Biogen's Regulatory Applications for Nusinersen as a Treatment for Spinal Muscular Atrophy Accepted by FDA and EMA

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Nusinersen Granted Priority Review by FDA

EMA Plans to Follow Accelerated Assessment Timeline

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Biogen (NASDAQ: BIIB) today announced that its New Drug Application (NDA) for nusinersen, an investigational treatment for spinal muscular atrophy (SMA), has been accepted by the U.S. Food and Drug Administration (FDA) for Priority Review, and that the company's Marketing Authorization Application (MAA) has been validated by the European Medicines Agency (EMA). Nusinersen had previously been granted Accelerated Assessment status by the EMA's Committee for Medicinal Products for Human Use (CHMP). The regulatory review process for these applications has now been initiated in the U.S. and EU. Both the Priority Review and Accelerated Assessment designations can reduce the standard review time. If approved, nusinersen would be the first therapy for SMA, a leading genetic cause of infant mortality.

Biogen intends to market nusinersen under the brand name SPINRAZA™. This name has been conditionally accepted by the FDA and the CHMP and will be confirmed upon approval.

"The FDA and EMA have acknowledged the potential for nusinersen to address the urgent need for an effective SMA treatment by granting special status to the applications, and FDA has shared that they plan to act early on our NDA under an expedited review," said Michael Ehlers, M.D., Ph.D., executive vice president, head of Research and Development at Biogen. "We are now focused on working with the agencies to hopefully bring this investigational treatment to the SMA community as quickly as possible."

The regulatory filing packages in the U.S. and EU are based on data that demonstrate the clinically meaningful efficacy and favorable safety profile of nusinersen from multiple studies. These include the results from the interim analysis of ENDEAR, the Phase 3 study evaluating nusinersen in infantile-onset (most likely to develop Type 1) SMA, as well as open-label data in other patient populations. The ENDEAR interim analysis demonstrated that infants receiving nusinersen experienced a statistically significant improvement in the achievement of motor milestones compared to those who did not receive nusinersen. Data from the other endpoints analyzed were also consistently in favor of the treated infants. Nusinersen was generally well-tolerated, with a favorable safety profile. No adverse events (AEs) were considered related to nusinersen.

Biogen is initiating regulatory filings in other countries in the coming months.

The Nusinersen Clinical Trial Program
The nusinersen Phase 3 program is comprised of two registrational studies, ENDEAR and CHERISH. ENDEAR is a thirteen-month study investigating nusinersen in 122 patients with infantile-onset SMA, including patients with the onset of signs and symptoms of SMA at up to six months of age. The endpoint pre-specified for the interim analysis of the study evaluated the proportion of motor milestone responders from the motor component of the Hammersmith Infant Neurological Examination (HINE). Given the results of the interim analysis, the ENDEAR study is being stopped and participants are able to transition into the SHINE open-label study, in which all patients will receive nusinersen.

CHERISH is a fifteen-month study investigating nusinersen in 126 non-ambulatory patients with later-onset SMA, including patients with the onset of signs and symptoms at greater than 6 months and an age of 2 to 12 years at screening. CHERISH was fully enrolled in March 2016.

Additionally, the SHINE open-label extension study for patients who previously participated in ENDEAR or CHERISH is open and is intended to evaluate the long-term safety and tolerability of nusinersen.

Two additional Phase 2 studies, EMBRACE and NURTURE, were designed to collect additional data on nusinersen. EMBRACE is studying a small subset of patients with infantile or later-onset SMA who do not meet the age and other criteria of ENDEAR or CHERISH. NURTURE is an open-label, ongoing study in pre-symptomatic infants who are up to six weeks of age at time of first dose to determine if treatment before symptoms begin would prevent or delay the onset of SMA symptoms. An interim analysis of NURTURE showed that infants treated for up to one year with nusinersen achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with Type 1 SMA. Three infants experienced adverse events considered possibly related to nusinersen, all of which resolved. In addition, no infants have discontinued or withdrawn from the study and no new safety concerns have been identified. NURTURE is currently active and enrolling. All studies are being conducted on a global scale.

About SMA [1-5]
SMA is genetic disease characterized by the loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing.

Due to a loss of, or defect in the *SMN1* gene, people with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein. People with Type 1 SMA, the most, severe life-threatening form, produce very little SMN protein and do not achieve the ability to sit without support or live beyond 2 years without respiratory support. People with Type 2 and Type 3 produce greater amounts of SMN protein and have less severe, but still life-altering forms of SMA. Currently, there is no approved treatment for SMA.

To support awareness and education in SMA, Biogen has launched *Together in SMA* in the United States. *Together in SMA* is a program created to provide informational materials and resources to the SMA community. Learn more at www.TogetherinSMA.com.

About Nusinersen
Nusinersen is an investigational, potentially disease-modifying therapy for the treatment of SMA that was discovered and developed by Ionis

Pharmaceuticals (NASDAQ: IONS), a leader in antisense therapeutics. Nusinersen is an antisense oligonucleotide (ASO) that is designed to alter the splicing of *SMN2*, a gene that is nearly identical to *SMN1*, in order to increase production of fully functional SMN protein.[7]

ASOs are short synthetic strings of nucleotides designed to selectively bind to target RNA and regulate gene expression. Through use of this technology, nusinersen has the potential to increase the amount of functional SMN protein in infants and children with SMA.

Both the U.S. and EU have granted nusinersen Orphan Drug status. Additionally, both the U.S. and EU regulatory agencies have granted special status to nusinersen, including Fast Track Designation and Priority Review in the U.S. and Accelerated Assessment in the EU.

Biogen exercised its option to worldwide rights to nusinersen in August 2016.

Biogen and Ionis Pharmaceuticals acknowledge support from the following organizations for nusinersen: Cure SMA, Muscular Dystrophy Association, and SMA Foundation, intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

About Biogen
Through cutting-edge science and medicine, Biogen discovers, develops and delivers worldwide innovative therapies for people living with serious neurological, autoimmune and rare diseases. Founded in 1978, Biogen is one of the world's oldest independent biotechnology companies and patients worldwide benefit from its leading multiple sclerosis and innovative hemophilia therapies. For more information, please visit www.biogen.com. Follow us on Twitter.

Biogen Safe Harbor
This press release contains forward-looking statements, including statements relating to the safety and efficacy of nusinersen, as well as clinical trial results and plans, potential regulatory filings and expected timelines and the submission of applications to regulatory authorities and the timing thereof. These statements may be identified by words such as "believe," "except," "may," "plan," "potential," "will" and similar expressions, and are based on our current beliefs and expectations. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Factors which could cause actual results to differ materially from our current expectations include the actual timing and content of submissions to and decisions made by the regulatory authorities regarding marketing authorization applications for nusinersen and the actual timing and final results of the nusinersen clinical trials. For more detailed information on the risks and uncertainties associated with our drug development and commercialization activities, please review the Risk Factors section of our most recent annual report or quarterly report filed with the Securities and Exchange Commission. Any forward-looking statements speak only as of the date of this press release and we assume no obligation to update any forward-looking statement.

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