Horizon Therapeutics plc Receives European Commission (EC) Approval of UPLIZNA® (inebilizumab) for the Treatment of Adults With Neuromyelitis Optica Spectrum Disorder (NMOSD)

May 2, 2022

-- NMOSD is a devastating autoimmune disease of severe and recurrent central nervous system attacks which can result in blindness, paralysis and death --

-- UPLIZNA is indicated as monotherapy for treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+), which represents 80% of NMOSD patients --

-- EC approval was supported by results from N-MOmemtum, the largest pivotal trial ever conducted in NMOSD, which showed 87.6% of AQP4-IgG+ NMOSD patients on UPLIZNA were attack free for 28 weeks, with the vast majority remaining attack free for at least four or more years --

-- UPLIZNA is the EU's first and only targeted CD19+ B-cell-depleting monotherapy proven to reduce attacks in adult AQP4-IgG+ NMOSD patients --

DUBLIN--(BUSINESS WIRE)--May 2, 2022-- Horizon Therapeutics plc (Nasdaq: HZNP) today announced the European Commission (EC) approval of UPLIZNA® (inebilizumab) as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+), following the positive opinion adopted by the Committee for Medicinal Products for Human Use of the European Medicines Agency on 11th November, 2021.

"NMOSD is a devastating disease with unpredictable attacks, cumulative and often irreversible damage and potential loss of vision and motor function, causing profound uncertainty for patients," said Vikram Karnani, executive vice president and president, international, Horizon. "Today's approval of UPLIZNA marks a significant milestone for patients in Europe and for Horizon, bringing a new, targeted treatment option to people living with NMOSD. As we continue our global expansion, we remain focused on bringing breakthrough medicines – and hope – to people living with challenging diseases. Across offices and manufacturing facilities on four continents, we deliver impact that goes beyond our medicines."

People impacted by NMOSD live with unpredictable attacks; 90% will experience repeat attacks within five years of an initial attack.[1] Even a single NMOSD attack can result in significant, irreversible damage, with each subsequent attack building upon the damage caused by the previous.[2] This damage is caused when CD19+-expressing B-cell lymphocytes (plasmablasts and some plasma cells) secrete AQP4-IgG, triggering an escalating autoimmune reaction. Depletion of CD19+ B-cells has proven effective at halting inflammation, lesion formation and astrocyte loss. As a targeted CD19 B-cell depleter, UPLIZNA offers a unique mode of action developed specifically to induce broad, deep and durable B-cell depletion and prevent attacks. Maintaining B-cell depletion and preventing attacks are key to limiting cumulative disability within NMOSD.[3,4,5]

In the N-MOmentum pivotal clinical trial (2014-000253-36), the largest NMOSD trial to date, UPLIZNA demonstrated a significant reduction in the risk of an NMOSD attack with only two infusions per year, following the initial loading doses. Additionally, 89% of patients in the AQP4-IgG+ group remained relapse-free during the six-month period post-treatment and more than 83% of patients on treatment remained attack free for at least four years.[3,4]

"We have made great strides in understanding the pathogenesis of NMOSD and in identifying new, effective therapies for its treatment, such as UPLIZNA, which can be transformative for patients in Europe who live with the devastating effects of this disease," said Professor Friedemann Paul, M.D., Charité-Universitätsmedizin Berlin, NeuroCure Clinical Research Center, NCRC Research Group, Clinical Neuroimmunology. "Just a single attack can cause life-altering impact, pain and debilitation, including potential vision loss. It is paramount we're able to diagnose and treat this disease early to prevent cumulative damage and permanent disability for patients."

Globally, the prevalence of NMOSD is approximately 0.5–4/100,000 people,[6,7] and women are nine times more likely to be impacted than men.[8] Consequences of this disease extend beyond the clinical impact, including physical, functional and psychological impact on patients' quality of life. [9,10] In Europe, it is estimated that at least 7,300 people live with NMOSD,[11] approximately 80% of whom are AQP4-IgG+.[12] Each year, approximately 370 new patients in Europe are diagnosed with the disease.[11]

The EC approval of UPLIZNA results in the granting of a centralised marketing authorisation, which is valid in all EU Member States, as well as in Iceland, Liechtenstein and Norway. Horizon will work with local health authorities to bring UPLIZNA to patients in a number of countries across Europe. Germany will be the first country where Horizon initiates commercialisation efforts.

UPLIZNA was approved by the U.S. Food and Drug Administration (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.

Mitsubishi Tanabe Pharma Corporation has the rights to develop and commercialise UPLIZNA in Japan, Thailand, South Korea, Indonesia, Vietnam, Malaysia, Philippines, Singapore and Taiwan. Hansoh Pharmaceutical Group Company Limited, another strategic partner to Horizon, has also recently received manufacturing and marketing approval from National Medical Products Administration of the People's Republic of China for UPLIZNA.

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.[13,14] Approximately 80% of all patients with NMOSD test positive for anti-AQP4 antibodies.[12] 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.[15] Clinically, this damage presents as an NMOSD attack, which can involve the optic nerve, spinal cord and brain.[15,16] Loss of vision, paralysis, loss of sensation, bladder and bowel dysfunction, and nerve pain can all be manifestations of the disease.[10] 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.[8,19]

Anti-AQP4 autoantibodies are produced by plasmablasts and some plasma cells. These B-cell populations are central to NMOSD disease pathogenesis, and a large proportion of these cells express CD19. Depletion of these CD19+ B-cells is thought to remove an important contributor to inflammation, lesion formation and astrocyte damage.

About the N-MOmentum Clinical Program

N-MOmentum was a multicentre, double-blind, randomised placebo-controlled Phase 2/3 clinical trial that was conducted in 25 countries. A total of 230 participants were enrolled: 213 were AQP4-IgG seropositive, and 17 were AQP4 IgG seronegative. Participants were randomly assigned at a ratio of 3 (on treatment) to 1 (on placebo). The study consisted of a 28-week randomised-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=75 AQP4+ patients).[3,4]

The trial Primary Endpoint was:

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

The trial key 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 standardised low-contrast Landolt C Broken Rings Chart held at a distance of three metres. The binocular score is the number of letters read correctly on an eye chart using both eyes simultaneously.
- **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 hospitalisations 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 hospitalisations (defined as a stay in hospital that goes beyond midnight of the first day of admission).

In the N-MOmentum trial, UPLIZNA had a favourable 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 is 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 annualised 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 trial was stopped early on the recommendation of the Independent Data Monitoring Committee.

About Horizon

Horizon is focused on the discovery, development and commercialisation 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, but not limited to, statements related to the timing of a potential commercial launch of UPLIZNA in the EU, the potential benefits of UPLIZNA to patients in EU and Horizon's global expansion plans. 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 of launching UPLIZNA in the EU, whether UPLIZNA is successfully commercialised in the EU, 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.

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