Biogen and Ionis Pharmaceuticals Report Nusinersen Meets Primary Endpoint at Interim Analysis of Phase 3 ENDEAR Study in Infantile-Onset Spinal Muscular Atrophy

August 1, 2016

— Biogen Intends to File Marketing Applications for Nusinersen with Regulatory Authorities in the Coming Months —

— Biogen Exercises Option to Develop and Commercialize Nusinersen Globally —

— Companies to Host Webcast Today at 9:00 a.m. EDT to Provide Program Update —

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--Biogen (NASDAQ:BIIB) and Ionis Pharmaceuticals (NASDAQ:IONS) today announced that nusinersen, their investigational treatment for spinal muscular atrophy (SMA), met the primary endpoint pre-specified for the interim analysis of ENDEAR, the Phase 3 trial evaluating nusinersen in infantile-onset (consistent with Type 1) SMA. The analysis found that infants receiving nusinersen experienced a statistically significant improvement in the achievement of motor milestones compared to those who did not receive treatment. Nusinersen demonstrated an acceptable safety profile in the trial. As a result of these findings, Biogen has exercised its option to develop and commercialize nusinersen globally and paid Ionis a $75 million license fee. Biogen will initiate regulatory filings globally in the coming months.

"We are grateful to the families participating in the clinical trials, who continue to inspire us. We want to thank them, along with the investigators who have worked tirelessly on this program and the broader SMA community, for their partnership. Without their contributions, we would not be here today," said Alfred Sandrock, M.D., Ph.D., executive vice president and chief medical officer at Biogen. "We share the community's sense of urgency as we strive to bring the first treatment for SMA, the leading genetic cause of infant mortality, to families facing this devastating disease. We remain committed to understanding the potential of nusinersen in the broader SMA population and will continue to focus on the rapid completion of our ongoing studies."

Based on the results of the pre-specified interim analysis, the ENDEAR study will be stopped and participants will be able to transition into the SHINE open-label study in which all patients receive nusinersen. Data from the other endpoints of ENDEAR will be analyzed when the full data set is available. Results will be presented at future medical congresses. Additionally, participants enrolled in the sham-controlled arm of EMBRACE, a Phase 2 study which also included infantile-onset patients, will have the opportunity to receive nusinersen.

The other studies in the nusinersen program, including CHERISH (later-onset consistent with Type 2) and NURTURE (pre-symptomatic infants), will continue as planned in order to collect the data to demonstrate the safety and efficacy of nusinersen in these populations.

"We are hopeful that nusinersen, if approved, will make a meaningful difference in the lives of patients and families affected by SMA. We look forward to working with Biogen on completing the clinical program and preparing for what we hope is a positive regulatory review," said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals. "Nusinersen is the first antisense drug from our neurological disease franchise to advance to regulatory review, and it illustrates the potential of our antisense technology to address severe diseases that other therapeutic modalities are unable to address adequately."

Biogen is working to open a global expanded access program (EAP) for eligible patients with infantile-onset SMA (consistent with Type 1) in the coming months. The EAP can be initiated at existing nusinersen clinical trial sites in countries where EAPs are permitted according to local laws and regulations, can be operationalized, and where there is a path that can support long-term availability of nusinersen. Once the EAP is operational and required local approvals are in place, individual participating sites may start enrollment after they have transitioned ENDEAR study participants to the open-label extension study.

"Today is a hopeful day for the SMA community, which has worked tirelessly to support research and development for this terrible disease. Many of our families have participated in this and other clinical trials in order to advance our understanding of SMA. We are excited about reaching this important milestone, and the opportunity these results create to potentially bring the first treatment option for SMA to patients and families. We will continue to relentlessly support research into SMA until we have therapies for all and, ultimately, a cure," commented Kenneth Hobby, President, Cure SMA.

Biogen is now responsible for all nusinersen development, regulatory and commercialization activities and costs. Ionis will complete the Phase 3 studies and work with Biogen on regulatory filings. The two companies will also work together to transition the clinical programs that Ionis is conducting to Biogen. Ionis is eligible to receive tiered royalties on any potential sales of nusineren up to a percentage in the mid-teens, in addition to up to $150 million in milestone payments based on regulatory approvals.

Webcast

The companies will host a live webcast to discuss the results of the Phase 3 ENDEAR interim results for nusinersen today, August 1, 2016, from 9:00 to 9:30 a.m. EDT. Participants may access the webcast through the Investors section of www.biogen.com or www.ionispharma.com. Following the live webcast, an archived version of the call will be available at the same URLs for one month.

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; the onset of signs and symptoms of SMA less than or equal to 6 months and age less than or equal to 7 months at screening. Based on insights gained from earlier-stage studies and discussions with regulators, a primary endpoint was added to ENDEAR earlier this year that evaluates the proportion of motor milestone responders from the motor component of the Hammersmith Infant Neurological Examination (HINE).

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

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. NURTURE is an 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 the onset of SMA symptoms. All studies are being conducted on a global scale.

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 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.

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 *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 regulatory agencies have granted special status to nusinersen in an effort to expedite the review process, including Orphan Drug Status and Fast Track Designation in the U.S. and Orphan Drug Designation in the 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 safety and efficacy of nusinersen, as well as clinical trial results and plans, potential regulatory filings and expected timelines, including expanded access for nusinersen, including the transition of the ENDEAR and EMBRACE clinical trial study participants to an open label study and the timing thereof, the submission of applications to regulatory authorities and the timing thereof, and the opening of an EAP and the timing thereof. These statements may be identified by words such as "believe," "expect," "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, the actual timing and final results of the nusinersen clinical trials and the uncertainties involved in operationalizing an EAP. 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 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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