The New England Journal of Medicine Publishes SPINRAZA® (nusinersen) Phase 3 Study Results in Individuals with Later-Onset Spinal Muscular Atrophy

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- SPINRAZA demonstrated stabilization or improvement in motor function in individuals with spinal muscular atrophy (SMA) where the natural history of the disease is a decline in motor function over time
- The majority of individuals treated with SPINRAZA demonstrated benefits in upper limb and general motor function, including crawling and standing with support
- The overall findings continue to support the robust efficacy and favorable safety profile of SPINRAZA, the only approved treatment for SMA, across a broad patient population

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--Feb. 14, 2018-- Biogen (Nasdaq: BIIB) and Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced end of study results from CHERISH, the Phase 3 study evaluating SPINRAZA® (nusinersen) for the treatment of individuals with later-onset spinal muscular atrophy (SMA), were published today in The *New England Journal of Medicine*. The full manuscript titled, "Nusinersen Versus Sham Control in Later-Onset Spinal Muscular Atrophy," appears in the February 15 issue of The *New England Journal of Medicine*.

This press release features multimedia. View the full release here: http://www.businesswire.com/news/home/20180214006094/en/

"The publication of CHERISH study results in The *New England Journal of Medicine* emphasizes SPINRAZA's meaningful motor function and upper limb improvements in individuals with later-onset SMA rarely seen in the natural course of the disease, which is typically a continued decline in motor function over time," said Eugenio Mercuri, M.D., lead study investigator, U.O.C. Neuropsichiatria Infantile – Policlinico Universitario "A. Gemelli," Rome, Italy. "During the study, some individuals treated with SPINRAZA achieved motor milestones including crawling or standing with assistance, or saw a stabilization or slowing of disease progression. We also saw an improvement in upper limb function, including raising objects."

The pre-specified CHERISH primary endpoint was improvement in motor function, as defined by change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE). The HFMSE is a validated tool specifically designed to assess motor function in individuals with SMA. The final analysis demonstrated a highly statistically significant and clinically meaningful improvement in motor function in individuals treated with SPINRAZA versus the sham control, as observed by the treatment difference of 4.9 points in the mean change from baseline to Month 15 in the HFMSE score (p=0.0000001). When measuring changes from baseline, individuals who received SPINRAZA (n=84) achieved a 3.9 point mean improvement at Month 15, while individuals who were not on treatment (n=42) experienced a mean decline of 1.0 point. Primary endpoint results of the end of study analysis were consistent with the interim analysis.

"As the first and only approved treatment for SMA, the data published in The *New England Journal of Medicine* continue to underscore the benefit of SPINRAZA for individuals with later-onset SMA," said Alfred Sandrock, M.D., Ph.D., executive vice president and chief medical officer at Biogen. "The CHERISH data are part of the largest clinical development program to date for the treatment of SMA. The program in its entirety shows that SPINRAZA has the potential to positively impact the motor function of children with SMA regardless of their age or stage of the disease."

Data from the other endpoints analyzed, including attainment of new motor milestones and upper limb motor function, were consistently in favor of individuals who received treatment and were considered clinically significant. Upper limb function, as measured by the Revised Upper Limb Module (RULM), improved in individuals treated with SPINRAZA (4.2 points) from baseline to Month 15 compared to untreated individuals (0.5 points). The RULM is an important measure of motor function in non-ambulatory individuals.

SPINRAZA demonstrated a favorable benefit-risk profile. Safety data were consistent with those expected in the general SMA later-onset population and in individuals undergoing lumbar puncture and were similar to those reported in an open-label study in later-onset SMA.

"The CHERISH data published today together with the results from the Phase 3 ENDEAR study in individuals with infantile-onset SMA, which were published last November in The *New England Journal of Medicine*, emphasizes the therapeutic potential of SPINRAZA in individuals with SMA," said C. Frank Bennett, Ph.D., senior vice president of research and leader of the neurological disease franchise at Ionis. "We believe the fact that both SPINRAZA pivotal studies have been published in a prestigious journal is a testament to the robustness of our SMA clinical development program."

Following the positive interim analysis, Biogen ended the CHERISH study early so all participants could have the option to receive SPINRAZA in the SHINE open-label extension study. In addition to SHINE, Biogen continues to collect and evaluate data to provide a deeper understanding of the efficacy and safety of SPINRAZA across SMA populations. The SPINRAZA clinical development program includes more than five years of data and is the largest body of evidence for an interventional approach in SMA.

End of study results from ENDEAR, the Phase 3 SPINRAZAstudy for the treatment of infantile-onset SMA, were published in the November 2, 2017 issue of The *New England Journal of Medicine*.

For more information about SPINRAZA and prescribing information in the United States, please visit www.SPINRAZA.com. Prescribing information in the European Union is available at http://www.ema.europa.eu/ema/.

