Horizon Therapeutics plc Receives CHMP Positive Opinion for UPLIZNA® (inebilizumab) as a Monotherapy for the Treatment of Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

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-- CHMP recommendation based on positive results from N-MOmentum, the largest clinical trial ever conducted in NMOSD to date --

-- In the trial, UPLIZNA was shown to reduce the risk of relapse by 77% compared to placebo in anti-aquaporin-4 antibody positive (AQP4-IgG+) adult patients --

-- Treatment is given via infusion every six months following an initial two treatments spaced two weeks apart --

-- UPLIZNA is under review by the European Medicines Agency (EMA) and was approved by the U.S. Food and Drug Administration (FDA) and the Japanese Ministry of Health, Labour and Welfare as a targeted CD19 B-cell depleting antibody for adults with AQP4-IgG+ NMOSD --

-- UPLIZNA received Breakthrough Therapy and Orphan Drug designation in the United States (U.S.) and Orphan Drug designation Japan --

DUBLIN--(BUSINESS WIRE)--Nov. 12, 2021-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending marketing authorization for UPLIZNA® (inebilizumab) as a monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+). UPLIZNA has been granted orphan designation by the European Commission (EC). That designation is subject to additional review by the Committee for Orphan Medicinal Products.

UPLIZNA has not been approved for commercial use in the European Union (EU). Based on the CHMP recommendation, a decision by the EC, if granted, would authorize marketing approval in the EU. This centralized marketing authorization would be valid in all EU Member States, as well as in Iceland, Liechtenstein and Norway.

“Today’s positive CHMP opinion is a significant milestone in Horizon’s global growth and long-term commitment to address critical needs of those living with rare, autoimmune and severe inflammatory diseases,” said Tim Walbert, chairman, president and chief executive officer, Horizon. "In Europe, people living with NMOSD currently have very limited targeted treatment options and we look forward to advancing care for these patients who live daily with unpredictable attacks, pain and disability.”

UPLIZNA was approved by the FDA in June 2020 and by the Japanese Ministry of Health, Labour and Welfare in March 2021 as a targeted CD19 B-cell depleting antibody for adult patients with AQP4-IgG+ NMOSD, to reduce the risk of attacks. UPLIZNA is the only approved NMOSD therapy in the U.S. that has demonstrated a clinically relevant and durable effect on delaying worsening of disability, with a significant reduction in hospitalization. In Japan, Mitsubishi Tanabe Pharma Corporation has the rights for development and commercialization of UPLIZNA. Long-term UPLIZNA treatment has been shown to be well tolerated and provide a sustained reduction in NMOSD attack risk for four or more years.[1]

NMOSD is a rare, severe autoimmune disease where the body’s defense cells (B-cells) start to attack the optic nerve, spinal cord and brain stem. [2,3] NMOSD is often misdiagnosed as multiple sclerosis (MS) and primarily damages the optic nerve(s) and spinal cord, causing permanent blindness, muscle weakness and paralysis.[4] NMOSD is characterized by unpredictable attacks and severe disability that often occurs following the first attack, accumulating with each subsequent relapse.[5] Preventing these attacks is the primary goal for disease management.[6] UPLIZNA works by depleting B-cells in a targeted manner, and patients need only take it once every six months, via infusion, following an initial two treatments spaced two weeks apart.[7]

AQP4 is a membrane protein that is predominantly found in the central nervous system. It has a protective effect by regulating the water homeostasis, a self-regulating process, to maintain the stability of the physiological function in the body.[8] A defining feature of NMOSD (seen in approximately 80% of patients) is the presence of serum autoantibodies which work *against* AQP4, leading to severe attacks in the central nervous system, resulting in substantial and often permanent disability.[9]

Globally, the prevalence of NMOSD is approximately 0.5–4/100,000 people.[10, 11] Europe has an estimated disease population of at least 7,300 patients, 75-80% of which are AQP4-IgG+. Each year, approximately 370 new patients in Europe are diagnosed with NMOSD.[12]

“NMOSD is a very devastating and serious condition where symptoms become worse over time and are followed by periods of less severe symptoms that do not completely cease, so my patients never know what to expect,” said Professor Friedemann Paul, M.D., Charité-Universitätsmedizin Berlin, NeuroCure Clinical Research Center, NCRC Research Group, „Clinical Neuroimmunology“. “During a relapse, damage to the optic nerves and/or spinal cord can lead to accumulating disability, therefore, preventing attacks is critical to a good long-term outcome. There continues to be a high need for new treatments, specifically developed for NMOSD, that can help to ease symptoms and prevent future relapses. This is why the news of the positive CHMP recommendation for UPLIZNA brings such hope to the NMOSD patient community.”

The CHMP positive opinion was granted based on the data from the N-MOmentum clinical development program (NCT02200770), which found that

UPLIZNA monotherapy reduced the risk of relapse by 77% compared to placebo in AQP4-IgG+NMOSD adult patients.[7]

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.[2,3] Approximately 80% of all patients with NMOSD test positive for anti-AQP4 antibodies.[9] 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.[13]

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.[14] 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.[13,15] Loss of vision, paralysis, loss of sensation, bladder and bowel dysfunction, nerve pain and respiratory failure can all be manifestations of the disease.[16] Each NMOSD attack can lead to further cumulative damage and disability.[17,18] NMOSD occurs more commonly in women and may be more common in individuals of African and Asian descent.[19,20]

About the N-MOmentum clinical program[21]

N-MOmentum was a multicenter, double-blind, randomized placebo-controlled Phase 2/3 clinical trial that was conducted in 25 countries. Participants were randomly assigned (3:1 with a ratio AQP4+: n=213 and AQP4-: n=17) to receive 300 mg of intravenous UPLIZNA or placebo. The study consisted of a 28-week randomized-controlled period (RCP), followed by an optional open-label period (OLP) of at least two years. The OLP lasted approximately four years, producing long-term data for a subset of patients (n=94 AQP4+ patients).

