Isis Reports Follow-Up Data From ISIS-SMN Rx Phase 1 Study in Children With Spinal Muscular Atrophy

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Improvements in muscle function continue to be observed up to fourteen months after a single dose

CARLSBAD, Calif., Sept. 19, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that follow-up preliminary data from a single dose, open-label Phase 1 study of ISIS-SMN_{Rx} in children with spinal muscular atrophy (SMA), show that most SMA children receiving the two highest doses of the drug (6 mg and 9 mg) continued to show improvements in muscle function tests up to 14 months after a single injection of the drug. The Phase 1 data, including these preliminary follow-on data, will be presented at the International Congress of the World Muscle Society by Dr. Kathy Swoboda on Oct. 3, 2013. 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.

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The preliminary data reported today is from a follow-up analysis of 24 children with SMA who participated in a Phase 1 single-dose, open-label study of ISIS-SMN_{Rx}. Analysis of motor function was performed in these children nine to 14 months following a single dose of ISIS-SMN_{Rx} using the Hammersmith Functional Motor Scale-Expanded (HFMSE). The improvements in HFSME scores were dose dependent with the largest improvements observed in children in the highest dose cohort (9 mg, mean = 5.75). Most children in the 9 mg dose cohort showed continuing improvements during follow up, with no children declining.

"SMA is a devastating disease that results in severe muscle weakness and respiratory compromise in the majority of affected patients. Treating children early in the course of the disease provides the greatest opportunity to reap substantial improvements in muscle strength and function, potentially resulting in a lifetime of benefit. ISIS-SMN_{Rx} targets the underlying primary cause of SMA, taking advantage of the backup gene, SMN2, present in all SMA patients," said Kathryn J. Swoboda, M.D., professor, department of neurology and director of pediatric motor disorders research program at the University of Utah, School of Medicine. "Preliminary results from Phase 1 clinical trials reveal a favorable safety profile, and appear to indicate that a single dose of the medication at the higher doses tested to date may result in sustained benefit over many months in some children. Thus, while early, we are excited to continue to work closely with Isis in further studies of ISIS-SMN_{Rx} in SMA."

"We are pleased with the progress we are making on ISIS-SMN_{Rx}. Although there was no placebo group, the continuing improvement for up to a year after a single dose observed in this study is encouraging, particularly when considered within the context of the dose response," said B. Lynne Parshall, chief operating officer at Isis. "Our ongoing Phase 2 program is proceeding well. The 6 mg dose group in our Phase 2 study in infants with Type I SMA has completed dosing. Based on the safety, pharmacokinetic and pharmacodynamic profile of ISIS-SMN_{Rx} we have observed to date, we have amended the infant study to increase the dose from 9 mg to 12 mg dose. We plan to start dosing this cohort soon. In our Phase 1b/2a multiple-dose study in children with Type II and Type III SMA, we have completed dosing in all three dose cohorts (3 mg, 6 mg and 9 mg), and we are considering adding a 12 mg dose cohort to this study. The FDA has expressed reservations about increasing the exposure in children with Type II and Type III SMA, and we are in ongoing discussions with them. We plan to report data from both of these ongoing studies late this year or early next year. We also plan to begin our Phase 3 clinical program early next year."

The Phase 1 study 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, children with Type II or Type III SMA received ISIS-SMN_{Rx} as a single dose of 1, 3, 6, or 9 mg administered intrathecally. In addition to measurements of drug concentration in plasma and cerebral spinal fluid, exploratory analyses of changes in motor function were conducted. Gross motor movements were measured using the 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.

Data from this study was reported at the American Academy of Neurology in March 2013, showing that a single-dose of ISIS-SMN_{Rx} was well tolerated in children with SMA at all dose levels tested and that improvements were observed in HFMSE scores in a number of children, with a mean increase in HFSME scores for the 9 mg cohort at three months was 3.1 points. The data to be reported at the World Muscle Congress in October is a follow on analysis of HFMSE in 24 children who had completed the Phase 1 study.

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 two Phase 1b/2a multiple-dose, dose-escalation studies. The first is in children with Type II or Type III SMA. The second is in infants with Type I SMA.

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.

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 30 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™, 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' strategic alliance with Biogen Idec, the planned clinical studies for ISIS-SMN$_{Rx}$ and the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-SMN$_{Rx}$ to treat patients with SMA. 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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