Isis Pharmaceuticals Initiates Phase 3 Study of ISIS-SMN Rx in Children With Spinal Muscular Atrophy

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-- Isis Earns $27 Million Milestone Payment
-- CHERISH Trial to Enroll 120 Children With SMA at Clinical Centers Globally

CARLSBAD, Calif., Nov. 25, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today the initiation of a pivotal Phase 3 study evaluating ISIS-SMN$_{Rx}$ in approximately 120 non-ambulatory children with spinal muscular atrophy (SMA). SMA is a severe and rare genetic neuromuscular disease characterized by muscle atrophy and weakness. The Phase 3 study, CHERISH, is the second Phase 3 study Isis has initiated in a global late-stage clinical development program for ISIS-SMN$_{Rx}$. Isis earned a $27 million milestone payment from its development partner, Biogen Idec, for the dosing of the first patient in this study. Isis is also evaluating ISIS-SMN$_{Rx}$ in the Phase 3 study, ENDEAR, in infants with SMA. Isis is conducting both Phase 3 studies with agreement from the U.S. Food and Drug Administration (FDA) for special protocol assessments, or SPAs.

"CHERISH is the second pivotal Phase 3 study of ISIS-SMN$_{Rx}$ we have initiated this year. The speed at which we have moved this drug from a preclinical development candidate to a late-stage development reflects the successful collaboration we have with Biogen Idec and the support from the SMA community. It is our hope that this study will build upon the encouraging results we observed in our open-label Phase 2 studies. Both Phase 3 studies are designed to evaluate the efficacy of ISIS-SMN$_{Rx}$ in either infants or children with SMA and to further assess the safety profile in these patients. We are further encouraged by the FDA's agreement on the trial design and planned analysis for both of these Phase 3 studies on ISIS-SMN$_{Rx}$," said B. Lynne Parshall, chief operating officer at Isis Pharmaceuticals. "Together with our partner Biogen Idec, we are also in the planning stages for additional clinical studies as part of our commitment to the clinical program for ISIS-SMN$_{Rx}$."

"SMA is a devastating disease that robs people of physical strength by affecting the motor nerve cells in the spinal cord. SMA is the number one genetic cause of death for infants. Children with SMA grow weaker as their disease progresses. Although the genetic cause of SMA is well understood, currently there are no effective drugs available for children with SMA," said Kenneth Hobby, president of Cure SMA. "We applaud Isis for investing in and leading drug development efforts for SMA. We remain hopeful that potential treatments, like ISIS-SMN$_{Rx}$, will be able to provide therapeutic benefit."

CHERISH, a Phase 3 study of ISIS-SMN$_{Rx}$, is a randomized, double-blind, sham-procedure controlled fifteen month study in approximately 120 children who are non-ambulatory with SMA between the ages of 2-12. The study will evaluate the efficacy and safety of a 12 mg dose of ISIS-SMN$_{Rx}$ with a primary endpoint of a change in the Hammersmith Functional Motor Scale-Expanded (HFMSE), a validated method to measure changes in muscle function in patients with SMA. 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.

In addition to the current Phase 3 clinical studies ENDEAR and CHERISH, Biogen Idec plans to conduct two additional ISIS-SMN$_{Rx}$ studies, which could begin in the first half of 2015:

- NURTURE will be a Phase 2 clinical study evaluating ISIS-SMN$_{Rx}$ in up to 25 pre-symptomatic newborns that are genetically predisposed to the disease.
- EMBRACE will be a Phase 2 clinical study evaluating safety and exploratory efficacy of ISIS-SMN$_{Rx}$ in approximately 20 patients with infantile or childhood-onset SMA. This study will bridge the gap in a small subset of patients that do not meet the age and inclusion criteria of the current Phase 3 studies ENDEAR and CHERISH.

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 FDA 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 is conducting two Phase 3 studies with agreement from the FDA for special protocol assessments, or SPAs. A SPA is a written agreement between the FDA and a drug sponsor intended to confirm that the clinical trial protocol is adequate to meet current scientific and regulatory requirements for a potential new drug application.

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 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.

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 patients with spinal muscular atrophy (SMA), ISIS-SMN_{Rx}, myotonic dystrophy type 1 (DM1), ISIS-$DMPK_{Rx}$, and an undisclosed neurodegenerative disease, ISIS-$BIIB3_{Rx}$.

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 34 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 and rare and cardiovascular diseases. These include a novel triglyceride lowering drug, ISIS-$APOCIII_{Rx}$, for patients with familial chylomicronemia syndrome; ISIS-TTR_{Rx}, which Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN_{Rx}, which Isis is developing with Biogen Idec to treat infants 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 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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