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

June 11, 2015

Webcast to review study data scheduled for Thursday, June 11 at 8:30 a.m. Eastern Time

CARLSBAD, Calif., June 11, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today provided an update on its ongoing open-label Phase 2 clinical study of ISIS-SMN$_{Rx}$ in infants with Type I spinal muscular atrophy (SMA). Previously the company reported data from this study on event-free survival, measures of muscle function and assessments of developmental milestones. The data reported today show continued increases in median event-free survival and muscle function scores as well as achievement of developmental milestones. The safety and tolerability profile of ISIS-SMN$_{Rx}$ to date continues to support further development. Isis is currently collaborating with Biogen to develop and potentially commercialize ISIS-SMN$_{Rx}$ to treat patients with SMA.

The study was designed to evaluate the safety and tolerability of ISIS-SMN$_{Rx}$ in infants with Type I SMA and to explore potential efficacy endpoints to support the Phase 3 program. A total of 20 infants with SMA were dosed with either 6 mg or 12 mg of ISIS-SMN$_{Rx}$. SMA infants 7 months or younger entered the study sequentially, such that the dosing of infants in the 12 mg cohort began five to 15 months after the first infant was dosed in the 6 mg cohort. Nineteen infants completed the three induction doses and are evaluable for efficacy. Clinical efficacy endpoints include event-free survival, as defined by time to permanent ventilation or death; CHOP-INTEND motor function scores; and assessments of developmental milestones. An analysis as of April 17, 2015 showed that since the last analysis as of September 2, 2014 (seven and a half months ago):

- The median event-free age has increased for infants in both dosing cohorts, from 16.3 months to 19.9 months for the four infants in the 6 mg cohort, and from 11.6 months (n=12) to 16.7 months (n=15) for the infants in the12 mg cohort.
    - For the seven infants in the 12 mg cohort who were in the original group and reported on at the American Academy of Neurology meeting in 2014, the median event-free age has increased from 9.6 months on April 7, 2014 to 21.4 months on April 17, 2015.
- Two of the four infants in the 6 mg cohort remain enrolled in the study and are now older than 27 months of age. In the 12 mg cohort, 11 of 15 infants (73%) are still event-free and older than 15 months of age.
- Muscle function scores have increased from baseline.
- Infants have achieved motor milestones since their baseline evaluations.
- Only a single event has occurred: One infant in the 12 mg cohort required permanent ventilation. There have been no deaths since the previous analysis.

As of April 17, 2015, the median time in study was 13.2 months. The lumbar puncture procedure in infants with SMA has been well tolerated and shown to be feasible. There have been no drug-related serious adverse events (SAEs) and the majority of SAEs were related to respiratory infections. Most of the adverse events (non-SAEs) have been mild or moderate in severity. There were no changes in the safety profile with repeated doses of ISIS-SMN$_{Rx}$.

Webcast

At 8:30 a.m. Eastern Time, June 11, 2015, Isis will conduct a webcast to discuss the latest ISIS-SMN$_{Rx}$ Phase 2 study data. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, www.isispharm.com. Interested parties may listen to the call by dialing 877-443-5662. A replay will be available for a limited time. The slides presented on the webcast will be available on Isis' website at www.isispharm.com at the time of the webcast and for a limited time after.

ABOUT SMA

SMA is a severe genetic disease that affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. There are no approved treatments for SMA. The disease 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 that are 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.

Natural history studies have been conducted in patients with SMA. Type I is the most severe form of SMA and most infants with Type I SMA die in infancy. In a 2009 paper by Rudnik-Schöneborn[1], the median age for event-free survival in infants with Type I SMA was 6.1 months. In a contemporaneous study published in 2014 by the Pediatric Neuromuscular Clinical Research group (PNCR)[2], the median age for event-free survival in infants with two copies of SMN2 was 10.5 months. The severity of SMA correlates with the amount of SMN protein. Infants with Type I SMA 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-SMN$_{Rx}$

ISIS-SMN$_{Rx}$ is designed to alter the splicing of SMN2, a gene that is closely related to SMN1, 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 collaborating with Biogen to develop and potentially commercialize the investigational compound, ISIS-SMN$_{Rx}$, for the treatment of SMA. Under the terms of the January 2012 agreement, Isis is responsible for global development and Biogen has the option to license the compound. In addition to the pivotal studies described below, Biogen is operationalizing two Phase 2 studies (NURTURE & EMBRACE) to augment the ongoing Phase 3 program.

Isis is conducting two Phase 3 studies of ISIS-SMN$_{Rx}$. One Phase 3 study, ENDEAR, in infants with SMA and a second Phase 3 study, CHERISH, in children 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 ISIS-SMN$_{Rx}$ with a primary endpoint of event-free survival. The CHERISH study is a randomized, double-blind, sham-procedure controlled fifteen month study in approximately 120 non-ambulatory children with SMA. The study will evaluate the efficacy and safety of ISIS-SMN$_{Rx}$ with a primary endpoint of a change in Hammersmith Functional Motor Scale-Expanded.

For further study information, please visit www.clinicaltrials.gov and search for ISIS-SMN$_{Rx}$ 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 ISIS and BIOGEN

Isis and Biogen have a broad strategic alliance 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's capability to develop therapies for neurological disorders. Isis is primarily responsible for drug discovery and early development of antisense therapies. Biogen has the option to license each antisense program at a particular stage in development. Current development-stage programs include antisense drugs to treat patients with spinal muscular atrophy (SMA), ISIS-SMN$_{Rx}$, myotonic dystrophy type 1 (DM1), ISIS-DMPK$_{Rx}$, and two undisclosed neurodegenerative diseases, ISIS-BIIB3$_{Rx}$, and ISIS-BIIB4$_{Rx}$. In addition to these four drugs, Isis and Biogen have numerous opportunities to evaluate additional targets for the development of drugs to treat neurological disorders.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 38 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 and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe/rare diseases and cardiovascular diseases. These include ISIS-APOCIII$_{Rx}$, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and familial partial lipodystrophy; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. 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, 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, 2014, 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.

[1] Rudnik-Schöneborn S, Berg C, Zerres K, et al. Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type 1 in Germany: implications for clinical trials and genetic counselling. *Clin Genet.* 2009;76(2):168-78.

[2] Finkel RS et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810-7.

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