Analysis from the Phase 3 N-MOmentum Study Demonstrates the Effectiveness of UPLIZNA® (inebilizumab-cdon) Among Neuromyelitis Optica Spectrum Disorder Patients with Genetic Variations

May 31, 2022

-- Data being presented at the CMSC Annual Meeting demonstrates UPLIZNA may reduce attack risk and disability among populations with genetic variables typically linked to poor treatment response --

DUBLIN--(BUSINESS WIRE)--May 31, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced data from the Phase 3 pivotal trial of UPLIZNA in NMOSD illustrating the treatment's effectiveness among patients with different genetic make-ups, including those with certain variations associated with reduced response to conventional monoclonal antibody (mAb) therapies. These data are being presented during the Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting, June 1-4.

Treatment for NMOSD includes the use of mAbs that bind to and deplete the B cells that drive disease activity. Increasingly, therapeutic research has shown that genetic variations in the immune system can affect the efficacy of these mAb therapies. Specifically, a variation, or polymorphism, in a gene that encodes the low-affinity Fc gamma receptor IIIa (FCGR3A) has been shown to reduce the effectiveness of certain mAbs, like rituximab, in diseases including NMOSD.[1-6]

UPLIZNA is a highly specific CD19 B-cell depleting agent that targets an extended range of B cells, including plasmablasts and plasma cells, which contribute to NMOSD. UPLIZNA was purposely engineered to allow for strong binding to the low-affinity Fc gamma receptor IIIa (FCGR3A). This molecular engineering has been shown to improve efficacy in patients regardless of FCGR3A genotype.[7-8]

Data from the N-MOmentum pivotal trial of UPLIZNA (NCT02200770) illustrates the potential advantage of the design of UPLIZNA. As part of the trial, 142 participants underwent genotyping to identify FCGR3A genotype. The study found no significant differences in disease attacks or disability regardless of FCGR3A genotype, indicating the design of UPLIZNA was effective even among those whose polymorphism is associated with reduced efficacy of other treatments.

"These data illustrate how mechanistic precision in treatment design can help patients gain benefit from their regimen regardless of the genetic make-up of their immune systems," 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. "These types of genetic analyses may help inform future screening mechanisms to tailor treatment strategies that can optimize the response rate for each patient."

"Inclusion of genetic biomarkers helps explain the true impact of our therapeutics on patient populations in need of innovative medicines," said Kristina Patterson, medical director, neuroimmunology, Horizon. "The results from the pivotal trial for UPLIZNA demonstrate the effectiveness of UPLIZNA across patient genotypes in NMOSD and further reinforce the mechanistic differentiation of its design."

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% 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 and genetic analyses and Horizon's research and development plans. 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.

References

1. Kim SH, Jeong IH, Hyun JW, Joung A, Jo HJ, Hwang SH, Yun S, Joo J, Kim HJ. Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. *JAMA Neurol*. 2015 Sep;72(9):989-95. doi: 10.1001/jamaneurol.2015.1276. PMID: 26167726.
2. Robledo G, Márquez A, Dávila-Fajardo CL, Ortego-Centeno N, Rubio JL, Garrido Ede R, Sánchez-Román J, García-Hernández FJ, Ríos-Fernández R, González-Escribano MF, García MT, Palma MJ, Ayala Mdel M, Martín J. Association of the FCGR3A-158F/V gene polymorphism with the response to rituximab treatment in Spanish systemic autoimmune disease patients. *DNA Cell Biol*. 2012 Dec;31(12):1671-7. doi: 10.1089/dna.2012.1799. Epub 2012 Oct 17. PMID: 23075294.
3. Pál I, Szamosi S, Hodosi K, Szekanecz Z, Váróczy L. Effect of Fcγ-receptor 3a (FCGR3A) gene polymorphisms on rituximab therapy in Hungarian patients with rheumatoid arthritis. *RMD Open*. 2017 Nov 1;3(2):e000485. doi: 10.1136/rmdopen-2017-000485. PMID: 29177079; PMCID: PMC5687551.
4. Kastbom A, Cöster L, Arlestig L, Chatzidionysiou A, van Vollenhoven RF, Padyukov L, Rantapää-Dahlqvist S, Saevarsdottir S. Influence of FCGR3A genotype on the therapeutic response to rituximab in rheumatoid arthritis: an observational cohort study. *BMJ Open*. 2012 Sep 22;2(5):e001524. doi: 10.1136/bmjopen-2012-001524. PMID: 23002160; PMCID: PMC3467642.

5. Ruyssen-Witrand A, Rouanet S, Combe B, Dougados M, Le Loët X, Sibilia J, Tebib J, Mariette X, Constantin A. Fcγ receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis*. 2012 Jun;71(6):875-7. doi: 10.1136/annrheumdis-2011-200337. Epub 2012 Feb 25. PMID: 22368231.
6. Md Yusof MY, Robinson J, El-Sherbiny Y, et al. SAT0009 The Effect FCGR3A Polymorphism on the Initial Depth of B-cell Depletion by Rituximab, Functional NK-cell Mediated Killing and Clinical Response in Systemic Lupus Erythematosus. *Annals of the Rheumatic Diseases.* 2019;78:1069-1070.
7. Niwa R, Hatanaka S, Shoji-Hosaka E, Sakurada M, Kobayashi Y, Uehara A, Yokoi H, Nakamura K, Shitara K. Enhancement of the antibody-dependent cellular cytotoxicity of low-fucose IgG1 Is independent of FcgammaRIIIa functional polymorphism. *Clin Cancer Res.* 2004 Sep 15;10(18 Pt 1):6248-55. doi: 10.1158/1078-0432.CCR-04-0850. PMID: 15448014.
8. Masuda K, Kubota T, Kaneko E, Iida S, Wakitani M, Kobayashi-Natsume Y, Kubota A, Shitara K, Nakamura K. Enhanced binding affinity for FcgammaRIIIa of fucose-negative antibody is sufficient to induce maximal antibody-dependent cellular cytotoxicity. *Mol Immunol.* 2007 May;44(12):3122-31. doi: 10.1016/j.molimm.2007.02.005. Epub 2007 Mar 26. PMID: 17379311.
9. 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.
10. What is NMO? Accessed April 15, 2021. Guthyjacksonfoundation.org. Accessed April 15, 2021. www.guthyjacksonfoundation.org/neuromyelitis-optica-nmo/
11. Layman's Guide to NMO. Sumairafoundation.org. Accessed April 25, 2021. https://www.sumairafoundation.org/laymans-guide-to-nmo/
12. 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.
13. Chihara N, et al. Interleukin 6 signaling promotes anti-aquaporin-4 autoantibody production from plasmablasts in neuromyelitis optica. *PNAS*. 2011;108(9):3701-3706.
14. 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).
15. Beekman J, et al. Neuromyelitis optica spectrum disorder: patient experience and quality of life. *Neural Neuroimmunol Neuroinflamm*. 2019;6(4):e580.
16. Kimbrough DJ, et al. Treatment of neuromyelitis optica: review and recommendations. *Mult Scler Relat Disord*. 2012;1(4):180-187.
17. 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.
18. Wingerchuk DM. Neuromyelitis optica: effect of gender. *J Neurol Sci.* 2009;286(1-2):18-23.
19. 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/20220531005361/en/

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

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

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

Source: Horizon Therapeutics plc