Biogen and Ionis Pharmaceuticals Announce SPINRAZA (nusinersen) Meets Primary Endpoint at Interim Analysis of Phase 3 CHERISH Study in Later-Onset Spinal Muscular Atrophy

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- Second Positive Phase 3 Study Provides Further Evidence of SPINRAZA's Efficacy and Favorable Safety Profile -

- Results Were Statistically Significant and Clinically Meaningful -

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--Nov. 7, 2016-- Biogen (NASDAQ:BIIB) and Ionis Pharmaceuticals (NASDAQ:IONS) announced that SPINRAZA™ (nusinersen), an investigational treatment for spinal muscular atrophy (SMA), met the primary endpoint at the interim analysis of CHERISH, the Phase 3 study evaluating SPINRAZA in later-onset (consistent with Type 2) SMA. The analysis found that children receiving SPINRAZA experienced a highly statistically significant improvement in motor function compared to those who did not receive treatment. SPINRAZA demonstrated a favorable safety profile in the study.

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"These results, along with our successful trial in infantile-onset SMA, reinforce the potential of SPINRAZA to benefit a broad range of SMA patients," said Michael Ehlers, M.D., Ph.D., executive vice president, head of Research and Development at Biogen. "We will make regulators around the globe aware of this data and will continue working closely with them to bring SPINRAZA to families affected by SMA as quickly as possible."

Biogen is preparing for the potential launch of SPINRAZA in the U.S. possibly as early as the end of 2016 or the first quarter of 2017.

Results From the CHERISH Interim Analysis

CHERISH is a fifteen-month study investigating SPINRAZA in 126 non-ambulatory patients with later-onset SMA (consistent with Type 2), including patients with the onset of signs and symptoms at greater than 6 months and an age of 2 to 12 years at screening.

Results from the primary endpoint of the pre-specified interim analysis demonstrated a difference of 5.9 points (p= 0.0000002) at 15 months between the treatment (n=84) and sham-controlled (n=42) study arms, as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). From baseline to 15 months of treatment, patients who received SPINRAZA achieved a mean improvement of 4.0 points in the HFMSE, while patients who were not on treatment declined by a mean of 1.9 points. The HFMSE is a reliable and validated tool specifically designed to assess motor function in children with SMA, and a change of three points or greater in the HFMSE has previously been identified as clinically meaningful. Data from the other endpoints analyzed were consistently in favor of children who received treatment. SPINRAZA demonstrated a favorable safety profile. The majority of the adverse events were considered to be either related to SMA disease, common events in the general population, or events related to the lumbar puncture procedure. No patients discontinued the study.

With the positive interim analysis, the CHERISH study will be stopped and participants will be able to transition into the SHINE open-label extension study to receive SPINRAZA. Full study results will be presented at future medical congresses.

"These data further validate the potential of SPINRAZA as a treatment for patients with SMA," said B. Lynne Parshall, chief operating officer of Ionis Pharmaceuticals. "We are grateful to all the families and clinicians who have participated in all of the SPINRAZA studies. Without their commitment and support, this program would not have been able to progress so quickly."

The U.S. Food and Drug Administration (FDA) recently accepted the company's New Drug Application (NDA) for SPINRAZA as a treatment for SMA and communicated they plan to act early on the NDA under an expedited review. Additionally, the European Medicines Agency (EMA) recently validated Biogen's Marketing Authorization Application (MAA) in the EU. The EMA's Committee for Medicinal Products for Human Use (CHMP) granted Accelerated Assessment status and the FDA granted Priority Review to SPINRAZA. Biogen is initiating regulatory filings in other countries in the coming months.

Biogen initiated a global expanded access program (EAP) in infantile-onset SMA earlier this year. The company will continue to explore where and when the EAP may be broadened to include patients with later-onset SMA (consistent with Type 2).

The SPINRAZA Clinical Trial Program

SPINRAZA has been studied in both presymptomatic and symptomatic patients with SMA including patients likely to develop or diagnosed with SMA Types 1, 2, and 3.

The SPINRAZA Phase 3 program is comprised of two registrational studies, ENDEAR and CHERISH. ENDEAR is a thirteen-month study investigating SPINRAZA 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 positive 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 SPINRAZA.

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 SPINRAZA.

Two additional Phase 2 studies, EMBRACE and NURTURE, were designed to collect additional data on SPINRAZA. 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 SPINRAZA 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 SPINRAZA, 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 SMA1-5

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 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 SPINRAZA (nusinersen)

SPINRAZA is an investigational, potentially disease-modifying therapy for the treatment of SMA that was discovered and developed by Ionis Pharmaceuticals, a leader in antisense therapeutics. SPINRAZA 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, SPINRAZA 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 SPINRAZA Orphan Drug status. Additionally, both the U.S. and EU regulatory agencies have granted special status to SPINRAZA, 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 SPINRAZA in August 2016.

Biogen and Ionis Pharmaceuticals acknowledge support from the following organizations for SPINRAZA: 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.

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 SPINRAZA (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 SPINRAZA, clinical trial results, potential regulatory approval and the timing thereof, and planning for launch readiness. 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 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 SPINRAZA or grant marketing approval that is different than anticipated; and risks relating to the potential launch of SPINRAZA, including preparedness of healthcare providers to treat patients, the ability to obtain and maintain adequate reimbursement for SPINRAZA and other unexpected difficulties or 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 SPINRAZA. 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.

1. Darras B, Markowitz J, Monani U, De Vivo D. Chapter 8 - Spinal Muscular Atrophies. In: Vivo BTD, ed. *Neuromuscular Disorders of Infancy, Childhood, and Adolescence (Second Edition).* San Diego: Academic Press; 2015:117-145.
2. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995;80(1):155-165.
3. Mailman MD, Heinz JW, Papp AC, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. *Genet Med.* 2002;4(1):20-26.
4. Monani UR, Lorson CL, Parsons DW, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. *Hum Mol Genet.* 1999;8(7):1177-1183.
5. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. *Brain.* 2014;137(Pt 11):2879-2896.
6. Rigo F, Hua Y, Krainer AR, Bennett CF. Antisense-based therapy for the treatment of spinal muscular atrophy. *J Cell Biol.* 2012;199(1):21-25
7. Hua Y, Sahashi K, Hung G, Rigo F, Passini MA, Bennett CF, Krainer AR. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. Genes Dev. 2010 Aug 1; 24(15):16344-44

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