Ionis Pharmaceuticals Reports Data Update from Nusinersen Phase 2 Study in Infants with Spinal Muscular Atrophy and Reviews Neurological Disease Franchise

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Webcast scheduled for Thursday, April 21 at 11:00 a.m. PDT/ 2:00 p.m. EDT

CARLSBAD, Calif., April 20, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today provided an update on its ongoing open-label Phase 2 clinical study of nusinersen in infants with spinal muscular atrophy (SMA) at the American Academy of Neurology (AAN) meeting in Vancouver, BC. The data reported today show that there have been no new events, as defined by progression to permanent ventilation or death, in the study since December 2014 with continued increases in event-free survival, muscle function scores as well as achievement of new developmental milestones. Data showing increases in neuromuscular electrophysiology measurements were also reported. The latest analysis also demonstrates that no nusinersen-related safety or tolerability concerns have been identified. Including the nusinersen data, Ionis and its collaborators presented more than 12 oral talks and posters on Ionis' neurological disease programs at the AAN meeting.

"The totality of these data in infants with SMA is encouraging, including the observed trends toward increases in muscle function as measured by CHOP INTEND and Hammersmith Infant Neurological Exam Motor Milestones. Nusinersen is the first drug in the clinic to target the underlying genetic cause of SMA and offers the promise of hope for this devastating disease," said Richard Finkel, M.D., chief, division of neurology, department of pediatrics, Nemours Children's Hospital. "SMA is the most common fatal genetic disease of infancy and treatment for these infants is limited to supportive care. Infants with Type I SMA have the most severe form of the disease; they almost never achieve important development milestones such as independent sitting. They never walk and usually succumb to early death due to progressive weakness of the muscles responsible for breathing and feeding."

The Phase 2 open-label study (n=20) was designed to evaluate the safety and tolerability of nusinersen in infants with Type I SMA. Clinical efficacy endpoints include event-free survival, as defined by time to permanent ventilation or death; CHOP-INTEND motor function scores; electrophysiology measurements (compound muscle action potential, or CMAP) and assessments of developmental milestones. An analysis as of January 26, 2016 showed that:

- No new events have occurred since December 2014. The event-free survival observed to date is different from the observed natural history in this patient population with nusinersen-treated infants living longer without the need for permanent ventilation.
- All infants continuing in the study (n=15) are older than two years of age, with some infants older than three years of age.
- Muscle function scores have increased from baseline with a mean increase of 22.2 points in the CHOP INTEND score at 26 months with no evidence of a therapeutic plateau.
- Infants have achieved new motor milestones since their baseline evaluations, including stable unsupported sitting (n=8), standing with or without support (n=5) and walking (n=2).
- CMAP measurements have increased from baseline, which is different from the observed natural history in this patient population where CMAP measurements decline rapidly before symptom onset, remain low and do not improve over the course of the course of the disease.

"We remain very encouraged with the performance of nusinersen. We and Biogen are committed to advancing nusinersen

as rapidly as possible. Together we are actively preparing for potential filing and commercial launch of nusinersen. We have completed enrollment in CHERISH, the Phase 3 study in children with SMA and are nearing completion of enrollment in ENDEAR, the Phase 3 study in infants with SMA. This progress places us on track to have data from both of these controlled, Phase 3 studies in the first half of 2017," said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals.

As of January 26, 2016, the median time in study was 22 months. The lumbar puncture procedure in infants with SMA has been well tolerated and shown to be feasible. There have been no drug-related serious adverse events (SAEs) and the majority of SAEs were related to respiratory infections. Most of the adverse events (non-SAEs) have been mild or moderate in severity. There have been no changes in the safety profile with repeated doses of nusinersen.

Including the nusinersen data, Ionis and its collaborators are presenting more than a dozen oral talks and posters at the AAN meeting including overviews on its programs on Huntington's disease, myotonic dystrophy type 1, Alzheimer's disease, Parkinson's disease and spinocerebellar ataxia type 2. Last year, Ionis initiated clinical studies in Huntington's disease and ALS, expanded its myotonic dystrophy type 1 (DM1) study to include patients with DM1, and added a number of research-stage programs into development.

"In the last several years, we have built our neurological disease franchise to encompass more than 25 programs, including two drugs in Phase 3 clinical development, three drugs in Phase 2 clinical development and multiple programs in research and preclinical development. Contributing to the speed of this progress is the expertise and resources that our partners have brought to these programs, said C. Frank Bennett, Ph.D., senior vice president of research at Ionis Pharmaceuticals. "The progress we have made in this franchise reflects the productivity of our technology and highlights the unique advantage of our antisense drugs to distribute broadly throughout the CNS and to target neurological diseases that have been largely untreatable in the past."

Webcast

At 11:00 a.m. PDT / 2:00 p.m. EDT, April 21, 2016, Ionis will conduct a webcast to discuss the latest data presented at the AAN meeting, including the nusinersen Phase 2 study data. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, www.ionispharma.com. Interested parties may listen to the call by dialing 877-443-5662. A replay will be available for a limited time. The slides presented on the webcast will be available on Ionis' website at www.ionispharma.com at the time of the webcast and for a limited time after.

