Isis Pharmaceuticals Reports Interim Results from ISIS-SMN Rx Multiple Dose Study in Children with Spinal Muscular Atrophy

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Average increase of 3.7 points observed in muscle function score in SMA children treated with 9 mg of ISIS-SMN Rx
ISIS-SMN Rx increases SMN protein in children with SMA
On track to initiate Phase 3 study in children with SMA later this year
Conference Call Scheduled for February 24, 2014 at 8:30 am Eastern Time

CARLSBAD, Calif., Feb. 21, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today announced top-line results from an ongoing open-label, multiple-dose study of ISIS-SMN_{Rx} in children with spinal muscular atrophy (SMA). In this study, ISIS-SMN_{Rx} was well tolerated at all dose levels in children with SMA. Consistent with single-dose observations, time- and dose-dependent increases in muscle function were observed in children treated with multiple doses of ISIS-SMN_{Rx}. In addition, results from a recently developed biomarker assay that was designed to measure levels of SMN protein in the cerebral spinal fluid (CSF), showed time- and dose-dependent increases in SMN protein levels in SMA children treated with ISIS-SMN_{Rx} from both single- and multiple-dose studies.

(Logo: http://photos.prnewswire.com/prnh/20130807/LA60006LOGO)

"We continue to be encouraged with the tolerability of ISIS-SMN_{Rx} we have observed in our clinical studies to date. We are also encouraged that we observed dose- and time-dependent increases in muscle function scores in children with SMA. The consistency of the results between the single-dose and the multiple-dose studies supports our earlier optimism around the single dose study results and gives us further confidence to advance ISIS-SMN_{Rx} into a Phase 3 program in children with SMA, which we plan to start later this year," said B. Lynne Parshall, chief operating officer.

In the interim analysis of this ongoing multiple-dose Phase 1b/2a study, children with Type II or Type III SMA were dosed intrathecally with 3 mg, 6 mg or 9 mg of ISIS-SMN_{Rx}. The 3 mg and 6 mg doses were administered on days 1, 29 and 85. The 9 mg dose was administered on days 1 and 85. Muscle function changes were measured using the Hammersmith Functional Motor Scale-Expanded (HFMSE), a validated method to measure changes in muscle function in patients with SMA. Using this test, dose-dependent increases in muscle function scores were observed in this study. SMA children in the 3 mg, 6 mg and 9 mg cohorts achieved mean increases in HFMSE scores of 1.5, 2.3 and 3.7 points, respectively, nine months following the first dose of ISIS-SMN_{Rx}. In addition, time-dependent increases in muscle function scores were observed. Children in the 9 mg cohort achieved mean increases in HFMSE scores of 2.7 and 3.7 points three and nine months after the first dose of ISIS-SMN_{Rx}, respectively. The increases in muscle function scores observed in this study at the three month time point is comparable to the single-dose data presented last year, which showed that children treated with 9 mg of ISIS-SMN_{Rx} achieved a mean increase in HFMSE score of 3.1 three months after the single-dose. All children in the multiple-dose study have completed dosing in the initial three cohorts and the first child has been dosed in the 12 mg cohort. Isis' plans to give all children who roll over into an extension study a maintenance dose of 12 mg of ISIS-SMN_{Rx} every six months. To date, ISIS-SMN_{Rx} has been well tolerated. Two serious adverse events (pneumonia and fentanyl-related hypersensitivity) that were not considered drug related were reported.

"A subgroup analysis that combines data from children in both the single- and multiple-dose studies demonstrated a mean 5 point increase in muscle function score in children who received at least 9 mg of ISIS-SMN_{Rx} between the ages of two and 10 who did not have severe scoliosis or baseline HFMSE scores at the extreme low or high ends of the scale. These results provide us with valuable insight into determining which children with SMA can achieve increases in Hammersmith scores that best correlate with increases in muscle function," said C. Frank Bennett, Ph.D., senior vice president of research. "Because we saw increases in muscle function scores up to 14 months after treatment in our single-dose study, we will continue to monitor the patients from our multiple dose study who enter the extension study for longer-term changes in muscle function scores. Given the long half-life of ISIS-SMN_{Rx} and the complexity of a process that starts with increasing SMN protein production and ends with improvements in muscle function, it makes sense that the effects of ISIS-SMN_{Rx} are both dose and time dependent."

In addition, analysis of CSF samples from both the single dose and the ongoing multiple dose studies demonstrated dose-dependent increases in SMN protein levels over time in patients treated with ISIS-SMN_{Rx}. In the single dose study, SMN protein levels more than doubled in the two highest dose cohorts with average increases of approximately 120% and 160% compared to baseline observed approximately 9-14 months after dosing in the 6 mg and 9 mg cohorts, respectively. Similarly, in the multiple dose study, patients in the 9 mg cohort all exhibited a substantial increase in SMN protein levels. At Day 86, SMN

protein levels more than doubled with an average increase of 115% compared to baseline.

Isis plans to report additional detail from this study at an upcoming medical conference. For further study information, please visit www.clinicaltrials.gov and search for ISIS-SMN$_{Rx}$ or by the identifier number, NCT01703988.

Conference Call
At 8:30 a.m. Eastern Time Monday, February 24, 2014, Isis will conduct a live conference call to discuss the top-line multiple-dose results. Interested parties may listen to the call by dialing 866-652-5200, or access the audio webcast at www.isispharm.com. A webcast replay will be available for a limited time at the same address.

ISIS-SMN$_{Rx}$ is also being evaluated in an open-label, multiple-dose, dose-escalation Phase 2 study in infants with Type I SMA. In the ongoing Phase 2 study, doses of either 6 mg or 12 mg are administered intrathecally on Days 1, 15 and 85. All infants from the 6 mg dose cohort have completed the three initially scheduled doses and, under the amended protocol, are eligible to receive an additional 12 mg dose six months after their initial three scheduled doses. Isis announced late in 2013 that the study was expanded to enroll up to 20 infants and that the first infant was dosed in the 12 mg dose cohort. Infants from the 12 mg dose cohort 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.

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 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 31 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 potential, safety and commercialization 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, 2012, 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, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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