Data Published in Neurology Show that Treatment with SPINRAZA® (nusinersen) Improved Motor Function and Provided Long-Term Benefit for Individuals with Later-Onset Spinal Muscular Atrophy

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- Patients, aged five up to 19, treated with SPINRAZA over three years demonstrated clinically significant improvements in motor function and stabilization of disease activity
- One individual gained the ability to walk independently – an achievement that has not been previously observed in untreated individuals with SMA Type 2
- Data also demonstrated long-term durability and safety of treatment in individuals with later-onset SMA, including SMA Type 3
- As of March 31, 2019, over 7,500 patients have been treated with SPINRAZA in more than 40 countries

CAMBRIDGE, Mass., April 30, 2019 (GLOBE NEWSWIRE) -- Biogen (Nasdaq: BIIB) today announced that data from CS2/CS12, an open-label study of the safety and tolerability of SPINRAZA in individuals with later-onset spinal muscular atrophy (SMA), were published in the peer-reviewed journal *Neurology*, the medical journal of the American Academy of Neurology. The data show that individuals with later-onset SMA, treated with SPINRAZA, regained motor function that had been previously lost and that treatment stabilized their disease activity leading to improvements in activities of daily living.

“These data give us new insight on how long-term treatment with SPINRAZA, over approximately three years, continues to help individuals with later-onset SMA and shows improved clinical efficacy,” said Basil Darras, M.D., lead study author, professor of neurology at Harvard Medical School. “A longitudinal analysis of this kind, which has not been available until now, provides a wealth of information about the ability to help prevent motor function loss, regain function and safely treat individuals with later-onset SMA. As we change the paradigm of living with SMA, long-term studies of this kind will be essential to understanding the disease.”

“These results add to the body of evidence of SPINRAZA as the foundation of care in SMA broadening its safety and efficacy profile. The data underscore the ability of the therapy to help improve the lives of people with SMA, including those with later-onset SMA, who without treatment typically experience a progressive decline in motor function,” said Wildon Farwell, M.D., executive medical director, clinical development at Biogen.

The full manuscript, “Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies” is available online and will appear in the May 21, 2019 print issue of *Neurology*. The open-label study evaluated 28 patients, aged five to 19 at time of study completion, with later-onset SMA including those most likely to develop SMA Type 2 (n=11) and 3 (n=17) that were treated with SPINRAZA for more than three years.

In addition to safety, the study also evaluated motor function measures through the Hammersmith Functional Motor Scale–Expanded (HFMSE); Upper Limb Module (ULM); and Six-Minute Walk Test (6MWT). The mean scores for each test showed clinically significant improvements. Key highlights include:

- Participants with SMA Type 2 increased HFMSE scores by 10.8 points while those with SMA Type 3 improved by 1.8 points. This compares to the natural history of the disease in which individuals with SMA Type 2 and 3 who are not being treated typically experience a 1.7-point decline in HFMSE scores after three years.[1]
- All non-ambulant children with SMA Type 3 achieved a maximum score of 18 points on the ULM assessment by day 350 and maintained that level of function through day 1,150. This compares to the natural history of the disease in which non-ambulant children with SMA Type 2 and 3 have an average ULM score of 10.23 points with an average 12-month gain of 0.04.[2]
- Individuals with SMA Type 2 had an average increase of 4.0 points in the ULM assessment up to three years after the baseline assessment. In the natural history of the disease, individuals experience a 0.04 gain over a 12-month period.[2]
- Participants with SMA Type 3 increased their distance walked by 92.0 meters in the 6MWT in comparison to a 1.5-meter decrease in natural history in the same test after one year.[3]
- One of the 11 non-ambulant children with SMA Type 2 gained the ability to walk independently through the course of the studies– an achievement that has never been reported in individuals with SMA Type 2 that are not undergoing treatment.
- Two of the four children with SMA Type 3, who had previously lost the ability to walk, regained the ability to walk independently during the course of the studies, suggesting that reversal of motor function loss may be possible for later-onset individuals treated with SPINRAZA.
- No participants discontinued treatment due to adverse events and no new safety concerns were identified during the three-year observation period.

The analysis is based on patients first treated during the CS2 study who continued treatment in the CS12 extension study. CS2 was a 253-day, multiple ascending dose (3, 6, 9, 12 mg), open-label, multicenter study that enrolled children with SMA aged two to 15 years. CS12 was a 715-day, single-dose level (12 mg) study. Time between studies varied by participant.

The SPINRAZA clinical development program includes over six years of data from 300 patients and is the largest body of evidence in SMA. As of March 31, 2019, over 7,500 individuals with SMA have been treated with SPINRAZA worldwide, based on patients across the post-marketing setting, Expanded Access Program (EAP) and clinical trial participants. 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 SPINRAZA® (nusinersen)[4-7]
SPINRAZA is the first and only approved medicine for the treatment of spinal muscular atrophy (SMA) and is currently available in more than 40 countries. As of March 31, 2019, over 7,500 individuals with SMA are being treated with SPINRAZA worldwide, based on patients across the post-marketing setting, Expanded Access Program (EAP) and clinical trial participants.