The trial Primary Endpoint was

- **Time to onset of NMOSD relapse on or before Day 197**

The trial Secondary Endpoints were

- **Percentage of patients with worsening in Expanded Disability Severity Scale (EDSS) from baseline to the last visit of the RCP**: EDSS and its associated functional system (FS) score provide a system for quantifying disability and monitoring changes in the level of disability over time.
- **Change from baseline in Low-Contrast Visual Acuity Binocular (LCVAB) Score to the last visit of the RCP:** The low-contrast visual acuity test is used to determine the number of letters that can be read on a standardized low-contrast Landolt C Broken Rings Chart held at a distance of three meters. The binocular score is the number of letters read correctly on an eye chart using both eyes simultaneously. The total score ranges from 0-70 and a higher score indicates better vision.
- **Number of active Magnetic Resonance Imaging (MRI) lesions during the RCP:** The number of new lesions were measured by MRI of the brain, optic nerve and spinal cord.
- **Number of NMOSD-related in-patient hospitalizations during the RCP**: Participants with relapsing NMOSD have recurrent attacks that can be severe and result in blindness, paralysis and even death and, consequently, such attacks frequently result in in-patient hospitalizations (defined as a stay in hospital that goes beyond midnight of the first day of admission).

In the N-MOmentum trial, UPLIZNA had a favorable safety profile. The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia. The full safety profile will be available in the summary of product characteristics (SmPC).

During the trial, B-cell counts were determined using high-resolution flow cytometry (captured as cells/µL). Disease activity was measured using annualized attack rates (AAR) and the number of new or enlarging T2 lesions in the brain or spine.

Due to demonstrated superior efficacy achieved in the UPLIZNA treatment arm versus placebo, the N-MOmentum was stopped early on the recommendation of the Independent Data Monitoring Committee.

About Horizon

Horizon is 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, please visit www.horizontherapeutics.com and follow us on Twitter, LinkedIn, Instagram and Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to statements regarding a potential decision by the European Commission with respect to a centralized marketing authorization in the EU, and the potential availability in the EU and benefits of UPLIZNA 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 Horizon's application seeking centralized marketing authorization and whether the authorization is granted, the fact that a positive CHMP opinion does not guarantee that marketing authorization will be granted, and those risks detailed from time-to-time under the caption "Risk Factors" and elsewhere in Horizon's filings and reports with the SEC. Horizon undertakes no duty or obligation to update any forward-

looking statements contained in this press release as a result of new information.

References

1. Rensel M, Zabeti A, Mealy M et al. Long-term efficacy and safety of inebilizumab in neuromyelitis optica spectrum disorder: Analysis of aquaporin-4–immunoglobulin G–seropositive participants taking inebilizumab for ⩾4 years in the N-MOmentum trial. *Multiple Sclerosis Journal*. 2021:135245852110472.
2. 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.
3. What is NMO? Guthyjacksonfoundation.org. www.guthyjacksonfoundation.org/neuromyelitis-optica-nmo/. Accessed April 15, 2021.
4. Neuromyelitis Optica Spectrum Disorder / Rare Disease Database. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Accessed October 29, 2021.
5. Jiwon O and Levy M. Neuromyelitis Optica: An Antibody-Mediated Disorder of the Central Nervous System. *Neurology Research International*. 2012;2012:460825.
6. Contetti EC, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. *Journal of Neuroinflammation.* 2021;18:208.
7. Cree BA, Bennett JL et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-Momentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *The Lancet.* 2019;394:1352-63.
8. Hofer L, Ramberger M, Gredler V et al. Comparative Analysis of T-Cell Responses to Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein in Inflammatory Demyelinating Central Nervous System Diseases. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.01188
9. Layman's Guide to NMO. Sumairafoundation.org. https://www.sumairafoundation.org/laymans-guide-to-nmo/. Accessed April 25, 2021.
10. Etemadifar M, et al. Epidemiology of neuromyelitis optica in the world: a systematic review and meta-analysis. *Mult Scler Int.* 2015;2015:174720.
11. Mori M, et al. Worldwide prevalence of neuromyelitis optica spectrum disorders. *Journal of Neurology, Neurosurgery & Psychiatry.* 2018;89:555-556.
12. Data on file. Horizon, June 2021.
13. 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.
14. Chihara N, et al. Interleukin 6 signalling promotes anti-aquaporin-4 autoantibody production from plasmablasts in neuromyelitis optica. *PNAS*. 2011;108(9):3701-3706.
15. Duan T, Smith AJ, Verkamn AS. Complement-independent bystander injury in AQP4-IgG seropositive cytotoxicity. *Acta Neuropathologica Comm*. 2019;7(112).
16. Beekman J, et al. Neuromyelitis optica spectrum disorder: patient experience and quality of life. *Neural Neuroimmunol Neuroinflamm*. 2019;6(4):e580.
17. Kimbrough DJ, et al. Treatment of neuromyelitis optica: review recommendations. *Mult Scler Relat Disord*. 2012;1(4):180-187.
18. 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.
19. Wingerchuk DM. Neuromyelitis optica: effect of gender. *J Neurol Sci.* 2009;286(1-2):18-23.
20. Flanagan EP, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol.* 2016;79(5):775-783.
21. National Institutes of Health. N-MOmentum: A Clinical Research Study of Inebilizumab in Neuromyelitis Optica Spectrum Disorders. https://www.clinicaltrials.gov/ct2/show/NCT02200770. Accesses November 1, 2021.

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