Isis Pharmaceuticals Initiates SHINE Study to Provide ISIS-SMN Rx for Patients With SMA Who Have Completed the Phase 3 ENDEAR and CHERISH Studies

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CARLSBAD, Calif., Oct. 15, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has initiated an open-label extension study, SHINE. The SHINE study provides ISIS-SMN_{Rx} to infants and children with spinal muscular atrophy (SMA) who have completed their participation in the Phase 3 ENDEAR and CHERISH studies and are eligible to participate in SHINE. All patients in the SHINE study will receive a 12 mg dose of ISIS-SMN_{Rx} every four months for infants who completed ENDEAR or every six months for children who completed CHERISH. Isis has earned an $11 million milestone payment from Biogen for the initiation of the SHINE study.

"Both the ENDEAR and CHERISH studies are enrolling on track. We are pleased to initiate the SHINE study; thus making ISIS-SMN_{Rx} available to the patients who have completed one of our Phase 3 studies, ENDEAR and CHERISH," said B. Lynne Parshall, chief operating officer at Isis Pharmaceuticals. "We sincerely appreciate the dedication and support of the SMA community, the patients and their families for participating in and helping us complete the ISIS-SMN_{Rx} Phase 3 program. Together with Biogen, we are committed to advancing ISIS-SMN_{Rx} toward the market as rapidly as possible. The initiation of the SHINE study supports that commitment and ensures that patients who completed the controlled portion of the Phase 3 program have continued access to ISIS-SMN_{Rx}."

Isis and Biogen are evaluating ISIS-SMN_{Rx} in a broad clinical program. Isis is conducting two Phase 3 randomized, double-blind, sham-procedure controlled studies of ISIS-SMN_{Rx} –ENDEAR and CHERISH. Isis plans to report data from both of these important studies in late 2016 or early 2017. The ENDEAR study is a thirteen month study in approximately 110 infants diagnosed with SMA. The CHERISH study is a fifteen month study in approximately 120 non-ambulatory children with SMA.

In addition to the Phase 3 studies, ENDEAR and CHERISH, ISIS-SMN_{Rx} is being evaluated in the following four Phase 2 studies:

- Biogen is evaluating ISIS-SMN_{Rx} in an open-label study, NURTURE, in approximately 25 pre-symptomatic newborns who are genetically diagnosed with SMA but presymptomatic.
- Biogen is evaluating ISIS-SMN_{Rx} in a randomized, double-blind, sham-procedure controlled study, EMBRACE, in 21 patients who do not meet the age and inclusion criteria of ENDEAR and CHERISH studies.
- Isis is evaluating ISIS-SMN_{Rx} in a Phase 2 open-label study in 20 infants with SMA. Infants in this study have been on treatment for up to 29 months. In June 2015, Isis reported that it had observed increases in median event-free survival and increases in muscle function scores as well as the achievement of developmental milestones in infants who received ISIS-SMN_{Rx} in its open-label Phase 2 study.
- Isis is evaluating ISIS-SMN_{Rx} in a Phase 2 open-label extension study in 30 children who have completed dosing in one of the earlier ISIS-SMN_{Rx} studies. Patients in this study have been on treatment for up to 46 months. In June 2015, Isis reported that it had observed increases in muscle function scores and additional motor function tests in children who received ISIS-SMN_{Rx}.

Isis has also completed dosing in three additional ISIS-SMN_{Rx} studies that evaluated a single or multiple dose of ISIS-SMN_{Rx} in 56 children with Type II and Type III SMA. Children who completed these studies were eligible to roll over into the Phase 2 open-label extension study.

Isis acknowledges support from the following organizations for ISIS-SMN_{Rx}: Cure SMA, Muscular Dystrophy Association, SMA Foundation and intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

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.

ABOUT SMA

SMA is a severe genetic disease that affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. Patients with SMA experience progressive loss of motor function and, in its most severe form, SMA is usually fatal. 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[i], 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)[ii], 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 walk. 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 correct the splicing defect that causes SMA by increasing the 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.

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-2.5$_{Rx}$, 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 volanesorsen, 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.

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[i] 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 counseling. *Clin Genet.* 2009;76(2):168-78.

[ii] 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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