Press Release

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Isis Reports Updated Results from ISIS-SMN Rx Clinical Studies in Infants and Children with Spinal Muscular Atrophy

Results presented at the American Academy of Neurology meeting
On track to initiate Phase 3 study in infants with SMA mid-year
On track to initiate Phase 3 study in children with SMA in the second half of the year
Isis to host an investor event and live webcast at 6:00 p.m. EDT on Tuesday, April 29 in Philadelphia

CARLSBAD, Calif., April 29, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today provided an update on both of its ongoing open-label Phase 2 clinical studies of ISIS-SMN_{Rx} in infants and children with spinal muscular atrophy (SMA) at the 66th American Academy of Neurology (AAN) meeting in Philadelphia, PA.

Results from Phase 2 study in infants with SMA

In the study in infants with SMA, a total of 15 infants have been dosed as of April 7, four infants in the 6 mg cohort and 11 infants in the 12 mg cohort. The 12 mg cohort is continuing to enroll patients.

In the 12 mg cohort:

- Seven infants have received all three induction doses and been evaluated after their last induction dose. These patients constitute the per protocol efficacy population (PPEP).
- Of these seven, five are alive without the need for permanent ventilation. The two infants who have had an event (one death and one permanent ventilation) each experienced the event in connection with pneumonia.
- The median age of the infants in the PPEP in the 12 mg cohort is 9.6 months (calculated using age at event or on April 7 for patients who have not experienced an event).
- Three of the infants not included in the PPEP remain on study and had not yet reached their third induction dose on April 7. One infant died prior to receiving a third induction dose.

In the 6 mg cohort:

- The PPEP in this cohort is comprised of all four infants dosed.
- Two infants are alive without the need for permanent ventilation, one is currently on long-term ventilation and one infant, unfortunately, died due to an accident.
- The median age of the infants in the 6 mg cohort is 14 months (calculated using age at event or on April 7 for patients who did not experience an event).

Although the study was not designed to provide evidence of improvement in functional activity, increases in muscle function scores were observed in infants in both cohorts using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), a motor assessment test that evaluates muscle strength in infants with SMA. In this test, infants with SMA are examined using 16 different assessments using a scoring scale of 0 to 4 for each assessment (max 64 points). Infants in the PPEP from both cohorts showed mean increases from baseline in CHOP INTEND of 5.4 points at the latest timepoint tested with the seven infants in the 12 mg cohort PPEP showing a mean increase of 8.3 points. Additional endpoints were also examined, including the Hammersmith Infant Neurological Exam Motor Milestones, which showed increased achievements consistent with increases in muscle function scores observed in CHOP INTEND, with nine of the 11 infants in the combined PPEP exhibiting improvements in motor milestones. In infants treated to date, ISIS-SMN_{Rx} has been well tolerated with most infants treated with the 12 mg dose. Isis plans to initiate a Phase 3 clinical study in infants with SMA mid-year.

"I am encouraged by the results presented today. These infants tolerated the treatment very well and the data suggest that the drug is reaching the target. The totality of these early 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. Here we have the first drug in the clinic to target the genetic basis of SMA that offers 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 and usually succumb to early death due to progressive weakness of the muscles responsible for breathing and feeding. The CHOP INTEND scale and the Hammersmith Infant Neurological Exam Motor Milestones exam are effective tools for evaluating changes in muscle function in these infants. In general, infants with Type I SMA decline over time in motor function testing, as measured by tests such as the CHOP INTEND and the Hammersmith Infant Motor Milestones."

Results from Phase 2 study in children with SMA

In the study in children with SMA, time and dose-dependent increases in muscle function scores, as measured by the Hammersmith Functional Motor Scale-Expanded (HFMSE), were observed in children treated with multiple-doses of ISIS-SMN$_{Rx}$. Children in the 3 mg, 6 mg and 9 mg cohorts achieved mean increases of 1.5, 2.3 and 3.7 points, respectively nine months following the first dose. Encouraging preliminary results were also observed in two additional functional tests: the six-minute walk test (6MWT), and the upper limb module (ULM) test. In the 6MWT, performed with nine ambulatory children, a mean increase of 22.7 meters was observed at 9 months. In the ULM test, which utilizes a 9 item scale (max score of 18), performed with 10 non-ambulatory children, a mean increase of 2.3 was observed at 9 months. In all children treated with ISIS-SMN$_{Rx}$ to date, the drug has been well tolerated at doses as high as 12 mg.

In addition, analysis of cerebral spinal fluid (CSF) samples from children in this study demonstrated dose-dependent increases in SMN protein levels over time in patients treated with ISIS-SMN$_{Rx}$ with the maximum effect observed in the 9 mg cohort in which the mean SMN protein level more than doubled by Day 86 from baseline (n=9). Children in the 12 mg cohort have not yet been evaluated. These results are consistent with the increases in SMN protein levels from the single-dose study, in which SMN protein levels more than doubled in the highest dose cohort.

