American Journal of Ophthalmology (AJO) Publishes Review Highlighting Lack of Treatments for Active Thyroid Eye Disease (TED)

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DUBLIN--(BUSINESS WIRE)--Aug. 19, 2019-- A rigorous evaluation of the state of care for thyroid eye disease (TED) published in the *American Journal of Ophthalmology* (AJO) highlights the lack of current therapies to adequately treat the disease. The invited 'Perspective' discusses the potential for Horizon's investigational medicine teprotumumab to change the treatment paradigm. The Biologics License Application (BLA) for teprotumumab is currently being reviewed by the U.S. Food and Drug Administration (FDA) and if approved, teprotumumab could be the first FDA-approved medicine for active TED. Teprotumumab is presently an investigational medicine and its safety and efficacy have not been established.

The review, "A New Era in the Treatment of Thyroid Eye Disease," discusses the challenges in treating this serious, progressive and vision-threatening autoimmune disease with off-label therapies that address only inflammatory symptoms, and the considerable burden of illness TED places on patients. The authors highlight that the optimal time to initiate therapy is while the disease is active, which is a one-to-three-year period characterized by inflammation. TED becomes inactive, and unresponsive to current pharmacotherapy, once the inflammation has stabilized. When TED is inactive, damage may be irreversible even with surgical interventions. This may result in permanent physical, visual and psychosocial impairment.

Research implicates the overexpression of insulin-like growth factor-1 receptor (IGF-1R) as a key contributor to TED, suggesting the fully human monoclonal IGF-1R antagonist antibody teprotumumab inhibits a central mechanism driving the disease. Recent clinical studies with teprotumumab have demonstrated its potential in treating patients with active TED.

"There is no approved medical treatment for TED, and available options for TED, which focus only on managing inflammation and symptomatic relief, do not address the biology of the disease," said Raymond Douglas, M.D., Ph.D., director of the Orbital and Thyroid Eye Disease Program, Cedars-Sinai Medical Center, senior author of the paper, and co-principal investigator of the Phase 3 confirmatory clinical trial for teprotumumab. "Our foremost goal is to preserve patients' vision, alleviate pain and avoid long-term, irreversible damage that could interfere with their daily function. The development of a targeted therapy such as teprotumumab serves as a potentially dramatic shift in the treatment paradigm."

The body of clinical evidence with teprotumumab includes top-line positive results from the Phase 3 confirmatory clinical trial, called OPTIC (Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis with Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study), presented at the 2019 American Association of Clinical Endocrinologists (AACE) meeting, as well as positive Phase 2 results. The OPTIC study found that significantly more patients treated with teprotumumab had a meaningful improvement in proptosis, or bulging of the eye, as compared with placebo (82.9% of teprotumumab patients compared to 9.5% of placebo patients). All secondary endpoints were also met, including reduced diplopia (double vision) and improved quality of life. Teprotumumab was generally well tolerated; the majority of adverse events were mild or moderate, manageable and resolved during or after treatment. The OPTIC study was initiated after clinically meaningful and highly statistically significant results from a Phase 2 study, published in *The New England Journal of Medicine* on May 4, 2017.

"Given advances in the understanding of the biological mechanisms of TED, our goal with teprotumumab is to offer an innovative and targeted solution for patients who currently suffer through the active phase of the disease and can be left with lifelong damage to their vision," said Shao-Lee Lin, M.D., Ph.D., executive vice president, head of research and development and chief scientific officer, Horizon. "This review illustrates some of the critical attributes of teprotumumab that could fundamentally advance the state of care for this disease."

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About Thyroid Eye Disease

TED is a serious, progressive and vision-threatening autoimmune disease with a limited window of active disease during which it may respond to medical intervention.[1,2,3] 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.[4,5] 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.[6,1] 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.[2,7] TED has only been shown to respond to pharmacotherapy while the disease is active and inflammation is ongoing.[8] Currently, patients must live with active TED until the disease becomes inactive – often left with permanent and sight-impairing consequences.[6,1]

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 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 for 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 accept the planned BLA for filing or approve the BLA, 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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