New Analysis of UPLIZNA® (inebilizumab-cdon) Phase 3 Trial Data Demonstrates Importance of Reducing Plasmablasts to Help Prevent Neuromyelitis Optica Spectrum Disorder (NMOSD) Attacks

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-- Separate analysis also being presented at ECTRIMS 2022 reinforces the efficacy of UPLIZNA in patients with genetic variations --

DUBLIN--(BUSINESS WIRE)--Oct. 26, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced new data from two analyses of the UPLIZNA Phase 3 pivotal trial being presented at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS 2022), Oct. 26-28 in Amsterdam. UPLIZNA is the first and only B-cell depleting monotherapy approved by the U.S. Food and Drug Administration and the European Commission for the treatment of NMOSD in adults who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+).

These data demonstrate how critical mechanisms of UPLIZNA effectively and distinctly treat NMOSD. Results showed UPLIZNA effectively depletes CD19+ B cells, including plasmablasts and plasma cells, which have been found to play a crucial role in the underlying pathophysiology of the disease. A separate analysis demonstrated the efficacy of UPLIZNA among patients with genetic variations typically associated with reduced response to other types of monoclonal antibody (mAb) B-cell depleting therapies.

Broad reduction of B cells, specifically plasmablasts, that correlate with NMOSD attacks

Proinflammatory CD19+ B cells are considered a key driver of NMOSD attacks; however, less is known about the association of attacks with various B-cell subsets, including plasmablasts and plasma cells. This analysis of the N-MOmentum trial (NCT02200770) aimed to clarify the relationship between peripheral B-cell subsets in the blood, AQP4-IgG levels and NMOSD attacks. To do so, absolute counts of CD20+ B cells and CD27+ memory B cells in the peripheral blood, plasma cell gene expression and AQP4-IgG titers were assessed.

Increases in plasma cells were seen in over half (57%, 12/21) of placebo participants at time of attack relative to baseline compared to 20% (4/20) and 16% (3/19) for total CD20+ B cells and CD27+ memory B cells respectively. Increases in plasma cells were also observed at the preceding visit relative to baseline ($p < 0.01$). No significant increases in any B cell subsets at time of attack were observed in participants treated with UPLIZNA relative to the preceding visit.

Surprisingly, in the placebo group, significant increases in AQP4-IgG+ titer were observed at time of attack relative to baseline ($p = 0.02$) but not in those treated with UPLIZNA ($p=0.76$); however, changes in AQP4-IgG titer from baseline to attack were not significantly different between treatment groups ($p = 0.15$). Moreover, 85% of placebo participants had AQP4 titer increases and/or increased plasma cells, representing a potential attack signal.

UPLIZNA significantly decreased AQP4-IgG+ titer relative to placebo. At the end of the randomized control period, 37% (59/159) of participants treated with UPLIZNA had a ≥2-fold decrease in AQP4-IgG titers from baseline compared to 18% (9/50) of those treated with placebo ($p=0.01$). For participants with high AQP4-IgG titers (>1:20,480), 51% (18/35) of participants treated with UPLIZNA had a ≥2-fold decrease in AQP4-IgG titers from baseline compared to 8% (1/12) of placebo participants.

“These findings suggest that plasmablasts and plasma cells may play a more crucial role in NMOSD attacks than was previously understood,” said Bruce Cree, M.D., Ph.D., MAS, study author and professor of clinical neurology at the University of California San Francisco Weill Institute for Neurosciences. “By targeting CD19, UPLIZNA reduces levels of plasmablasts in addition to memory B cells, which has been shown to provide deep protection. Additional analyses may help clarify the therapeutic impact associated with targeting CD19, particularly on plasmablasts and the associated reduction in AQP4-IgG, to reduce attacks.”

Efficacy across genetic variations typically associated with poor response

A separate analysis from the Phase 3 trial provides insights into the efficacy of UPLIZNA among trial participants with different genetic make-ups, including those with variations associated with reduced response to conventional mAb therapies. Research has shown that genetic variations in the immune system can impact the efficacy of these mAb therapies, specifically a variation, or polymorphism, in a gene that encodes the low-affinity Fc gamma receptor IIIa (FCGR3A).[1-6] UPLIZNA was purposely engineered for strong binding to the low-affinity Fc gamma receptor IIIa (FCGR3A), which has been shown to improve efficacy in patients regardless of FCGR3A genotype.[7-8]

This analysis of the full N-MOmentum trial builds upon a prior analysis from the first six months of the trial and further illustrates the potential therapeutic advantages of the mechanism of UPLIZNA. For this analysis, genotyping conducted in 142 participants found no significant differences in attack rates, disease relapse risk or disability worsening (on the Expanded Disability Status Scale) regardless of FCGR3A genotype. Depletion of CD20+ B cells was similar among the genotypes and was sustained throughout the duration of the study. These data indicate that regardless of genotype differences, those treated with UPLIZNA experienced similar clinical outcomes, suggesting the treatment can be an effective option even for those patients whose polymorphism has been associated with reduced efficacy of other mAbs.