"The debilitating progressive muscle weakness observed in children with SMA can vary substantially from child to child and can have a profound effect on their quality of life. As such, even small increases in muscle function can translate into significant changes in quality of life for these children. The Hammersmith muscle function scoring method is a well-established test that was designed to track the progressive loss of muscle function in children with SMA. Using this test, dose- and time-dependent increases in muscle function scoring in children treated with ISIS-SMN$_{Rx}$ have been observed in both the single- and multiple-dose studies. These results are encouraging and suggest that ISIS-SMN$_{Rx}$ could have the potential to bring benefit to these children," said Claudia Chiriboga, M.D., M.P.H., associate professor of clinical neurology and clinical pediatrics at Columbia University Medical Center.

"We continue to be encouraged with the dose- and time-dependent increases in both muscle function scores and SMN protein levels observed in children with SMA treated with ISIS-SMN$_{Rx}$. To date, 54 children with SMA have been treated with a total of 138 doses. Although our studies were not placebo controlled, the consistency of the data supports our optimism that ISIS-SMN$_{Rx}$ may be able to improve the lives of infants and children with SMA and gives us further confidence to advance ISIS-SMN$_{Rx}$ into a Phase 3 program," said C. Frank Bennett, Ph.D., senior vice president of research at Isis. "We are on track to start the Phase 3 study in children with SMA later this year."

Investor Event

At 6:00 p.m. Eastern Daylight Time Tuesday, April 29, 2014, Isis will host an investor event and live webcast to discuss ISIS-SMN$_{Rx}$ data presented at the AAN. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, **http://www.isispharm.com**. A replay will be available for a limited time. The slides presented at the AAN meeting are available on Isis' website at **http://www.isispharm.com**.

ABOUT ISIS-SMN$_{Rx}$

ISIS-SMN$_{Rx}$ is designed to alter the splicing of a closely related gene (SMN2) to increase production of fully functional SMN protein. The United States Food and Drug Administration granted orphan drug status and fast track designation to ISIS-SMN$_{Rx}$ for the treatment of patients with SMA. Isis is currently in collaboration with Biogen Idec to develop and potentially commercialize the investigational compound, ISIS-SMN$_{Rx}$, to treat all types of SMA. Under the terms of the January 2012 agreement, Isis is responsible for global development and Biogen Idec has the option to license the compound until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies.

Isis is evaluating ISIS-SMN$_{Rx}$ in an open-label, multi-dose, dose-escalation Phase 2 study in infants with SMA, with doses of either 6 mg or 12 mg administered intrathecally on Days 1, 15 and 85. Infants in this study will also be eligible to receive an additional 12 mg dose six months after they have completed the initial three scheduled doses. Infants may enroll in the Phase 2 study if they are between the ages of three weeks and seven months, live in close proximity to a study site and pass screening evaluations conducted at study sites. The study is being conducted at centers in the United States and Canada. For further study information, please visit **www.clinicaltrials.gov** and search for ISIS-SMN$_{Rx}$ or by the identifier number, NCT01839656. ISIS-SMN$_{Rx}$ is also being evaluated in an open-label, multiple-dose, dose-escalation Phase 1b/2a study in children with Type II and Type III SMA. In this study, doses of 3 mg, 6 mg, 9 mg and 12 mg were administered intrathecally. The 3 mg, 6 mg and 12 mg doses were administered on Days 1, 29 and 85. The 9 mg dose was administered on Days 1 and 85. Children will be eligible to receive additional 12 mg doses in an open-label extension study which is open to the more than 50 children with SMA who have completed dosing with ISIS-SMN$_{Rx}$ in the ongoing Phase 2 and other studies.

Isis acknowledges support from the following organizations for ISIS-SMN$_{Rx}$: Muscular Dystrophy Association, SMA Foundation, Families of SMA and intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

ABOUT SMA

SMA is a severe genetic disease that affects approximately 30,000-35,000 patients in the United States, Europe and

Japan. SMA 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 responsible for neuromuscular growth and function. One in 50 people, the equivalent of about 6 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. The severity of SMA correlates with the amount of SMN protein. Infants with Type I SMA, the most severe form of the disease, produce very little SMN protein and have a life expectancy of less than two years. Children with Type II have greater amounts of SMN protein but still have a shortened lifespan and are never able to stand independently. Children with Type III have a normal lifespan but accumulate life-long physical disabilities as they grow.

ABOUT ISIS and BIOGEN IDEC

Biogen Idec and Isis have established four collaborations focused on leveraging antisense technology to advance the treatment of neurological and neuromuscular disorders. This alliance combines Isis's expertise in antisense technology to evaluate potential neurological targets and discover antisense drugs with Biogen Idec's capability to develop therapies for neurological disorders. Isis is primarily responsible for drug discovery and early development of antisense therapies. Biogen Idec has the option to license each antisense program at a particular stage in development. Current development-stage programs include antisense drugs to treat SMA, ISIS-SMN_{Rx}, and myotonic dystrophy type 1, ISIS-$DMPK_{Rx}$.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 32 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States for the treatment of patients with HoFH. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at **www.isispharm.com**.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' alliance with Biogen Idec, the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-SMN_{Rx} and the discovery, development and therapeutic potential of an antisense drug for the treatment of spinal muscular atrophy. Any statement describing Isis' 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. Isis' 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 Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, 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, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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