Horizon Therapeutics plc Announces the FDA has Granted Priority Review of the Teprotumumab Biologics License Application (BLA) for the Treatment of Active Thyroid Eye Disease (TED)

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-- If Approved, Teprotumumab Would be the First FDA-Approved Medicine for this Vision-Threatening Disease --

DUBLIN--(BUSINESS WIRE)--Sep. 9, 2019-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that the U.S. Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for teprotumumab, an investigational medicine for the treatment of active thyroid eye disease (TED), and granted it **Priority Review** designation. The FDA grants Priority Review designation to applications for medicines that have the potential to provide significant improvements in the treatment of serious conditions. Priority Review is associated with an accelerated six-month review period compared to the standard ten-month review period. If approved, teprotumumab would be the first FDA-approved medicine for the treatment of active TED.

“Priority Review for the teprotumumab BLA is another positive step toward our goal to make a difference in the lives of people who are living with active TED – a painful, debilitating and vision-threatening rare disease,” said Timothy Walbert, chairman, president and chief executive officer, Horizon. “The accelerated review timeline is particularly important given that there is no FDA-approved medical treatment for TED and the window of time for treatment is limited before patients experience potentially long-term, permanent damage to their eyes.”

The FDA has completed its filing review and determined that the application is sufficiently complete to permit a substantive review. Therefore, a priority review classification was established and the Prescription Drug User Fee Act (PDUFA) goal date is **March 8, 2020.** In its letter, the FDA noted that it has established internal review timelines for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings) and that these timelines described in current FDA guidelines are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). The letter further notes that the FDA will inform Horizon of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, the FDA plans to communicate proposed labeling and, if necessary, any post marketing requirement/commitment requests by late **December 2019**.

The FDA also indicated that it is currently planning to hold an advisory committee meeting to discuss the application per guidelines for new molecular entities.[1] Additionally, the FDA notified Horizon that, at this time, it has not identified any potential review issues, although its current filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during the review.

The accepted BLA for teprotumumab includes 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), 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), improved quality of life (QoL) and reductions in Clinical Activity Score (CAS). Teprotumumab was generally well tolerated; the majority of adverse events were mild or moderate, manageable and resolved during or after treatment. Results of the OPTIC study were presented during the 2019 American Association of Clinical Endocrinologists (AACE) Annual Scientific & Clinical Congress. The OPTIC study was initiated after the Phase 2 study demonstrated clinically meaningful and highly statistically significant results in reducing proptosis and in the symptoms of active TED (pain, swelling, redness and inflammation) as measured by Overall Treatment Response (combined CAS and proptosis improvement). The Phase 2 study was published in *The New England Journal of Medicine* in May 2017.

About 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.[2,3,4] 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.[5,6] 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.[7,2] 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.[3,8] TED has only been shown to respond to pharmacotherapy while the disease is active and inflammation is ongoing.[9] Currently, patients must live with active TED until the disease becomes inactive – often left with permanent and vision-impairing consequences.[7,2]

About Teprotumumab

Teprotumumab is a fully human monoclonal antibody (mAb) and a targeted inhibitor of the insulin-like growth factor 1 receptor (IGF-1R). By targeting the IGF-1R signal, teprotumumab reduces inflammation and prevents excessive muscle and fat cell expansion behind the eye. 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 timing of an FDA decision on the teprotumumab BLA, expectations regarding an advisory committee meeting related to the review of the BLA and the potential availability and benefits of teprotumumab to patients. 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 the actual timing and process of review of the teprotumumab BLA and whether the BLA is ultimately approved, 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. Food and Drug Administration Amendments Act of 2007. https://www.congress.gov/bill/110th-congress/house-bill/3580. Accessed Aug. 29, 2019.
2. Graves’ Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. *Journal of Ophthalmology.* 2015. https://www.hindawi.com/journals/joph/2015/249125/cta/. Accessed Sept. 4, 2019.
3. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *European Thyroid Journal.* March 2016. https://www.ncbi.nlm.nih.gov/pubmed/27099835. Accessed Sept. 4, 2019.
4. Shan SJ, Douglas RS. The Pathophysiology of Thyroid Eye Disease. *Journal of Neuro-Ophthalmology*. 2014; 34: 177-185.
5. Graves' Ophthalmopathy. *The New England Journal of Medicine.* Feb. 25, 2010. https://www.nejm.org/doi/full/10.1056/NEJMra0905750. Accessed Sept. 4, 2019.
6. Igs from patients with Graves' disease induce the expression of T cell chemoattractants in their fibroblasts. *The Journal of Immunology.* Jan. 15, 2002. https://www.ncbi.nlm.nih.gov/pubmed/11777993. Accessed Sept. 4, 2019.
7. Update on thyroid eye disease and management. *Clinical Ophthalmology.* Oct. 19, 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770865/. Accessed Sept. 4, 2019.
8. Clinical features of dysthyroid optic neuropathy: A European Group on Graves' Orbitopathy (EUGOGO) survey. *British Journal of Ophthalmology.* Oct. 11, 2006. https://www.ncbi.nlm.nih.gov/pubmed/17035276. Accessed Sept. 4, 2019.
9. Mamoojee Y, Pearce SHS. Natural History. In: Wiersinga WM, Kahaly GJ (eds): *Graves’ Orbitopathy: A Multidisciplinary Approach – Questions and Answers.*Basel, Karger. 2017:93-104.

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