Isis Pharmaceuticals Reports Data From ISIS-SMN Rx Phase 2 Studies in Infants and Children With Spinal Muscular Atrophy

October 10, 2014

Phase 3 ENDEAR study in infants with SMA enrolling; on track to initiate Phase 3 study in children with SMA later this year

Isis to host a webcast at 11:30 a.m. EDT on Friday, October 10

CARLSBAD, Calif., Oct. 10, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today provided an update on its ongoing open-label Phase 2 clinical studies of ISIS-SMN_{Rx} in infants and children with spinal muscular atrophy (SMA) at the 19th International World Muscle Society (WMS) Congress in Berlin, Germany. Isis is currently treating infants with SMA with ISIS-SMN_{Rx} in a Phase 3 study called ENDEAR, and plans to initiate a second Phase 3 study, called CHERISH, in children with SMA later this year.

"I am encouraged with the totality of the data presented today, which show that median event-free ages for SMA infants in both the 6 mg and 12 mg cohorts compare favorably to that observed in a recent natural history study. These data combined with the safety and tolerability profile observed to date support my enthusiasm to further evaluate ISIS-SMN_{Rx} in a Phase 3 study in infants with Type I SMA," said Richard Finkel, M.D., chief, division of neurology, department of pediatrics, Nemours Children's Hospital. "Often infants with Type I SMA succumb to early death due to progressive weakness of the muscles responsible for breathing and feeding. In the PNCR natural history study, for which I was the lead investigator, in a group of untreated patients similar to those in the Isis Phase 2 study, the median event-free age was 10.5 months, with less than 20% of patients event free at 18 months. In addition to the positive data on event-free survival, substantial and persistent increases in muscle function as measured by the CHOP INTEND and Hammersmith Infant Neurological Examination were also observed in ISIS-SMN_{Rx}-treated infants up to 9 months on study. This is an important finding because in general, infants with Type I SMA decline over time in their motor function as reflected in scores on these tests."

Event-free survival data from Phase 2 study in infants with SMA

In the Phase 2 study in infants with SMA, a total of 20 infants were dosed as of September 2, 2014, four infants in the 6 mg cohort and 16 infants in the 12 mg cohort. As of April 7, 2014, the date of Isis' previous data update, the per protocol efficacy populations (PPEP) (patients who completed the three dose induction regimen in the study) constituted four patients in the 6 mg and seven patients in the 12 mg dose cohorts. As of September 2, 2014, the date for this data update, the PPEP constituted four patients in the 6 mg and 12 patients in the 12 mg dose cohorts.

In the 6 mg cohort:

- No patients have had an event (death or permanent ventilation) since April 2014. As of September 2, 2014, there have been two events (one accidental death and one permanent ventilation) in the 6 mg cohort.
- Isis previously reported a median event-free age of 14 months for the infants in the PPEP on April 7, 2014. The median event-free age on September 2, 2014 for the infants in this group is now 16.3 months.

In the 12 mg cohort:

- Dosing in the 12 mg cohort began five months after the initiation of dosing for the 6 mg cohort. As a result, the patients in the 12 mg cohort have participated in the study for a shorter time than those in the 6 mg cohort. As of April 7, the PPEP in the 12 mg dose cohort contained 7 infants. As of September 2, the PPEP for the 12 mg dose cohort contained 12 infants, which included an additional five infants who had more recently entered the study.
- Isis previously reported a median event-free age of 9.6 months for the infants who constituted the 12 mg PPEP as of April 7, 2014. The median event-free age at September 2, 2014 for these infants is now 13.8 months.
- The median event-free age of the 12 infants in the PPEP as of September 2, 2014 for the 12 mg cohort is 11.6 months. Of these 12 infants, nine are alive without the need for permanent ventilation.
- As of September 2, 2014, there have been four events (one permanent ventilation and three deaths, all related to respiratory infections) in the 16 infants from the 12 mg cohort.

Increases in muscle function scores in this study in infants with SMA

Measures of muscle function are also being assessed in this study. Increases in muscle function scores were observed in infants in both dosing cohorts using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), a motor assessment test that is used to evaluate muscle strength in infants with SMA.

