Data From ISIS-SMN Rx Phase 1 Study in Children With Spinal Muscular Atrophy Presented at the American Academy of Neurology Meeting

March 20, 2013

Isis to host an investor event and live webcast at 7:30 am PT on Thursday, March 21 in San Diego

CARLSBAD, Calif., March 20, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced that data from the Phase 1 study of ISIS-SMN$_{Rx}$ in children with spinal muscular atrophy (SMA) were presented today at the 65th American Academy of Neurology (AAN) Annual Meeting by Dr. Claudia Chiriboga, from Columbia University Medical Center. In the presentation, Dr. Chiriboga reported that, in this single-dose, open-label study, ISIS-SMN$_{Rx}$ was well tolerated in children with SMA at all dose levels tested and that improvements were observed in Hammersmith scores, a measure of muscle function, in a number of the children. SMA is a severe and rare genetic neuromuscular disease characterized by muscle atrophy and weakness and is the most common genetic cause of infant mortality. ISIS-SMN$_{Rx}$ is an antisense drug designed to treat all types of SMA.

"SMA is a devastating disease that results in severe muscle weakness and respiratory failure in infants and children. Current treatments are supportive and do not address the underlying genetic cause of SMA, the loss of SMN protein, which is critical to the health and survival of nerve cells responsible for neuromuscular growth and function. ISIS-SMN$_{Rx}$ is designed to address the underlying genetic problem for patients with SMA by increasing the production of functional SMN protein," said Claudia Chiriboga, M.D., associate professor of clinical neurology and pediatrics at Columbia University Medical Center. "I am pleased to report that ISIS-SMN$_{Rx}$ administration was very well tolerated in these young children with a safety profile that supports additional development of the drug. The improvements in muscle function observed in this study following a single dose of the drug were encouraging. For these reasons, I am very excited about the potential benefit of ISIS-SMN$_{Rx}$ for children with this terrible disease."

In the presentation titled, 'Results of an Open-Label, Escalating Dose Study To Assess the Safety, Tolerability, and Dose Range Finding of a Single Intrathecal Dose of ISIS-SMN$_{Rx}$ in Patients with Spinal Muscular Atrophy', Dr Chiriboga reported that ISIS-SMN$_{Rx}$ was well tolerated when administered intrathecally as a single dose directly into the spinal fluid and that no safety concerns related to the drug were identified. In addition, the intrathecal injection procedure was well tolerated in children with SMA. Concentrations of ISIS-SMN$_{Rx}$ measured in cerebral spinal fluid were consistent with levels predicted from preclinical studies, indicating that the drug half-life in nervous system tissues is very long and that dosing once every six to nine months is feasible. Although the study was not designed to provide evidence of functional activity, clinically significant, dose-dependent improvements in the Hammersmith Functional Motor Scale-Expanded (HFMSE), a measure of muscle function, were observed in these children. The mean increase in the HFMSE scores observed in the highest dose cohort (9 mg) at 3 months was 3.1 points or a 17.6% increase from baseline, with six of ten patients experiencing an increase of 4 to 7 points. Observed improvements in HFMSE scores equal to or greater than a 4 point increase were distributed by age with half (3) in children under the age of five and half in children five and older. Children who participated in this study are allowed to either enter the ongoing multiple-dose Phase 1b/2a study or a separate re-dosing study. Please click here to access Dr. Chiriboga's AAN slide presentation.

"SMA is a heartbreaking disease. Children with SMA are bright and engaging, but often never achieve the simplest motor milestones like walking, crawling, or sitting up. In its most severe form, children do not live beyond 2 years of age. Even in milder cases, SMA patients inexorably grow weaker and experience the loss of the few abilities they did acquire. In addition to motor losses, SMA patients young and old are at constant risk of tragic consequences from simple respiratory infections that you and I take in stride," said Karen S. Chen, Ph.D., chief scientific officer at the SMA Foundation. "The landmark science behind ISIS-SMN$_{Rx}$ is compelling and it has a chance to fill the therapeutic void for SMA and transform the hopes and futures of thousands of patients and families."

The Phase 1 study of ISIS-SMN$_{Rx}$ was an open-label, single-dose, dose-escalation study designed to assess the safety, tolerability and pharmacokinetic profile of ISIS-SMN$_{Rx}$ in medically stable children from age 2-14. In this study, 28 children, including 15 with Type II SMA and 13 with Type III SMA, received ISIS-SMN$_{Rx}$ as a single dose of 1, 3, 6, or 9 mg administered intrathecally. ISIS-SMN$_{Rx}$ concentrations in plasma and cerebral spinal fluid were measured to provide information on the dose concentration and frequency for future studies. In addition, exploratory analyses of changes in motor function were conducted. Gross motor movements were measured in all children throughout the study using the Hammersmith Motor Function Scale-Expanded (HFMSE), a modified version of the Hammersmith Functional Motor Scale. The HFMSE is used to assess responses on 33 motor function tasks, each scored on a scale from 0 to 2 and allows for assessment of any SMA patient aged 2 or older. HFMSE has demonstrated good test-retest reliability in other studies.

"ISIS-SMN$_{Rx}$ is our first drug to modify the splicing of RNA to increase the production of a functional SMN protein. This Phase 1 study is the first time that we have administered an antisense drug to patients as young as 2 years of age. We are very encouraged that the drug was safe and that intrathecal dosing was tolerated well by these children even at the highest dose level," said C. Frank Bennett, Ph.D., senior vice president of research at Isis.

"Early evidence of activity in these children is encouraging, but it is important to note that this was an open-label study without a control arm," said Stanley T. Crooke, M.D., Ph.D., chairman of the board and chief executive officer at Isis. "We are cautiously optimistic with the observed improvements in muscle function in the higher dose cohort, however, we will need further clinical data from a controlled study to assess the safety and activity of this drug in patients with SMA. We plan to have additional clinical data from our ongoing multiple-dose study in children with SMA by late 2013 or early 2014. We also plan to initiate a Phase 2/3 program in infants this year and a Phase 2/3 study in children in the first half of 2014."

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. ISIS-SMN$_{Rx}$ is currently being evaluated in a Phase 1b/2a multiple-dose, dose-escalation study in children with SMA. In this study, children will either receive two or three doses of ISIS-SMN$_{Rx}$ over the course of the study.

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.

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.

INVESTOR EVENT
At 7:30 a.m. Pacific Time Thursday, March 21, 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 Web site, www.isispharm.com. A replay will be available for a limited time. The slides presented at the AAN meeting are available on Isis' Web site at www.isispharm.com.

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 28 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO™, inthe United States for the treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets, including Europe. 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' strategic alliance with Biogen Idec, and the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-SMN_{Rx}. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, 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, 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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