New Data from Phase 3 Teprotumumab Trial (OPTIC) Shows Dramatic Reduction in Proptosis, or Eye Bulging, the Main Cause of Morbidity in Active Thyroid Eye Disease (TED)

-- Efficacy Demonstrated Across Measures Not Addressed by Current Therapies --

-- New Data at the 2019 American Association of Clinical Endocrinologists (AACE) Scientific and Clinical Congress Demonstrates Significant Proptosis Reduction and Improvement in Overall Response Rate --

DUBLIN – April 26, 2019 – Horizon Pharma plc (Nasdaq: HZNP) today announced that new data from the Phase 3 confirmatory clinical trial (OPTIC) evaluating the investigational medicine teprotumumab for the treatment of active thyroid eye disease (TED) were presented as part of a late-breaking oral presentation at the 2019 American Association of Clinical Endocrinologists (AACE) Scientific and Clinical Congress in Los Angeles. In addition to primary endpoint data previously announced on Feb. 28, 2019, the presentation includes new data from two secondary endpoints that show a dramatic reduction in proptosis (eye bulging) and a substantial improvement in overall response rate in patients treated with teprotumumab compared with placebo. These data demonstrate the potential for teprotumumab as a treatment for Active TED, which currently has no U.S. Food and Drug Administration (FDA) approved treatments. Teprotumumab is an investigational medicine and its safety and efficacy have not been established.

"People living with Active TED who received teprotumumab in the study achieved key outcomes that are not addressed by current therapeutic approaches," 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, who presented the data at AACE. "Currently, patients with Active TED suffer through life-altering symptoms and – once the active phase of disease ends – are often left with permanent damage. The results of this confirmatory study, together with the Phase 2 results, suggest that teprotumumab may help reduce proptosis and alleviate the inflammatory symptoms of Active TED, potentially avoiding the need for multiple complex surgeries."

The primary endpoint of the Phase 3 confirmatory trial, titled OPTIC (Treatment of Graves' **O**rbitopathy (Thyroid Eye Disease) to Reduce **P**roptosis with **T**eprotumumab **I**nfusions in a Randomized, Placebo-Controlled, **C**linical Study), was the percentage of patients with a $\geq$ 2 mm reduction of proptosis from baseline in the study eye without deterioration of proptosis in the non-study eye at study week 24. Horizon previously reported that, 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 ($p<0.001$).

The following new data on two secondary endpoints was presented at AACE:

- Average change in proptosis throughout 24 weeks of treatment:
    - Throughout the 24 week treatment period, patients treated with teprotumumab had an average proptosis reduction of 2.82 mm compared with 0.54 mm for those who received placebo ($p<0.001$).
    - There was a significant difference in proptosis reduction from baseline between teprotumumab and placebo at all study time points: Week 6 (-2.00 mm vs. -0.38), Week 12 (-2.70 vs. -0.64), Week 18 (-3.26 vs. -0.59) and Week 24 (-3.32 vs. -0.53).
- Overall responder rate at Week 24, which includes proptosis reduction of $\geq$2 mm plus Clinical Activity Score (CAS) improvement of $\geq$2 points, was significantly better for patients treated with

teprotumumab. CAS is a scale used to assess the disease activity of TED, and measures the degree of inflammation, including pain, swelling and redness.
    - Patients treated with teprotumumab had an overall responder rate of 78% compared with 7.1% in the placebo group at week 24 ($p<0.001$).
    - Overall response rate to teprotumumab was significantly better than placebo from baseline at all study time points: Week 6 (43.9% vs. 4.8%), Week 12 (63.4% vs. 11.9%), Week 18 (73.2% vs 11.9%) and Week 24 (78.0% vs. 7.1%).
- As previously reported, all secondary OPTIC trial endpoints were met ($p\leq0.001$), which – in addition to the above – include the effect of teprotumumab vs. placebo on:
    - 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 Graves' Ophthalmopathy (GO) Quality of Life questionnaire from baseline to Week 24.

"After initially sharing primary endpoint results from the OPTIC trial, this is the first of several additional presentations that will explore and analyze secondary endpoints – all of which met statistical significance," said Shao-Lee Lin, M.D., Ph.D., executive vice president, head of research and development and chief scientific officer, Horizon Pharma plc. "As Horizon continues its evolution into a research focused company, we strive to address some of the most challenging and overlooked rare diseases. We've met with and learned from the thyroid eye disease community – those living with the disease and the physicians who treat them – and these interactions have given us urgency to bring forward an effective option where none currently exist."

As previously reported, 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 and debilitating autoimmune disease with a limited window of active disease during which it may respond to medical intervention.[1,2] 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.[3,4] This leads to a cascade of negative effects, which may 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 may need 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] There are currently no U.S. Food and Drug Administration (FDA) approved treatments for Active TED.

Data Briefing on Horizon Website
On Monday, April 29, Horizon will post an audio presentation featuring Dr. Douglas, who will review his OPTIC data presented at AACE. The webcast may be accessed at http://ir.horizon-pharma.com.

About Teprotumumab
Teprotumumab is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor 1 receptor (IGF-1R). The robust 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*. 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. 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., 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. Teprotumumab is an investigational medicine and its safety and efficacy have not been established.

About Horizon Pharma plc
Horizon Pharma plc is focused on researching, developing and commercializing innovative medicines that address unmet treatment needs for rare and rheumatic diseases. By fostering a growing pipeline of medicines in development and exploring all potential uses for currently marketed 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, 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 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.

References

1. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. *Journal of Ophthalmology.* 2015. https://www.hindawi.com/journals/joph/2015/249125/cta/. Accessed Feb 22, 2019.
2. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *European Thyroid Journal.* 2 March 2016. https://www.ncbi.nlm.nih.gov/pubmed/27099835. Accessed Feb 22, 2019.
3. Graves' Ophthalmopathy. *The New England Journal of Medicine.* 25 February 2010. https://www.nejm.org/doi/full/10.1056/NEJMra0905750. Accessed Feb 22, 2019.
4. Igs from patients with Graves' disease induce the expression of T cell chemoattractants in their fibroblasts. *The Journal of Immunology.* 15 January 2002. https://www.ncbi.nlm.nih.gov/pubmed/11777993. Accessed Feb 22, 2019.
5. Update on thyroid eye disease and management. *Clinical Ophthalmology.* 19 October 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770865/. Accessed Feb 22, 2019.
6. Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey. *British Journal of Ophthalmology.* 11 October 2006. https://www.ncbi.nlm.nih.gov/pubmed/17035276. Accessed Feb 22, 2019.
7. Quality of Life and Occupational Disability in Endocrine Orbitopathy. *DA International.* 24 April 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2689575/. Accessed Feb 22, 2019.
8. Public health relevance of Graves' orbitopathy. *The Journal of Clinical Endocrinology & Metabolism.* 26 November 2012. https://www.ncbi.nlm.nih.gov/pubmed/23185037. Accessed Feb 22, 2019.

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