“Taken together, these analyses offer more precise illustrations of the differentiated mechanisms of UPLIZNA that are contributing to improved clinical outcomes,” said Kristina Patterson, M.D., PhD, medical director, neuroimmunology, Horizon. “This is important information for clinicians to consider as they make treatment decisions for their patients because even just one attack can result in devastating consequences, like paralysis and blindness.”

About Neuromyelitis Optica Spectrum Disorder (NMOSD)

NMOSD is a unifying term for neuromyelitis optica (NMO) and related syndromes. NMOSD is a rare, severe, relapsing, neuroinflammatory autoimmune disease that attacks the optic nerve, spinal cord, brain and brain stem.[9-10] Approximately 80 percent of all patients with NMOSD test positive for anti-AQP4 antibodies.[11] AQP4-IgG binds primarily to astrocytes in the central nervous system and triggers an escalating immune response that results in lesion formation and astrocyte death.[12]

Anti-AQP4 autoantibodies are produced by plasmablasts and plasma cells. These B-cell populations are central to NMOSD disease pathogenesis, and a large proportion of these cells express CD19.[13] Depletion of these CD19+ B cells is thought to remove an important contributor to inflammation, lesion formation and astrocyte damage. Clinically, this damage presents as an NMOSD attack, which can involve the optic nerve, spinal cord and brain.[12-14] Loss of vision, paralysis, loss of sensation, bladder and bowel dysfunction, nerve pain and respiratory failure can all be manifestations of the disease.[15] Each NMOSD attack can lead to further cumulative damage and disability.[16,17] NMOSD occurs more commonly in women and may be more common in individuals of African and Asian descent.[18,19]

About UPLIZNA

INDICATION

UPLIZNA is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

IMPORTANT SAFETY INFORMATION

UPLIZNA is contraindicated in patients with:

- A history of life-threatening infusion reaction to UPLIZNA
- Active hepatitis B infection
- Active or untreated latent tuberculosis

WARNINGS AND PRECAUTIONS

Infusion Reactions: UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash or other symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Administer pre-medication with a corticosteroid, an antihistamine and an anti-pyretic.

Infections: The most common infections reported by UPLIZNA-treated patients in the randomized and open-label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%) and influenza (7%). Delay UPLIZNA administration in patients with an active infection until the infection is resolved.

Increased immunosuppressive effects are possible if combining UPLIZNA with another immunosuppressive therapy.

The risk of Hepatitis B Virus (HBV) reactivation has been observed with other B-cell-depleting antibodies. Perform HBV screening in all patients before initiation of treatment with UPLIZNA. Do not administer to patients with active hepatitis.

Although no confirmed cases of Progressive Multifocal Leukoencephalopathy (PML) were identified in UPLIZNA clinical trials, JC virus infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies and other therapies that affect immune competence. At the first sign or symptom suggestive of PML, withhold UPLIZNA and perform an appropriate diagnostic evaluation.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating UPLIZNA.

Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.

Reduction in Immunoglobulins: There may be a progressive and prolonged hypogammaglobulinemia or decline in the levels of total and individual immunoglobulins such as immunoglobulins G and M (IgG and IgM) with continued UPLIZNA treatment. Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion especially in patients with opportunistic or recurrent infections.

Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA.

Adverse Reactions: The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia.

For additional information on UPLIZNA, please see the Full Prescribing Information at www.UPLIZNA.com.

About Horizon

Horizon is a global biotechnology company focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory 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, visit www.horizontherapeutics.com and follow us on Twitter, LinkedIn, Instagram and Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including statements regarding the potential benefits of UPLIZNA. 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

future results of clinical trials and data analyses will be consistent with preliminary results or results of prior trials or other data or Horizon's expectations, the risks associated with clinical development and adoption of novel medicines and risks related to competition or other factors that may change physician treatment strategies. 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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