About CHERISH

CHERISH is a Phase 3, multicenter, randomized, double-blind, sham-procedure controlled study to assess the efficacy and safety of SPINRAZA in individuals with later-onset SMA. The 15-month study investigated SPINRAZA in 126 non-ambulatory individuals 2 to 12 years old who experienced symptom onset at greater than 6 months of age. The CHERISH primary efficacy endpoint measured improvement in motor function, as defined by change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE).

SPINRAZA Program Status

SPINRAZA is the first and only approved medicine for the treatment of SMA and is currently approved in the United States, the European Union, Brazil, Japan, Switzerland, Australia, South Korea, and Canada. Biogen has submitted regulatory filings in additional countries and plans to initiate additional filings in other countries.

Globally, starting in 2016, in response to the urgent need for treatment for the most severely affected individuals living with SMA, Biogen sponsored one of the largest, pre-approval Expanded Access Programs (EAP) in rare disease, free of charge.

Biogen licensed the global rights to develop, manufacture and commercialize SPINRAZA from Ionis, a leader in antisense therapeutics. Biogen and Ionis conducted an innovative clinical development program that moved SPINRAZA from its first dose in humans in 2011 to its first regulatory approval in five years.

About SMA[1-5]

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 form that requires the most intensive and supportive care, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two 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.

About SPINRAZA® (nusinersen)

SPINRAZA is being developed globally for the treatment of SMA.

SPINRAZA is an antisense oligonucleotide (ASO), using Ionis' proprietary antisense technology, that is designed to treat SMA caused by mutations or deletions in the SMN1 gene located in chromosome 5q that leads to SMN protein deficiency. SPINRAZA alters the splicing of SMN2 pre-mRNA in order to increase production of full-length SMN protein.[6] 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 full-length SMN protein in individuals with SMA.

SPINRAZA must be administered via intrathecal injection, which delivers therapies directly to the cerebrospinal fluid (CSF) around the spinal cord,[7] where motor neurons degenerate in individuals with SMA due to insufficient levels of SMN protein.[8]

SPINRAZA demonstrated a favorable benefit-risk profile. The most common adverse reactions reported for SPINRAZA were upper respiratory infection, lower respiratory infection, and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients. Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some ASOs. Individuals may be at increased risk of bleeding complications. Renal toxicity has been observed after administration of some ASOs. SPINRAZA is present in and excreted by the kidney.

About Biogen

At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases. Founded in 1978 as one of the world's first global biotechnology companies by Charles Weissman, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp, today Biogen has the leading portfolio of medicines to treat multiple sclerosis; has introduced the first and only approved treatment for spinal muscular atrophy; and is focused on advancing neuroscience research programs in Alzheimer's disease and dementia, multiple sclerosis and neuroimmunology, movement disorders, neuromuscular disorders, pain, ophthalmology, neuropsychiatry, and acute neurology. Biogen also manufactures and commercializes biosimilars of advanced biologics. We routinely post information that may be important to investors on our website at www.biogen.com. To learn more, please visit www.biogen.com and follow us on social media – Twitter, LinkedIn, Facebook, YouTube.

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 three dozen drugs in development.

SPINRAZA® (nusinersen) has been approved in global markets for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. Drugs that have successfully completed Phase 3 studies include inotersen, an antisense drug Ionis is developing to treat patients with hereditary TTR amyloidosis (hATTR), and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Volanesorsen filings for marketing approval have been submitted in the U.S., EU and Canada. Inotersen is progressing toward regulatory filings for marketing authorization. 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 made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 relating to the potential benefits, safety, and efficacy of SPINRAZA, the results of certain real-world data, the status of Biogen's current regulatory filings, Biogen's plans for additional regulatory filings in other jurisdictions, and availability of patient access and reimbursement pathways, which may vary on a country-by-country basis. These forward-looking statements may be accompanied by words such as "aim," "anticipate," "believe," "could," "estimate," "except," "forecast," "intend," "may," "plan," "potential," "possible," "will," and other words and terms of

similar meaning. Drug development and commercialization involve a high degree of risk. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation uncertainty of success in commercialization of SPINRAZA, which may be impacted by, among other things, the level of preparedness of healthcare providers to treat patients, difficulties in obtaining or changes in the availability of reimbursement for SPINRAZA, the effectiveness of sales and marketing efforts, problems with the manufacturing process for SPINRAZA, the occurrence of adverse safety events and/or unexpected concerns that 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 Biogen's drug candidates or expansion of product labeling; Biogen may encounter other unexpected hurdles which may be impacted by, among other things, the occurrence of adverse safety events, failure to obtain regulatory approvals in certain jurisdictions, or failure to protect intellectual property and other proprietary rights; product liability claims; or third party collaboration risks. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this press release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments, or otherwise.

Ionis Pharmaceuticals' 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, 2016, 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 Ionis.

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