New Data Presented at World Muscle Society Congress Support Potential Benefit of Investigational Treatment Nusinersen in Spinal Muscular Atrophy

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- Initial Phase 3 Safety Data Presented in Infantile-onset Spinal Muscular Atrophy Demonstrated Favorable Safety Profile with no Treatment Related Adverse Events -

- Analysis of Ongoing Phase 2 Open-label Study Demonstrated Beneficial Effect in Infants Prior to Onset of Symptoms –

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--New data from the clinical program for nusinersen, an investigational treatment for spinal muscular atrophy (SMA), were presented by Biogen (NASDAQ: BIIB) and Ionis Pharmaceuticals (NASDAQ: IONS) in the late-breaking session at the 2016 World Muscle Society Congress in Granada, Spain. The presentations included safety results from the interim analysis of the Phase 3 ENDEAR study in infantile-onset SMA (most likely to develop Type 1), encouraging preliminary results from NURTURE, a Phase 2 open-label study in pre-symptomatic infants, and a recent analysis of the ongoing Phase 2 open-label study in patients with later-onset SMA (consistent with Types 2 or 3).

"We continue to be encouraged by the consistently positive results with nusinersen across our clinical program, including our first data in infants treated before they show signs of the disease," said Wildon Farwell, senior director SMA clinical development at Biogen. "NURTURE is the first study to evaluate an investigational therapy in pre-symptomatic infants genetically at risk for SMA. In this analysis, infants treated for up to one year achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with Type 1 SMA."

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. Submission of the Marketing Authorization Application to the European Medicines Agency is planned in the next week. Biogen will initiate regulatory filings in other countries in the coming months.

Interim Data from Phase 3 ENDEAR Trial
In the interim analysis of the controlled, Phase 3 ENDEAR study in infantile-onset SMA, infants treated with nusinersen demonstrated a statistically and clinically significant improvement in the primary endpoint ($p<0.0001$), defined as the proportion of motor milestone responders as measured by the Hammersmith Infant Neurological Examination (HINE). A responder was defined as a patient who improved in more motor milestone categories (kicking, head control, rolling, sitting, crawling, standing, walking) than worsened.

Nusinersen was generally well-tolerated, with an acceptable safety profile. No adverse events (AEs) were considered related to treatment. Based on the results of the positive interim analysis, patients who elect to do so will be transitioned to SHINE, an open-label extension study, in which they will be able to receive nusinersen. Following the transition of patients, the ENDEAR study will close. Detailed efficacy data will be presented at a future medical conference once participants complete their final study visit in ENDEAR.

First Clinical Data in Pre-Symptomatic SMA Patients
The interim analysis of the ongoing, open-label, 30-month, Phase 2 NURTURE study showed that nusinersen-treated infants exhibited improvements in motor function and motor milestones such as full head control, independent sitting, standing with support, standing unaided, and walking with support, as measured by validated scales. The primary endpoint was defined as time to respiratory intervention (invasive or non-invasive ventilation for 6 hours or more per day continuously for 7 or more days or tracheostomy) or death. At the time of the interim analysis all patients were alive and did not require respiratory intervention. This analysis included data from 13 genetically diagnosed, pre-symptomatic SMA patients who had been enrolled for a minimum of 64 days and up to 13 months. Three infants experienced AEs considered possibly related to nusinersen, all of which were resolved. In addition, no infants have discontinued or withdrawn from the study and no new safety concerns have been identified. The NURTURE study is currently active and enrolling.

"These findings reinforce the potential of nusinersen, and we remain focused on bringing this investigational treatment to patients and families as quickly as possible," noted C. Frank Bennett, Ph.D., senior vice president of research and leader of the neurological disease franchise at Ionis Pharmaceuticals. "We are grateful for the commitment and contributions of the investigators, patients and families that have made the rapid development of nusinersen possible across a range of patients."

Supportive data from ongoing open-label Phase 2 trials
In addition, exploratory efficacy and safety data from the open-label Phase 2 trials (CS2/CS12) in twenty-eight patients with later-onset SMA (consistent with Types 2 or 3), showed that children with SMA treated with nusinersen exhibited improvement on several measures of motor function for up to nearly three years. These results contrast to the stable or slow decline in scores typically observed in patients with later-onset SMA over time. Overall, most AEs were mild to moderate and not considered related to nusinersen and there were no serious adverse events (SAEs) related to the study drug.

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 less than or equal to 6 months of age and who are screened at an age of less than or equal to 7 months. 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). Given 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.

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 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 collecting 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.

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 www.TogetherinSMA.com.

About Nusinersen

Nusinersen is an investigational, potentially disease-modifying therapy 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-TTRRx, 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 potential safety and efficacy of nusinersen, clinical trial results, and potential regulatory submissions 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 risk that unexpected concerns may arise from additional data or analysis from our nusinersen clinical trials, regulatory submissions may take longer or be more difficult to complete than expected, 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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