New Analysis of MRI Findings Show UPLIZNA® (inebilizumab-cdon) Reduced the Formation of Asymptomatic Optic Nerve Lesions in People With Neuromyelitis Optica Spectrum Disorder (NMOSD)

March 14, 2023

DUBLIN--(BUSINESS WIRE)--Mar. 14, 2023-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the presentation of new MRI imaging data from the Phase 3 clinical trial showing UPLIZNA reduced the formation of subclinical (asymptomatic) optic nerve lesions in people with NMOSD. These findings are being presented during the 49th annual meeting of the North American Neuro-Ophthalmology Society (NANOS) March 11-16, 2023, in Orlando, Florida.

UPLIZNA is the first and only B-cell depleting monotherapy approved by the U.S. Food and Drug Administration, the European Commission and the Brazilian Health Regulatory Agency (ANVISA) for the treatment of NMOSD in adults who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+). The N-MOmentum pivotal trial (NCT02200770) is also the only Phase 3 clinical trial in NMOSD that collected MRI data and integrated MRI into its attack adjudication criteria. Results from the study demonstrated the significant effect of UPLIZNA in reducing the risk of NMOSD-associated attacks. This new post-hoc analysis based on MRI imaging provides a deeper understanding of the treatment effect on subclinical lesions.

“Data presented at the NANOS meeting show that gadolinium enhancement events of the optic nerve may occur in NMO patients without causing optic neuritis,” 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. “Although these subclinical optic nerve findings were smaller than those associated with optic neuritis attacks and were not predictive of future attacks, that the enhancement events occur shows there is a greater degree of complexity to attack pathogenesis in NMO than was previously appreciated. How these subclinical enhancement events contribute to the overall disease burden in NMO remains to be determined. Nevertheless, it is encouraging to see that repeated use of UPLIZNA decreased the rate of these subclinical optic nerve enhancements events over time.”

During the trial, MRI imaging was conducted on the spinal cord, optic nerve and brain/brainstem to quantify the frequency, prognosis and treatment response to UPLIZNA of subclinical lesions. This imaging was captured at the time of screening and at the end of the randomized controlled period (RCP), at the time of any attack and annually during the open label portion (OLP) of the trial.

The MRI findings showed that a high proportion of participants experienced subclinical optic nerve findings without new symptoms at the end of the RCP. These were shorter (median length 6 mm) than in those with an optic nerve attack (15 mm, $p<0.001$) and were not found to be associated with future attacks. Importantly, while the total subclinical findings in the optic nerve were not reduced during the RCP, the number of clinical optic neuritis attacks was significantly reduced during this time period. Moreover, the formation of these subclinical findings was reduced with repeated UPLIZNA treatment over the course of the OLP.

“The use of MRI in the Phase 3 clinical trial has enabled us to better quantify not only the most visible effects of NMOSD attacks, but also changes in disease patterns at the subclinical level that may compound over time,” said Kristina Patterson, M.D., PhD, medical director, neuroimmunology, Horizon. “These data help deepen our understanding of the real biological impact of this medicine not just on the attacks, but also on asymptomatic activity, further reinforcing the robust clinical profile of UPLIZNA in controlling the effects of this challenging disease and supporting long-term patient care.”

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 brainstem.[1-2] Approximately 80% of all patients with NMOSD test positive for anti-AQP4 antibodies.[3] 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.[4]

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.[5] 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, brain and brainstem.[4-6] Loss of vision, paralysis, loss of sensation, bladder and bowel dysfunction, nerve pain and respiratory failure can all be manifestations of the disease.[7] Each NMOSD attack can lead to further cumulative damage and disability.[8-9] NMOSD occurs more commonly in women and may be more common in individuals of African and Asian descent.[10-11]

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 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.

References

1. Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. *J Neurol Sci*. 2018;384:96-103.
2. What is NMO? Accessed April 15, 2021. Guthyjacksonfoundation.org. www.guthyjacksonfoundation.org/neuromyelitis-optica-nmo/
3. What We Know About NMO. Accessed Aug. 2, 2022. Sumairafoundation.org. https://www.sumairafoundation.org/what-to-know-about-nmo/
4. Liu Y, et al. A tract-based diffusion study of cerebral white matter in neuromyelitis optica reveals widespread pathological alterations. *Mult Scler*. 2011;18(7):1013-1021.
5. Chihara N, et al. Interleukin 6 signaling promotes anti-aquaporin-4 autoantibody production from plasmablasts in neuromyelitis optica. *PNAS*. 2011;108(9):3701-3706.
6. Duan T, Smith AJ, Verkamn AS. Complement-independent bystander injury in AQP4-IgG seropositive neuromyelitis optica produced by antibody dependent cellular cytotoxicity. *Acta Neuropathologica Comm*. 2019;7(112).

7. Beekman J, et al. Neuromyelitis optica spectrum disorder: patient experience and quality of life. *Neural Neuroimmunol Neuroinflamm*. 2019;6(4):e580.
8. Kimbrough DJ, et al. Treatment of neuromyelitis optica: review and recommendations. *Mult Scler Relat Disord*. 2012;1(4):180-187.
9. Baranello RJ, Avasarala, JR. Neuromyelitis optica spectrum disorders with and without aquaporin 4 antibody: Characterization, differential diagnosis, and recent advances. *J Neuro Ther.* 2015;1(1):9-14.
10. Wingerchuk DM. Neuromyelitis optica: effect of gender. *J Neurol Sci.* 2009;286(1-2):18-23.
11. Flanagan EP, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol.* 2016;79(5):775-783.

View source version on businesswire.com: https://www.businesswire.com/news/home/20230314005537/en/

Tina Ventura
Senior Vice President, Chief Investor Relations Officer
Investor-relations@horizontherapeutics.com

U.S. Media Contact:
Rachel Vann
Director, Product Communications
media@horizontherapeutics.com

Ireland Media Contact:
Gordon MRM
Ray Gordon
ray@gordonmrm.ie

Source: Horizon Therapeutics plc