- Increases in CHOP INTEND scores occurred in a majority of infants in the study. Infants in the PPEP from the 6 mg and 12 mg cohorts combined showed mean increases from baseline in CHOP INTEND of 9.3 points with 14 of the 16 infants

showing an increase in CHOP INTEND scores.
- Infants from the 12 mg dose cohort PPEP showed mean increases from baseline in CHOP INTEND of 11.7 points with 11 of the 12 infants showing an increase in CHOP INTEND scores.

Developmental milestones are also being examined in this study using the Motor Milestones portion of the Hammersmith Infant Neurological Examination, with 14 out of the 16 infants in the combined PPEP exhibiting improvements in motor milestones.

The safety and tolerability profile of ISIS-SMN$_{Rx}$ to date supports continued development. As of September 2, 2014, 20 infants have been exposed to doses of either 6 mg or 12 mg of ISIS-SMN$_{Rx}$ for a total of 67 intrathecal injections. The lumbar puncture procedure in SMA infants has been well tolerated and shown to be feasible. In all infants dosed, there have been no drug-related serious adverse events. Most of the adverse events (non-SAEs) have been mild or moderate in severity and not related to drug. There were no changes in the safety profile with repeated doses of ISIS-SMN$_{Rx}$.

Clinical data on ISIS-SMN$_{Rx}$ Mechanism of Action

Today, Isis reported the results from an analysis of spinal cord tissue samples from autopsies showing that ISIS-SMN$_{Rx}$ is distributed throughout the central nervous system. The results of these analyses also showed greater levels of full length SMN2 mRNA and full length SMN protein in tissues in ISIS-SMN$_{Rx}$-treated SMA infants compared to the levels of SMN2 mRNA and full length SMN protein in the tissues analyzed from untreated SMA infants. These analyses were conducted on tissue samples collected in three infants who had received three or more doses of ISIS-SMN$_{Rx}$ and were compared to tissue samples from four untreated SMA infants and three infants without SMA at a similar age range.

- Analysis of spinal cord tissue showed that ISIS-SMN$_{Rx}$ concentration in spinal cord tissues was greater than the concentration that resulted in biological activity in animal studies. ISIS-SMN$_{Rx}$ was found in multiple segments of the spinal cord and brain and in motor neurons.
- Greater level of full-length (containing exon 7) SMN2 mRNA was observed in the spinal cord and brain tissue of ISIS-SMN$_{Rx}$-treated SMA infants compared to the level of full-length SMN2 mRNA in the untreated SMA infants.
- In patients treated with ISIS-SMN$_{Rx}$, greater amounts of SMN protein were observed in the spinal cord compared to the amount of SMN protein observed in the untreated SMA infants.
- SMN protein was observed in neurons of tissues analyzed in ISIS-SMN$_{Rx}$-treated SMA infants in which ISIS-SMN$_{Rx}$ was present.

"The results on ISIS-SMN$_{Rx}$ presented today form an encouraging profile of a potential new therapy for patients with SMA," continued Dr. Finkel. "The consistency of observations in event-free survival, CHOP INTEND and development milestones, combined with the clinical data supporting the mechanism of action by which ISIS-SMN$_{Rx}$ was designed to act, creates strong support to continue evaluation of ISIS-SMN$_{Rx}$."

"We are encouraged that we have been able to evaluate both the distribution of ISIS-SMN$_{Rx}$ in spinal cord tissues and motor neurons, and the levels of full length SMN protein in the spinal cord of ISIS-SMN$_{Rx}$-treated infants. We are very fortunate to have access to these tissue samples, and thankful to the families who have allowed us to use them to advance the study of SMA and ISIS-SMN$_{Rx}$. Access to these tissues has enabled us to confirm what we observed in our earlier preclinical work; that ISIS-SMN$_{Rx}$ is broadly distributed throughout the central nervous system of ISIS-SMN$_{Rx}$-treated infants. We are also pleased to observe that the levels of ISIS-SMN$_{Rx}$ in tissues analyzed from ISIS-SMN$_{Rx}$-treated infants are greater than the concentrations at which we observed biological activity in our animal studies. We are also encouraged with the greater levels of full-length SMN2 mRNA and commensurate increases in SMN protein we observed in tissues analyzed from ISIS-SMN$_{Rx}$-treated SMA infants as compared to the levels of full-length SMN2 mRNA and SMN protein we observed in tissues analyzed from untreated SMA infants," said C. Frank Bennett, Ph.D., senior vice president of research at Isis Pharmaceuticals.

