SPINRAZA™ (nusinersen) Approved in U.S. to Treat Broad Range of Patients with Spinal Muscular Atrophy

December 23, 2016

- First Treatment Approved for SMA -
- SPINRAZA Improved Motor Function in Patients with SMA; Greater Percentage of Infantile-Onset Patients on SPINRAZA Survived -
- FDA Approval Received Within 3 Months of Regulatory Filing -

CARLSBAD, Calif., Dec. 23, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) announced today that the U.S. Food and Drug Administration (FDA) has approved SPINRAZA™ (nusinersen) under Priority Review for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. SPINRAZA is the first and only treatment approved in the U.S. for SMA, a leading genetic cause of death in infants and toddlers that is marked by progressive, debilitating muscle weakness. SPINRAZA was discovered and developed by Ionis and Biogen, and licensed to Biogen who is responsible for future development, manufacturing, and commercialization of SPINRAZA.

In ENDEAR, a pivotal controlled clinical study, infantile-onset SMA patients treated with SPINRAZA achieved and sustained clinically meaningful improvement in motor function compared to untreated study participants. In addition, a greater percentage of patients on SPINRAZA survived compared to untreated patients. In open-label studies, some patients achieved milestones such as ability to sit unassisted, stand or walk when they would otherwise be unexpected to do so and maintained milestones at ages when they would be expected to be lost. The overall findings of these studies support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment.

"At Ionis, we have had the privilege of discovering and, together with Biogen, developing SPINRAZA. We are very pleased with today's announcement, which is an important milestone for the entire SMA community. Now we look forward to the benefit that SPINRAZA can bring to patients with SMA and their families. SPINRAZA is truly a precision medicine that works by altering the processing of a single cellular RNA. We are proud that SPINRAZA exists because Ionis created and validated a new platform for drug discovery, antisense technology," said Stanley T. Crooke, M.D., Ph.D., chief executive officer and chairman of Ionis. "We want to thank the families, physicians and their staff who participated in our clinical trials. Their dedication and support have been crucial to the approval of SPINRAZA for all those with SMA."

The FDA approval of SPINRAZA was based on positive results from multiple clinical studies in more than 170 patients. Ionis and Biogen 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. The data package included the interim analysis of ENDEAR, a Phase 3 controlled study evaluating SPINRAZA in patients with infantile-onset SMA, as well as open-label data in pre-symptomatic and symptomatic patients with SMA, or likely to develop, Types 1, 2 and 3 SMA.

"I believe SPINRAZA is a game changer for patients with SMA and their families," said John Day, M.D., Ph.D., director of the Neuromuscular Disorders Clinic at Lucile Packard Children's Hospital Stanford and professor of neurology and pediatrics at the Stanford University School of Medicine. "Until now we had to tell parents that the only treatment was to manage symptoms as their children became weaker. Now, SPINRAZA offers patients currently living with SMA hope for disease stabilization or improvement, and it raises the possibility that infants with SMA could be prevented from developing weakness if identified early enough. More generally, the success of SPINRAZA increases our optimism that antisense oligonucleotides could also control other neurodegenerative disorders."

"This is a watershed moment for the entire SMA community, which has worked tirelessly to finally see the day when a therapy for SMA would be made available. Cure SMA and our families have supported research into this terrible disease for more than 30

years, and many have participated in the critical clinical trials for SPINRAZA. We are excited to now have the first ever treatment option for SMA, and thank all our supporters and the dedicated researchers who made this possible," commented Kenneth Hobby, President, Cure SMA.

"SPINRAZA is the first of many antisense programs for neurological diseases in our discovery and clinical development pipeline with the potential to treat a variety of other severe neurological diseases that are not adequately addressed today," said C. Frank Bennett, Ph.D., senior vice president of research and leader of the neurological disease franchise at Ionis. "We are excited by the potential of our antisense technology to treat diseases that other therapeutic modalities are unable to address or adequately treat."

In conjunction with approval in the U.S., Ionis earned a $60 million milestone payment from Biogen and is eligible to receive $90 million in additional milestone payments based on regulatory approvals in Europe and Japan. Ionis is also eligible to receive tiered royalties on sales of SPINRAZA up to a percentage in the mid-teens. To date, Ionis has earned nearly $320 million from Biogen related to SPINRAZA.

Biogen plans to make SPINRAZA available for shipment in the U.S. to healthcare providers in approximately one week. Biogen anticipates there may be variation in time to treatment as institutions and treatment centers learn about SPINRAZA. Biogen also plans to present results from the interim analysis of the Phase 3 ENDEAR study at the British Pediatric Neurology Association conference being held in Cambridge, UK January 11-13, 2017.

"We are pleased with Biogen's preparations for launch and the speed with which they are implementing them," said B. Lynne Parshall, chief operating officer of Ionis. "We look forward to receiving the first commercial revenues from sales of SPINRAZA next year. These revenues will build on our current solid financial foundation and will add to the substantial revenues we expect to receive from our successful collaborations with Biogen and our other collaboration partners."

SPINRAZA (nusinersen) is under regulatory review with the European Medicines Agency (EMA), which has validated Biogen's Marketing Authorization Application (MAA) and granted Accelerated Assessment status. Biogen has also submitted regulatory filings in Japan, Canada and Australia and is initiating regulatory filings in additional countries in 2017.

For additional information about SPINRAZA (nusinersen), please visit www.spinraza.com.

About SMA
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.

SPINRAZA is the only approved treatment for SMA.

ABOUT SPINRAZA (nusinersen)
SPINRAZA is an antisense oligonucleotide (ASO) that is designed to treat SMA caused by mutations in the chromosome 5q that leads to SMN protein deficiency. It was discovered and co-developed by Ionis Pharmaceuticals, a leader in antisense therapeutics, and Biogen. SPINRAZA is designed to selectively bind to and alter the splicing of a single RNA from the SMN2 gene, a gene that is nearly identical to SMN1, 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 the potential to increase the amount of functional SMN protein in infants and children with SMA.

SPINRAZA is administered via intrathecal injection, which delivers therapies directly to the cerebrospinal fluid (CSF) around the spinal cord, where motor neurons degenerate in patients with SMA due to insufficient levels of SMN protein.

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 antisense oligonucleotides. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

Both the U.S. and E.U. granted SPINRAZA Orphan Drug status. Additionally, both the U.S. and E.U. regulatory agencies granted special status to SPINRAZA, including Fast Track Designation and Priority Review in the U.S. and Accelerated Assessment status in the E.U.

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.

For additional information about SPINRAZA (nusinersen), please visit www.spinraza.com.

THE SPINRAZA PHASE 3 REGISTRATIONAL STUDY, ENDEAR

ENDEAR was a randomized, double-blind, sham-controlled study in patients with infantile-onset (most likely to develop Type 1) SMA. At a planned interim analysis of ENDEAR, a greater percentage of infants treated with SPINRAZA achieved a motor milestone response compared to those who did not receive treatment (40% versus 0%; p<0.0001) as measured by the Hammersmith Infant Neurological Examination (HINE). Additionally, a smaller percentage of patients on SPINRAZA died (23%) compared to untreated patients (43%). Data from the other efficacy endpoints analyzed were consistently in favor of infants who received treatment.

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; and IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis. SPINRAZA (nusinersen) is a drug that has been approved in the U.S. for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercialization of SPINRAZA. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

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, the therapeutic and commercial potential of Ionis' technologies and other products in development, including IONIS-TTR_{Rx} and volanesorsen. 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.

In this release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/spinraza-nusinersen-approved-in-us-to-treat-broad-range-of-patients-with-spinal-muscular-atrophy-300383512.html

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