ABOUT SMA

SMA is a severe genetic disease that affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. There are no approved treatments for SMA. The disease is caused by a loss of, or defect in, the survival motor neuron 1 (SMN1) gene, leading to a decrease in the survival motor neuron (SMN) protein. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuromuscular growth and function. One in 50 people, the equivalent of about six million people in the United States, are carriers of a defective SMN1 gene, which is unable to produce fully functional SMN protein. Carriers experience no symptoms and do not develop the disease. However, when both parents are carriers, there is a one in four chance that their child will have SMA.

Natural history studies have been conducted in patients with SMA. Type 1 is the most severe form of SMA and most infants with Type 1 SMA die in infancy. In a 2009 paper by Rudnik-Schöneborn[i], the median age for event-free survival in infants with Type 1 SMA was 6.1 months. In a contemporaneous study published in 2014 by the Pediatric Neuromuscular Clinical Research group (PNCR)[ii], the median age for event-free survival in infants with two copies of SMN2 was 10.5 months. The severity of SMA correlates with the amount of SMN protein. Infants with Type 1 SMA produce very little SMN protein and have a life expectancy of less than two years. Children with Type 2 have greater amounts of SMN protein but still have a shortened lifespan and are never able to walk. Children with Type 3 have a normal lifespan but accumulate life-long physical disabilities as they grow.

ABOUT NUSINERSEN

Nusinersen, also referred to as IONIS-SMN$_{Rx}$, is designed to alter the splicing of SMN2, a gene that is closely related to SMN1, to increase production of fully functional SMN protein. The United States Food and Drug Administration granted orphan drug status and fast track designation to nusinersen for the treatment of patients with SMA. The European regulatory agency granted orphan drug designation to nusinersen for the treatment of patients with SMA. Ionis is currently collaborating with Biogen to develop and potentially commercialize the investigational compound, nusinersen, for the treatment of SMA. Under the terms of the January 2012 agreement, Ionis is responsible for global development and Biogen has the option to license the compound.

Ionis is conducting two Phase 3 studies of nusinersen. One Phase 3 study, ENDEAR, in infants with SMA and a second Phase 3 study, CHERISH, in children with SMA. The ENDEAR study is a randomized, double-blind, sham-procedure controlled thirteen-month study in approximately 110 infants diagnosed with SMA. The study will evaluate the efficacy and safety of nusinersen with a primary endpoint of event-free survival. The CHERISH study is a randomized, double-blind, sham-procedure controlled fifteen-month study in approximately 120 children diagnosed with SMA. The study will evaluate the efficacy and safety of nusinersen with the Hammersmith Functional Motor Scale – Expanded (HFMSE) score as the primary endpoint.

In addition to the Phase 3 studies, ENDEAR and CHERISH, nusinersen is being evaluated in the following four Phase 2 studies:

- Biogen is evaluating nusinersen in an open-label study, NURTURE, in approximately 25 pre-symptomatic newborns who are genetically diagnosed with SMA but presymptomatic.
- Biogen is evaluating nusinersen in a randomized, double-blind, sham-procedure controlled study, EMBRACE, in 21 patients who do not meet the age and inclusion criteria of ENDEAR and CHERISH studies.
- Ionis is evaluating nusinersen in a Phase 2 open-label study in 20 infants with SMA.
- Ionis is evaluating nusinersen in a Phase 2 open-label extension study in 47 children who have completed dosing in one of the earlier nusinersen studies.

Ionis has also completed three additional nusinersen studies that evaluated a single or multiple dose of nusinersen in 56 children with Type II and Type III SMA. Children who completed these studies were eligible to roll over into the Phase 2 open-label extension study.

For further study information, please visit www.clinicaltrials.gov and search for IONIS-SMN$_{Rx}$ or visit the nusinersen study site at www.smastudy.com.

Ionis acknowledges support from the following organizations for nusinersen: Muscular Dystrophy Association, SMA Foundation, Cure SMA and intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

ABOUT IONIS and BIOGEN

Ionis and Biogen have a broad strategic alliance focused on leveraging antisense technology to advance the treatment of neurological and neuromuscular disorders. This alliance combines Ionis' expertise in antisense technology to evaluate potential neurological targets and discover antisense drugs with Biogen's capability to develop therapies for neurological disorders. Ionis is primarily responsible for drug discovery and early development of antisense therapies. Biogen has the option to license each antisense program at a particular stage in development. Current development-stage programs include antisense drugs to treat patients with spinal muscular atrophy (SMA), nusinersen; myotonic dystrophy type 1 (DM1), IONIS-DMPK-2.5$_{Rx}$; amyotrophic lateral sclerosis (ALS), IONIS-SOD1$_{Rx}$; and three programs to undisclosed neurodegenerative diseases, IONIS-BIIB4$_{Rx}$, IONIS-BIIB5$_{Rx}$ and IONIS-BIIB6$_{Rx}$. In addition, Ionis and Biogen have numerous opportunities to evaluate additional targets for the development of drugs to treat neurological disorders.

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; IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and nusinersen, a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' strategic relationship with Biogen, the discovery, development, activity, therapeutic and commercial potential and safety of nusinersen for the treatment of spinal muscular atrophy and the discovery, development, activity, therapeutic potential, safety and commercialization of drugs in Ionis' neurological disease franchise. 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, which is on file with the SEC. Copies of this 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.

[i] Rudnik-Schöneborn S, Berg C, Zerres K, et al. Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type 1 in Germany: implications for clinical trials and genetic counselling. *Clin Genet.* 2009;76(2):168-78.

[ii] Finkel RS et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810-7.

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