Results from Phase 2 study in children with SMA

In the ongoing, open-label study in children with SMA, 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$_{Rx}$. As previously reported in April 2014, children in the 3 mg, 6 mg and 9 mg cohorts achieved mean increases from baseline of 1.5, 2.3 and 3.7 points, respectively, nine months following their first dose (six months after last dose). Further evaluation of these children showed that the previously observed mean increases in muscle function scores continued to show increases from baseline for an extended period after their last dose with mean increases from baseline of 1.7, 3.2 and 2.3, respectively, eight to 13 months after last dose.

Increases in two additional functional tests were also observed eight to 13 months after last dose in the six-minute walk test (6MWT) and the upper limb mobility (ULM) test. In the 6MWT, performed with 10 ambulatory children, a mean increase of 24.4 meters was observed 12 to 16 months after the patients' baseline visits, compared to the previously reported increase of 22.7 meters at nine months. In the ULM test, a mean increase of 3.1 points was observed 11 to 16 months after the patients' baseline visits, compared to the previously reported increase of 2.3 points at nine months.

The safety and tolerability profile of ISIS-SMN$_{Rx}$ continues to support continued development. As of September 2, 2014, 56 children have been exposed to doses ranging from 1 mg to 12 mg of ISIS-SMN$_{Rx}$. The majority of these children have received multiple doses of drug and in total 183 doses of ISIS-SMN$_{Rx}$ have been administered. The lumbar puncture procedure in SMA children has been well tolerated and shown to be feasible. In all children dosed, there have been no drug-related serious adverse events. Most of the adverse events (non-SAEs) have been mild or moderate in severity and not related to drug. There were no changes in the safety profile with repeated doses of ISIS-SMN$_{Rx}$.

"SMA is a heartbreaking disease. Children with SMA are bright and engaging, but due to progressive muscle weakness, grow weaker over time and suffer a decline in their physical abilities. Because of the inevitable gradual decline that patients with SMA exhibit, I am encouraged with the consistency of the muscle function scores in these children. Not only do these children experience increases in muscle function scores, even after a

single dose of ISIS-SMN$_{Rx}$, but it now appears that these increases can be sustained for a significant time after dosing," said Basil Darras, M.D., professor of neurology, director of clinical neurology at the Boston Children's Hospital and Harvard Medical School.

"The consistency of the increases in muscle function scores across different SMA patient populations, including both children and infants with SMA, and the dose- and time-dependency of these increases is encouraging. The observation of increases in SMN protein in the spinal cord in tissues analyzed from ISIS-SMN$_{Rx}$-treated infants, suggest that ISIS-SMN$_{Rx}$ is acting by the mechanism of action through which it was designed to act," concluded Dr. Bennett.

Investor Event

At 11:30 a.m. Eastern Time, October 10, 2014, Isis will conduct a webcast to discuss ISIS-SMN$_{Rx}$ data presented at the WMS. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, www.isispharm.com. A replay will be available for a limited time. The slides presented at the WMS meeting are available on Isis' website at 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-SMN$_{Rx}$ is being evaluated in a pivotal Phase 3 study, ENDEAR, in infants 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 a 12 mg dose of ISIS-SMN$_{Rx}$ with a primary endpoint of survival or permanent ventilation. Additional efficacy endpoints are also included in the study. For further study information, please visit www.clinicaltrials.gov and search for ISIS-SMN$_{Rx}$ or the identifier number NCT02193074 or visit the ISIS-SMN$_{Rx}$ study site at www.smastudy.com.

Isis acknowledges support from the following organizations for ISIS-SMN$_{Rx}$: Muscular Dystrophy Association, SMA Foundation, Cure 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 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. 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' 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, 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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