Biogen Plans to Initiate Phase 3b Study Evaluating Potential Benefit of a Higher Dose of Nusinersen in Patients Previously Treated with Evrysdi® (risdiplam)

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- Clinical data available to date suggest there are remaining unmet needs in some spinal muscular atrophy (SMA) patients treated with Evrysdi[1-3]
- The ASCEND study aims to evaluate whether treatment with a higher dose of nusinersen has the potential to improve clinical outcomes in these patients
- Building on the proven efficacy and well-established safety of the currently approved 12-milligram dose, patients in this study will receive an investigational higher dose of nusinersen, which is also being evaluated in the DEVOTE study

CAMBRIDGE, Mass., Sept. 15, 2021 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) today announced plans to initiate a global Phase 3b clinical study, ASCEND. The ASCEND study is designed to evaluate the clinical outcomes and assess the safety of a higher dose of nusinersen* in children, teens and adults with later-onset spinal muscular atrophy (SMA) following treatment with Evrysdi® (risdiplam).

People with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the ongoing maintenance of motor neurons that support sitting, standing and movement. Over time, people with SMA may lose their ability to perform everyday activities, including brushing their teeth, turning on a light switch or drinking from a cup.[4,5] The goal of treatment in SMA is to sufficiently protect motor neurons and help preserve function.

“We believe that lower drug exposure may be contributing to less-than-optimal treatment outcomes for some patients treated with Evrysdi. The ASCEND study seeks to understand if nusinersen may address that unmet medical need and will help inform the future of SMA treatment, with the hope of improving patients’ outcomes for the long term,” said Maha Radhakrishnan, M.D., Chief Medical Officer at Biogen.

Available data suggest that exposure to Evrysdi diminishes with increased age and weight, with an approximately 40 percent reduction in drug concentration in adults compared to infants.[6,7] Evrysdi’s dosing is capped at 5 milligrams (mg) once patients reach 20 kilograms (kg). [8]

At the approved 12-mg dose, motor neuron exposure to nusinersen remains similar as patients age and grow.[9] Further, nusinersen has demonstrated proven, sustained efficacy and a well-characterized safety profile, with long-term data in patients treated for more than 7 years across ages and SMA types. Taken together, these data support further exploration of whether a higher dose can deliver even greater efficacy to patients. The ASCEND study will assess if nusinersen at a higher dose may address outstanding clinical needs among later-onset SMA patients treated with Evrysdi who want to make a change in their treatment regimen. The same investigational higher dose of nusinersen is also being evaluated in the ongoing DEVOTE study.

“There have been significant advances in SMA treatment; however, there is still no cure and unmet medical needs remain,” said Professor Tim Hagenacker, Head of Neuromuscular Diseases Unit, Essen University in Germany, and a member of the ASCEND study steering committee. “As part of my clinical practice, we’ve observed an opportunity to potentially further improve patient outcomes. With a higher dose of nusinersen, we are positioned to explore what may be possible.”

The ASCEND protocol has been submitted to the U.S. Food and Drug Administration and is planned to be an approximately 2.5-year study projected to enroll up to 135 later-onset, non-ambulatory individuals with SMA (aged 5 to 39). All participants must have been previously treated with Evrysdi at the maximum recommended dose of 5 mg and be willing and able to change their treatment regimen to a higher dose of nusinersen. Participants must also fall within a particular Revised Upper Limb Module (RULM) measurement range to enter the study. Individuals enrolled in ASCEND will receive two loading doses of nusinersen 50 mg two weeks apart, followed by a maintenance dose of 28 mg every four months during the study period. Efficacy is planned to be assessed by RULM. Additional clinical outcomes include safety, Hammersmith Functional Motor Scale Expanded (HFMSE) and caregiver burden. The study will also evaluate upper limb fine motor function in participants aged 13 and older using the mobile application Konectom™, and neurofilament levels as a marker of biological disease activity, both exploratory endpoints.

The study aims to include children, teens and adults naïve to treatment with nusinersen, as well as adults who were previously treated with nusinersen prior to Evrysdi. The company aims for the first eligible patients to be enrolled in 2021.

In addition to ASCEND, as a leader in SMA Biogen supports over 15 SMA disease registries with more than 4,000 patients across the globe, which will help support treatment decisions within the context of currently approved therapies, including the 12-mg dose of nusinersen.

**Nusinersen is currently commercialized under the brand name SPINRAZA®, and the U.S. Food and Drug Administration-approved dose is 12 mg.*

About SPINRAZA® (nusinersen)
The SPINRAZA clinical development program encompasses 10 clinical studies, which have included more than 300 individuals across a broad spectrum of patient populations,[10] including two randomized controlled studies (ENDEAR and CHERISH). The ongoing SHINE and NURTURE open-label extension studies are evaluating the long-term impact of SPINRAZA. The most common adverse events observed in clinical studies were respiratory infection, fever, constipation, headache, vomiting and back pain. Laboratory tests can monitor for renal toxicity and coagulation abnormalities, including acute severe low platelet counts, which have been observed after administration of some ASOs.

Biogen licensed the global rights to develop, manufacture and commercialize SPINRAZA from Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), the leader in antisense therapeutics. Please click here for Important Safety Information and full Prescribing Information for SPINRAZA in the U.S., or visit your respective country’s product website.

About Spinal Muscular Atrophy (SMA)
SMA is a rare, genetic, neuromuscular disease that affects individuals of all ages. It is characterized by a loss of motor neurons in the spinal cord and

lower brain stem, resulting in progressive muscle atrophy and weakness.[11] SMA is caused by a deficiency in the production of survival motor neuron (SMN) protein due to a damaged or missing *SMN1* gene, with a spectrum of disease severity.[11] Some individuals with SMA may never sit; some sit but never walk; and some walk but may lose that ability over time.[12] In the absence of treatment, children with the most severe form of SMA would not be expected to reach their second birthday.[11]

SMA impacts approximately 1 in 11,000 live births,[13] is a leading cause of genetic death among infants[13] and causes a range of disability in teenagers and adults.[12]

About Biogen
At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today Biogen has the leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, commercializes biosimilars of advanced biologics and is focused on advancing research programs in multiple sclerosis and neuroimmunology, Alzheimer's disease and dementia, neuromuscular disorders, movement disorders, ophthalmology, neuropsychiatry, immunology, acute neurology and neuropathic pain.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media – Twitter, LinkedIn, Facebook, YouTube.

Biogen Safe Harbor
This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, about the potential benefits, safety and efficacy of nusinersen; the results of certain real-world data; the identification and treatment of SMA; our research and development program for the identification and treatment of SMA; the clinical development program for nusinersen, including the study protocol and enrollment of the ASCEND study and the timing thereof; and risks and uncertainties associated with drug development and commercialization. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "possible," "potential," "will," "would" and other words and terms of similar meaning. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation risks relating to the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis, including from the planned ASCEND study; the risk that we may not fully enroll our clinical trials, including the planned ASCEND study, or enrollment will take longer than expected; failure to obtain regulatory approvals in other jurisdictions; risks of unexpected costs or delays; failure to protect and enforce our data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; regulatory authorities may require additional information or further studies; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from our expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this news release. We do not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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