Biogen Completes Rolling Submission of New Drug Application to FDA for Nusinersen as a Treatment for Spinal Muscular Atrophy

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Submission of Marketing Authorization Application to the European Medicines Agency Planned in the Coming Weeks

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--Biogen (NASDAQ: BIIB) and Ionis (NASDAQ:IONS) today announced that Biogen has completed the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the approval of nusinersen, an investigational treatment for spinal muscular atrophy (SMA). Biogen has also applied for Priority Review which, if granted, would shorten the review period of nusinersen following the Agency's acceptance of the NDA.

"Since announcing the positive results of the ENDEAR interim analysis in infantile-onset SMA last month, we have heard from many families expressing their excitement about nusinersen. Their stories continue to inspire us and they are in the forefront of our minds as we work to support the FDA's review of nusinersen," noted Alfred Sandrock, M.D., Ph.D., executive vice president and chief medical officer at Biogen. "We appreciate the FDA's collaboration with us during the application process, and we look forward to continuing this productive dialogue, with the goal of rapidly bringing the first treatment for SMA to as many patients as possible."

In addition to the NDA filing with FDA, Biogen plans to submit a Marketing Authorization Application (MAA) for nusinersen to the European Medicines Agency (EMA) in the coming weeks. The EMA's Committee for Medicinal Products for Human Use (CHMP) recently granted Accelerated Assessment to nusinersen, which can reduce the standard review time. Biogen will initiate regulatory filings in other countries in the coming months.

"Our ability to advance the nusinersen program as quickly as we have is largely due to the tremendous contributions of the entire SMA community, from the patients and families who participated in the clinical trials to the doctors, nurses and advocates who work tirelessly on their behalf," said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals. "We are deeply appreciative of their unwavering commitment to finding a treatment for SMA and today's milestone is truly a collective achievement."

The regulatory submissions are comprised of results from the pre-specified interim analysis of ENDEAR, the controlled Phase 3 study evaluating nusinersen in infantile-onset (most likely to develop Type 1) SMA, as well as all other clinical and preclinical data currently available, which includes open-label data in other patients types. 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 treatment. Biogen anticipates hearing from regulatory authorities regarding the acceptance and validation of these submissions within the next couple of months.

The Nusinersen Clinical Trial Program

The nusinersen clinical trial program is comprised of two controlled studies, ENDEAR and CHERISH. ENDEAR was designed as a thirteen-month study investigating nusinersen in 122 patients with infantile-onset SMA; the onset of signs and symptoms of SMA less than or equal to 6 months of age and age less than or equal to 7 months at screening. Based on the results of the pre-specified interim analysis, the ENDEAR study will be stopped; patients who elect to are currently being transitioned to the SHINE open-label study where they will all receive nusinersen. Results from the ENDEAR interim analysis will be presented at future medical congresses.

CHERISH is a fifteen-month study investigating nusinersen in 126 non-ambulatory patients with later-onset SMA, consistent with Type 2; onset of signs and symptoms greater than 6 months and age 2 to 12 years at screening. CHERISH was fully enrolled in May 2016 and remains ongoing.

Additionally, the SHINE open-label extension study, for patients who previously participated in ENDEAR and 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. The EMBRACE study is designed to collect additional data on a small subset of patients with infantile or later-onset SMA who do not meet the age and other criteria of ENDEAR or CHERISH. Due to the evidence demonstrated in the infantile-onset SMA (most likely to develop Type 1) population, the sham arm of the EMBRACE study is being stopped and patients are being given the option to receive nusinersen through an open-label extension study. NURTURE is an open-label, ongoing study in pre-symptomatic infants who are less than or equal to 6 weeks of age at time of first dose to determine if treatment before symptoms begin would prevent or delay onset of SMA symptoms.

About SMA [1-5]

Spinal Muscular Atrophy (SMA) is characterized by 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 SMA 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 is launching *Together in SMA* in the United States, a program created to provide informational materials and resources to the SMA community. Learn more at TogetherinSMA.com.

About Nusinersen

Nusinersen is an investigational, potentially disease-modifying therapy[6] for the treatment of SMA. Nusinersen is an antisense oligonucleotide (ASO) that is designed to alter the splicing of pre-mRNA from the *SMN2* gene in order to increase production of fully functional SMN protein. *SMN2* is a gene that is nearly identical to *SMN1*.[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 regulatory agencies have granted special status to nusinersen in an effort to expedite the review process, including Fast Track Designation in the U.S. Additionally, nusinersen has received an Orphan Drug designation in both U.S. and EU.

We acknowledge support from the following organizations for nusinersen: Muscular Dystrophy Association, SMA Foundation, Cure SMA and 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.

About Ionis Pharmaceuticals Inc.

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Ionis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and nusinersen, a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

Biogen Safe Harbor

This press release contains forward-looking statements, including statements relating to the submission of marketing authorization applications for nusinersen to regulatory authorities and the timing thereof and the anticipated regulatory filing review process. 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 risk that unexpected concerns may arise from additional data or analysis, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates or grant marketing approval that is more restricted than anticipated, or we may encounter other unexpected hurdles. 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.

Ionis Forward-Looking Statement

This press release includes forward-looking statements regarding Ionis' strategic relationship with Biogen and the development, activity, therapeutic potential, safety and commercialization of nusinersen. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2015, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

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