



Horizon Pharma plc Announces Phase 3 Confirmatory Trial Evaluating Teprotumumab (OPTIC) for the Treatment of Active Thyroid Eye Disease (TED) Met Primary and All Secondary Endpoints

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- Demonstrated dramatic reduction in proptosis, or eye bulging, the main cause of morbidity in TED -

- There are no FDA-approved treatments available for TED, a devastating rare eye disease that affects 15,000 to 20,000 people each year in the United States -

- Continue to expect mid-2019 Biologics License Application (BLA) submission -

- Management to host conference call today at 8 a.m. ET -

DUBLIN--(BUSINESS WIRE)--Feb. 28, 2019-- Horizon Pharma plc (Nasdaq: HZNP) today announced topline results from its Phase 3 confirmatory trial evaluating teprotumumab for the treatment of active thyroid eye disease (TED). The study met its primary endpoint, showing more patients treated with teprotumumab compared with placebo had a meaningful improvement in proptosis, or bulging of the eye: 82.9 percent of teprotumumab patients compared to 9.5 percent of placebo patients achieved the primary endpoint of a 2 mm or more reduction in proptosis ($p < 0.001$). Proptosis is the main cause of morbidity in TED. All secondary endpoints were also met and the safety profile was consistent with the Phase 2 study of teprotumumab in TED.

Horizon expects to submit a Biologics License Application to the U.S. Food and Drug Administration (FDA) in mid-2019. Teprotumumab has received Breakthrough Therapy, Orphan Drug and Fast Track designations from the FDA. Detailed Phase 3 data will be submitted for publication in a peer-reviewed journal and presented at a medical congress later this year.

"The dramatic results of the teprotumumab Phase 3 confirmatory trial, in addition to positive Phase 2 data, form a highly convincing body of clinical evidence supporting teprotumumab for the treatment of active thyroid eye disease," said Timothy P. Walbert, chairman, president and chief executive officer, Horizon Pharma plc. "This is a key milestone as we evolve into a research-focused company developing innovative new medicines to address challenging diseases with very few effective options. We are one step closer to delivering the first FDA-approved treatment to people living with active thyroid eye disease, and we are grateful to the patients, physicians and investigational sites who have partnered with Horizon to make the teprotumumab research and development program possible."

"In the study, patients treated with teprotumumab had an unprecedented reduction in proptosis, which is currently only treatable via surgery after the active disease has ended," said Raymond Douglas, M.D., Ph.D., the study's co-principal investigator and director of the orbital and thyroid eye disease program, Cedars-Sinai Medical Center. "If approved, teprotumumab would give physicians the first medicine shown to reduce proptosis during active thyroid eye disease, in addition to treating other painful symptoms."

Highlights from the Phase 3 confirmatory trial, titled OPTIC (Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study):

- Designed to investigate the efficacy, tolerability and safety of teprotumumab in patients with active TED.
- Eighty-three patients were assigned to receive teprotumumab or placebo in eight intravenous infusions (10mg/kg for their first infusion followed by 20mg/kg for the remaining seven infusions) every three weeks for 21 weeks.
- The primary endpoint was a 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 teprotumumab and 4/42 (9.5%) patients receiving placebo were proptosis responders at Week 24 ($p < 0.001$).
- All secondary endpoints were also met ($p \leq 0.001$), which include the effect of teprotumumab vs. placebo on:
 - Overall responder rate at Week 24 (primary endpoint in the Phase 2 study): 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.
 - Percent of participants with a CAS value of 0 or 1 at Week 24 in the study eye.
 - Percent of patients with a change from baseline of at least one grade in diplopia (double vision).
 - Mean change in proptosis measurement from baseline to Week 24 in the study eye.
 - Mean change in Graves' Ophthalmopathy Quality of Life from baseline to Week 24.
- The safety profile of teprotumumab in OPTIC was similar to that seen in the Phase 2 study with no new safety observations. The drop-out rate was low ($< 5\%$) 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 received orbital decompression surgery and discontinued study; in the teprotumumab 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.

TED is a progressive, debilitating autoimmune disease with a limited window of active disease during which it can be treated without surgical intervention.^{1,2} While TED often occurs in people living with hyperthyroidism or Graves' disease, it is a distinct disease that is caused by autoantigens activating an IGF-1R-mediated signaling complex on cells within the orbit.^{3,4} This leads to a cascade of negative effects, which cause long-term, irreversible damage. Active TED lasts for up to three years and is characterized by inflammation and tissue expansion behind the eye.^{5,1} 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.^{2,6} Currently, patients must suffer through active TED until the disease becomes inactive – often left with permanent and sight-impairing consequences – before they can have complex and costly surgical procedures that may never fully restore vision or appearance.^{5,1,7} People living with TED often experience long-term functional, psychological and economic burdens, including inability to work and perform activities of daily living.^{7,8}

Webcast

At 8 a.m. ET/1 p.m. IST today, the Company will host a live webcast to discuss the results of the OPTIC trial and current treatment landscape for TED. The live webcast and a replay may be accessed at <http://ir.horizon-pharma.com>. Please connect to the Company's website at least 15 minutes prior to the live webcast to ensure adequate time for any software download that may be needed to access the webcast. A replay of the webcast will be available approximately two hours after the live webcast.

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 is an investigational medicine and its safety and efficacy have not been established. The [Phase 3 OPTIC](#) confirmatory clinical study 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., Johannes Gutenberg University Medical Center. In addition to the Phase 3 OPTIC trial, Horizon is conducting the [OPTIC-X extension trial](#) to gather further insight into the long-term efficacy and safety of teprotumumab. The robust clinical development program for teprotumumab in the treatment of TED includes positive Phase 2 results published in [The New England Journal of Medicine](#).

About Horizon Pharma plc

Horizon Pharma plc is focused on developing and commercializing innovative medicines that address unmet treatment needs for rare diseases, and rheumatic diseases, with a special interest for diseases for which a deep understanding of immunology may lead to innovative ways to control the disease. By fostering a growing pipeline of medicines in development and through aggressive life cycle management of our medicines, we strive to make a powerful difference for patients, their caregivers and physicians. For us, it's personal: by living up to our own potential, we are helping others live up to theirs. For more information, please visit www.horizonpharma.com, follow us [@HZNPplc](#) 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 expectations regarding the submission of a BLA for teprotumumab, expected publications and presentations of data from the Phase 3 teprotumumab clinical trial, potential regulatory approval of teprotumumab and the potential for teprotumumab as a treatment for TED. Forward-looking statements speak only as of the date of this press release and Horizon Pharma 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 Horizon Pharma experiences delays in submitting a BLA for teprotumumab, whether the FDA will accept the planned BLA for filing or approve the BLA, risks associated with clinical development of medicine candidates and whether Horizon Pharma will be able to successfully commercialize teprotumumab, if approved. For a further description of these and other risks facing Horizon Pharma, please see the risk factors described in Horizon Pharma'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 Pharma undertakes no obligation to update or revise these statements, except as may be required by law.

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