The New England Journal of Medicine Publishes First Phase 3 Study Results of SPINRAZA® for the Treatment of Spinal Muscular Atrophy

November 1, 2017

- SPINRAZA, the first and only approved treatment for spinal muscular atrophy (SMA), is supported by the largest well-controlled SMA clinical development program conducted to date
- The majority of infants treated with SPINRAZA in the ENDEAR study achieved motor milestones compared to untreated infants
- SPINRAZA significantly reduced the risk of death or permanent ventilation in infants with SMA

CAMBRIDGE, Mass. & CARLSBAD, Calif.--(BUSINESS WIRE)--Biogen (Nasdaq: BIIB) and Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced that the end of study results from ENDEAR, the Phase 3 study of SPINRAZA® (nusinersen) for the treatment of spinal muscular atrophy (SMA), were published today in The *New England Journal of Medicine*. SPINRAZA is the first and only approved treatment for SMA. The full manuscript titled, "Nusinersen Versus Sham Control in Infantile-Onset Spinal Muscular Atrophy," appears in the November 2 issue of The *New England Journal of Medicine*.

"The publication of the ENDEAR study results in The *New England Journal of Medicine* underscores the clinical benefit and safety of SPINRAZA and highlights the therapeutic potential of this breakthrough treatment for people living with SMA, a debilitating and often fatal disease," said Richard Finkel, M.D., chief, division of neurology, department of pediatrics, Nemours Children's Hospital in Orlando, FL. "As a practicing physician, I have observed the profound impact this treatment can offer to individuals with SMA and their families. I feel privileged to have played a role in SPINRAZA's development, and to have watched this therapy bring the first real sense of optimism to the SMA community."

The two pre-specified ENDEAR primary endpoints were percentage of motor milestone responders, defined as improvements in motor milestone categories in the Hammersmith Infant Neurological Examination (HINE), and time to death or permanent ventilation. The final analysis demonstrated that a greater proportion of infants treated with SPINRAZA were motor milestone responders, compared to untreated infants (51% vs. 0%, P<0.001), including full head control, ability to roll over, and independent sitting and standing.

SPINRAZA also met the pre-specified primary endpoint of death or permanent ventilation in the end of study analysis, demonstrating a statistically significant 47% reduction in the risk of death or use of permanent assisted ventilation (P=0.005) and 76% reduction for those with shorter disease duration.

SPINRAZA demonstrated a favorable benefit-risk profile. Safety data was consistent with those expected in the general SMA infant population and were similar to those reported in an open-label study in infantile-onset SMA.

"The data published in The *New England Journal of Medicine* further emphasize the benefit SPINRAZA can provide to individuals with SMA, as the first and only approved SMA treatment in multiple countries. At the end of the ENDEAR study, most infants receiving SPINRAZA showed meaningful benefit, regardless of their age or stage of the disease," said Alfred Sandrock, M.D., Ph.D., executive vice president and chief medical officer at Biogen. "We are incredibly grateful for the support of the scientists, clinical investigators, and the individuals and families who participated in the studies and continue to contribute to the largest clinical development program to date for the treatment of SMA."

"The study results demonstrate that SPINRAZA has the potential to impact the course of the disease for people with SMA," said C. Frank Bennett, Ph.D., senior vice president of research and leader of the neurological disease franchise at Ionis. "SPINRAZA is the first approved treatment for SMA, and we look forward to the potential of antisense technology to treat patients with other neurological diseases who currently have no therapeutic options."

The SPINRAZA clinical development program includes over five years of data and is the largest body of evidence for an interventional approach in SMA. Following the positive interim analysis, Biogen ended the ENDEAR study early so that 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.

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 ENDEAR
ENDEAR is a randomized, double-blind, sham-procedure controlled 13-month study in individuals with infantile-onset spinal muscular atrophy (SMA). The end of study efficacy analysis included all patients (n=121) who had their final study visit after the interim analysis (n=78) and had the opportunity to attend the six-month study visit assessment. ENDEAR had two primary efficacy endpoints. The first was the proportion of Hammersmith Infant Neurological Examination (HINE) motor milestone responders. The HINE is a reliable and clinically validated tool to assess motor milestone achievement in infants. The second primary efficacy endpoint was event-free survival, defined as the time to death or permanent assisted ventilation (tracheostomy or ≥16 hours of ventilator support per day continuously for >21 days in the absence of an acute reversible event).

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, 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 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, 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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