SPINRAZA is an antisense oligonucleotide (ASO) developed using Ionis' proprietary antisense technology that is designed to treat the root cause of SMA. SPINRAZA alters the splicing of SMN2 pre-mRNA in order to increase production of full-length SMN protein. 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 been shown to increase the amount of full-length SMN protein in individuals with SMA. SPINRAZA is administered via intrathecal injection, which delivers therapies directly into the cerebrospinal fluid (CSF) around the spinal cord, where motor neurons degenerate in individuals with SMA due to insufficient levels of SMN protein.

In the clinical trial program, SPINRAZA demonstrated a favorable benefit-risk profile. The most common adverse reactions that occurred in the SPINRAZA group were 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.

Biogen licensed the global rights to develop, manufacture and commercialize SPINRAZA from Ionis Pharmaceuticals, Inc. (Nasdaq: IONS), a leader in antisense therapeutics. Biogen and Ionis conducted an innovative clinical development program, the largest of its kind in SMA, that moved SPINRAZA from its first dose in humans in 2011 to its first regulatory approval in five years.

About the SPINRAZA Clinical Program
NURTURE is an ongoing, open-label study of infants up to six weeks of age at time of first dose, who were genetically diagnosed with SMA and had not experienced any symptoms by the time of first dose. Data presented at the World Muscle Society in October 2018 demonstrated unprecedented efficacy in treating patients pre-symptomatically. In that analysis, all NURTURE study participants were alive and did not require permanent ventilation, in contrast to natural history of SMA. Study participants achieved motor milestones with 100 percent sitting independently and 88 percent able to walk. All NURTURE study participants were 14 months or older at the time of the analysis.

Participants included infants with two copies of the SMN2 gene (n=15) who are likely to develop a fatal, early-onset form of SMA known as Type 1, and infants with three copies of the SMN2 gene (n=10) who typically develop SMA Type 2 or 3. People living with SMA Types 2 and 3 may never be able to walk or will lose that ability over time. No new safety concerns were identified.

The ENDEAR study was a thirteen-month, international, phase 3, multicenter, double-blind, sham-controlled study of 121 patients with infantile-onset SMA (most likely to develop SMA Type 1). Results from the pivotal study, which were published in *The New England Journal of Medicine*, evaluated the efficacy and safety in patients that onset of signs and symptoms of SMA before six months of age. Patients treated with SPINRAZA in the ENDEAR study achieved clinically meaningful improvement in achievement of motor milestones compared to untreated study participants with 51 percent vs. 0 percent demonstrating Hammersmith Infant Neurological Examination section 2 (HINE-2) motor milestone response, an assessment which evaluates eight motor-milestone categories, based on the defined criteria.

CHERISH was a fifteen-month, phase 3, randomized, double-blind, sham-controlled study investigating SPINRAZA in 126 non-ambulatory patients with later-onset SMA (most likely to develop SMA Type 2 or 3). Patients included had onset of signs and symptoms at greater than 6 months of age, and an age of 2 to 12 years at screening. The final analysis of CHERISH data found that children receiving SPINRAZA experienced a highly statistically significant and clinically meaningful improvement in motor function compared to those who did not receive treatment with a treatment difference of 4.9 points on the Hammersmith Functional Motor Scale Expanded. SPINRAZA demonstrated a favorable benefit-risk profile in the study.

About SMA[8]
SMA is a rare, genetic, neuromuscular disease that is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscle atrophy and weakness. About 1 in 10,000 live births have a diagnosis of SMA. Ultimately, individuals with SMA can lose the ability to walk and have difficulty performing the basic functions of life, such as breathing and swallowing, which results in significant healthcare intervention and caregiver assistance. Left untreated, the majority of infants with the most severe form of the disease (Type 1) do not live beyond their second birthday without respiratory intervention. People with childhood or adult onset SMA (Type 2 or 3) produce greater amounts of SMN protein resulting in less severe, but still life-altering forms of the disease.

Due to a deletion of, or mutation 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 an individual has. 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 typically 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 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 as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray, and Nobel Prize winners Walter Gilbert and Phillip Sharp, and today 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 MS and neuroimmunology, Alzheimer's disease and dementia, movement disorders, neuromuscular disorders, acute neurology, neurocognitive disorders, pain, and ophthalmology. Biogen also 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.

Biogen Safe Harbor
This news 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; our research and development program for the treatment of SMA; and availability of patient access and reimbursement pathways, which may vary on a country-by-country basis. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "possible," "potential," "will," "would" and other words and terms of similar meaning. 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. Results in early stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. 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 the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis; risks of unexpected costs or delays; failure to protect and enforce our data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; and third party collaboration risks. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from our expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risk factors identified in our most recent annual or quarterly report and in other reports we have filed with the Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this news release. We do not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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