



SPINRAZA® (nusinersen) Approved in the European Union

First Approved Treatment in EU for SMA

Approved to Treat Broad Range of People with SMA

Ionis Earns \$50 Million Milestone

Carlsbad, Calif., June 1, 2017 – Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that the European Commission (EC) has granted marketing authorization for SPINRAZA® (nusinersen) for the treatment of 5q spinal muscular atrophy (SMA). 5q SMA is the most common form of the disease and represents approximately 95% of all SMA cases. SPINRAZA is the first approved treatment in the European Union (EU) for SMA, a leading genetic cause of death in infants that is marked by progressive, debilitating muscle weakness. SPINRAZA was reviewed under the European Medicines Agency’s (EMA) accelerated assessment program, intended to expedite access to patients with unmet medical needs.

In conjunction with the SPINRAZA approval in the EU, Ionis earned a \$50 million milestone payment from Biogen. Ionis is also eligible to receive tiered royalties on global sales of SPINRAZA. To date, Ionis has earned more than \$375 million from Biogen related to SPINRAZA.

“This is a landmark day for the European SMA community. The approval of SPINRAZA to treat a broad range of patients with SMA provides patients currently living with SMA hope for disease stabilization or improvement. Further, I am encouraged that the approval of SPINRAZA may demonstrate the potential of other antisense oligonucleotides to treat more neurodegenerative disorders,” Eugenio Mercuri, MD, Università Cattolica del Sacro Cuore, Rome, Italy.

The approval of SPINRAZA was primarily based on results from two pivotal multicenter, controlled studies, including end of study data from ENDEAR (infantile-onset SMA) and an interim analysis of CHERISH (later-onset SMA), both of which demonstrated the clinically meaningful efficacy and favorable benefit-risk profile of SPINRAZA. The approval was also supported by results from open-label studies in pre-symptomatic and symptomatic individuals with, or most likely to develop, Types 1, 2 or 3 SMA.

“The approval of SPINRAZA by the European Commission is a triumph for our community. Patients and families affected by SMA in Europe may now have a brighter future than before SPINRAZA was available. We are grateful for the perseverance of the European SMA community as we waited for this day, and for the rigorous clinical work that resulted in a broad label that may offer access to many patients in Europe,” said Joanna Mitchell, CEO of SMA Trust.

“We would like to convey our gratitude to the patients, families, physicians and their teams in the EU who participated in our clinical trials. Their support and dedication have been critical in achieving this important milestone,” said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals. “In the U.S., the initial

launch of SPINRAZA is off to a strong start and we continue to be pleased with the dedication, passion, and commitment of our partners at Biogen. We are pleased that this approval makes SPINRAZA widely available in the EU to treat a broad range of people with SMA.”

Biogen licensed the global rights to develop, manufacture and commercialize SPINRAZA from Ionis Pharmaceuticals in August 2016 and is now responsible for all development, regulatory and commercialization activities and costs for SPINRAZA. SPINRAZA was first approved by the U.S. Food and Drug Administration (FDA) on December 23, 2016, within three months of regulatory filing. Biogen has also submitted regulatory filings in Japan, Canada, Australia, Brazil and Switzerland and plans to initiate additional filings in other countries in 2017. Ionis is eligible to receive a \$40 million milestone payment from Biogen following the approval of SPINRAZA in Japan, which Biogen expects could happen later this year.

ABOUT ENDEAR and CHERISH STUDIES

In the ENDEAR end of study analysis, a statistically significant greater percentage of patients achieved the definition of motor milestone responder in the SPINRAZA group (51%) compared to the sham-control group (0%) ($p < 0.0001$). Some infants in the SPINRAZA group achieved motor milestones including full head control, ability to roll, sitting, and standing. Additionally, infants treated with SPINRAZA demonstrated a statistically significant reduction (47%) in the risk of death or permanent ventilation ($p = 0.0046$).

In the CHERISH pre-specified interim analysis, there was a statistically significant and clinically meaningful improvement in motor function in children with later-onset SMA (most likely to develop Type 2 or Type 3) treated with SPINRAZA compared to untreated children. Improvements were measured by the Hammersmith Functional Motor Scale Expanded (HFMSSE) and demonstrated a treatment difference of 5.9 points in the mean change from baseline to Month 15 in the HFMSSE score ($p = 0.0000002$). The HFMSSE is a reliable and validated tool specifically designed to assess motor function in children with SMA. The Phase 3 end of study data were consistent with the interim analysis and presented at the American Academy of Neurology annual meeting in Boston, Mass., April 2017.

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 type 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 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 Pharmaceuticals' 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. It was discovered and co-developed by Ionis Pharmaceuticals, a leader in antisense therapeutics, and Biogen. 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, where motor neurons degenerate in patients with SMA due to insufficient levels of SMN protein.

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. The EAP has successfully led to the initiation and ongoing treatment of more than 350 eligible individuals with infantile-onset SMA (most likely to develop Type 1) in 17 European countries.

SPINRAZA demonstrated a favorable benefit-risk profile. For SPINRAZA prescribing information in the EU, please visit <http://www.ema.europa.eu/ema/>.

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) 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. Drugs that have successfully completed Phase 3 studies include volanesorsen, a drug Ionis is developing and plans to commercialize through its subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; and inotersen (IONIS-TTR_{Rx}), a drug Ionis is developing with GSK to treat patients with TTR amyloidosis. Both drugs are progressing toward regulatory filings in the second half of 2017. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

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, 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 the Company.

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

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA® is a registered trademark of Biogen.

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