging) and diplopia (double vision), as well as improvements in quality of life (QoL). These data were presented at the 89th Annual Meeting of the American Thyroid Association (ATA). This is the first presentation of the pooled analyses and builds on the individual positive results of the Phase 2 and Phase 3 clinical studies.

Teprotumumab is an investigational medicine and its safety and efficacy have not been established. The teprotumumab Biologics License Application (BLA) was granted Priority Review by the U.S. Food and Drug Administration (FDA) and if approved, teprotumumab would be the first FDA-approved medicine for the treatment of active TED. The Prescription Drug User Fee Act (PDUFA) goal date is March 8, 2020.

“This is the largest placebo-controlled evaluation of active thyroid eye disease to date and an important step towards better understanding the devastating, vision-threatening effects of this disease,” said George Kahaly, M.D., Ph.D., of the Johannes Gutenberg University Medical Center in Mainz, Germany and lead study author. “These data highlight the urgent need for targeted intervention strategies and illustrate the potential for teprotumumab to reduce the painful and disfiguring symptoms of thyroid eye disease, and importantly, to help improve quality of life.”

The pooled analysis of the Phase 2 (NCT01868997) and Phase 3 OPTIC (NCT03298867) studies presented during ATA represent the experience of 171 patients with recent onset of TED (less than nine months) treated with teprotumumab or placebo every three weeks for a total of eight infusions.

Key study findings include the following:

- Proptosis: At Week 24, 77.4% of patients receiving teprotumumab experienced a ≥2 mm reduction in proptosis, compared to 14.9% of patients receiving placebo ($p<0.001$). The reduction in average change from baseline through Week 24 in proptosis was greater in patients who received teprotumumab (-2.63 mm) than in those who received placebo (-0.31 mm, $p<0.001$).
- Diplopia: The diplopia responder rate, which is defined as the percentage of patients whose diplopia improved 1 or more grades, was higher with teprotumumab (69.7%) versus placebo (30.5%; $p<0.001$) in those with baseline diplopia.
- Quality of Life: Patients treated with teprotumumab experienced improvements in average change from baseline through week 24 in QoL scores (overall 15.55 vs 5.92, $p<0.001$), including visual functioning (16.81 vs 6.10, $p<0.001$) and appearance (13.51 vs 5.78, $p=0.002$). The GO-QoL scale consists of two subscales to evaluate the quality of life of patients with TED (Graves’ Ophthalmology), including impacts on visual function and self-assessment of appearance. A change of 6 points is considered clinically significant.[1]
- Clinical Activity Score (CAS): At Week 24, nearly two-thirds of teprotumumab-treated patients (61.9%) had no or minimal inflammatory symptoms as measured by CAS (described as a CAS of 0 or 1) compared to 21.8% of placebo-treated patients ($p<0.001$). 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 signs or symptoms of inflammation.[2]
- In addition, 73.8% of teprotumumab patients versus 13.8% of placebo patients had an overall response at Week 24 – defined as the percent of patients with ≥ 2-point reduction in CAS and ≥ 2 mm reduction in proptosis from baseline.

As previously reported, the majority of adverse events experienced with teprotumumab treatment were graded as mild to moderate and were managed in the trials, with few discontinuations. In the Phase 2 clinical study, the only drug-related adverse event identified by the investigators was hyperglycemia. Other adverse events included 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. The safety profile of teprotumumab in the Phase 3 clinical study was similar to that seen in the Phase 2 study with no new safety observations.

“The combined integrated results of the Phase 2 and Phase 3 teprotumumab clinical trials demonstrate compelling data in a disease state that is currently lacking therapies for the painful symptoms, disfigurement and vision impairment that TED patients endure,” said Shao-Lee Lin, M.D., Ph.D., executive vice president, head of research and development and chief scientific officer, Horizon. “We are excited by the positive effects demonstrated in the areas that matter most to patients – proptosis, double vision and quality of life – and we are excited about the potential teprotumumab has to be the first FDA-approved treatment for thyroid eye disease.”

About Thyroid Eye Disease

Thyroid eye disease (TED) is a serious, progressive and vision-threatening autoimmune disease with a limited window of activity that can last up to

three years.[3,4,5] 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 orbit.[6,7] This leads to a cascade of negative effects, which may cause long-term, irreversible damage. Active TED is characterized by inflammation and tissue expansion behind the eye.[3,8] 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.[4,9] TED has only been shown to respond to pharmacotherapy while the disease is active and inflammation is ongoing.[10] Currently, patients must live with active TED until the disease becomes inactive – often left with permanent and vision-impairing consequences.[3,8]

About Teprotumumab

Teprotumumab is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor 1 receptor (IGF-1R). Teprotumumab has received Priority Review, Orphan Drug, Fast Track and Breakthrough Therapy designations from the FDA. The clinical development program for teprotumumab in the treatment of TED includes positive results from the Phase 3 OPTIC confirmatory clinical trial as well as positive Phase 2 results, which were published in The New England Journal of Medicine. 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. Horizon is also conducting the OPTIC-X extension trial to gather further insight into the long-term efficacy and safety of teprotumumab.

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 regulatory approval of teprotumumab and the potential benefits of teprotumumab as a treatment for active TED. 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. These forward-looking statements are based on management's 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, but are not limited to, risks regarding whether the FDA will approve teprotumumab as a treatment for active TED, risks associated with clinical development of medicine candidates and whether Horizon will be able to successfully commercialize teprotumumab, if approved. For a further description of these and other risks facing Horizon, please see the risk factors 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 undertakes no obligation to update or revise these statements, except as may be required by law.

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