ISIS PHARMACEUTICALS INITIATES CLINICAL STUDY OF ISIS-HTT$_{RX}$ IN PATIENTS WITH HUNTINGTON'S DISEASE

First therapy designed to directly target the cause of disease

Isis Earns $22 Million Milestone Payment from Roche

Carlsbad, Calif., July 21, 2015 –Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today announced that it has initiated a Phase 1/2a clinical study of ISIS-HTT$_{Rx}$ in patients with Huntington's disease (HD). ISIS-HTT$_{Rx}$ is the first therapy to enter clinical development that is designed to directly target the cause of the disease by reducing the production of the protein responsible for HD. HD is a rare genetic neurological disease in which patients experience deterioration of both mental abilities and physical control. Presently, there are no disease-modifying treatments for HD, with current therapies focused only on treating disease symptoms. ISIS-HTT$_{Rx}$ has been granted orphan drug designation by the European Medicines Agency for the treatment of patients with HD. Orphan drug designation is granted to products designed to diagnose, prevent or treat life-threatening or very serious conditions that affect not more than five in 10,000 persons in the European Union.

"Although the toxic protein produced from the huntingtin (HTT) gene in HD patients has been a target of interest for many years, no therapies have advanced to clinical trials to treat the underlying cause of the disease. Our antisense technology has enabled us to discover and develop ISIS-HTT$_{Rx}$, the first therapeutic approach designed to treat the genetic cause of HD. Together with Roche, we are committed to investigating this approach to treat patients with HD, a devastating disease that typically affects generations of families," said C. Frank Bennett, Ph.D., senior vice president of research at Isis Pharmaceuticals.

"Initiating the clinical study of ISIS-HTT$_{Rx}$ in patients with HD is the first step in developing a treatment that could significantly impact a patient's disease. It is also an important milestone in our collaboration with Roche. As we advance this program, we will continue to benefit from Roche's scientific expertise in developing therapeutics for neurodegenerative conditions," said B. Lynne Parshall, chief operating officer of Isis Pharmaceuticals.

The randomized, placebo-controlled, dose escalation Phase 1/2a clinical study will evaluate the safety and activity of ISIS-HTT$_{Rx}$ in patients with early stage HD. In this study, ISIS-HTT$_{Rx}$ will be administered intrathecally as an injection directly into the cerebral spinal fluid. Intrathecal administration of antisense drugs has been shown to be well tolerated in multiple clinical studies in patients.

"The initial development of this antisense drug for Huntington's disease came out of a longstanding productive partnership between Isis and CHDI, and its advancement now to clinical trial is testament to Isis' perseverance and scientific expertise," said Robi Blumenstein, president of CHDI Management, which oversees the activities of CHDI Foundation, a nonprofit research organization exclusively dedicated to the development of therapies that will slow the progression of HD. "It's exciting that therapeutic candidates grounded in the biology of Huntington's disease are finally making their way to clinical trial."

ABOUT ISIS and ROCHE

Roche and Isis are collaborating to develop antisense drugs to treat HD. The alliance combines Isis' antisense expertise with Roche's scientific knowledge in developing neurodegenerative therapeutics. With the initiation of the Phase 1/2a study for ISIS-HTT_{Rx}, Isis earned a $22 million milestone payment from Roche. To date, Isis has earned $52 million in upfront and milestone payments from its relationship with Roche and is eligible to earn additional milestone payments as the drug progresses in development, as well as royalties on sales of ISIS-HTT_{Rx} if it is commercialized. Roche has the option to license ISIS-HTT_{Rx} from Isis through the completion of the Phase 1/2a study. Prior to option exercise, Isis is responsible for the discovery and development of ISIS-HTT_{Rx}. If Roche exercises its option, it will assume responsibility for global development, regulatory and commercialization activities for the drug.

CHDI Foundation, Inc. provided financial and scientific support to Isis' HD drug discovery program through a development collaboration with Isis. Over time, CHDI will be reimbursed for its support of Isis' program out of milestone payments received by Isis.

ABOUT ISIS-HTT_{Rx} and Huntington's Disease

ISIS-HTT_{Rx} is a Gen. 2.0+ antisense drug in development for the treatment of Huntington's disease. ISIS-HTT_{Rx} is designed to reduce the production of all forms of the huntingtin (HTT) protein, which is the protein responsible for HD. As such, ISIS-HTT_{Rx} offers a unique approach to treat all patients with HD. HD is a rare genetic, progressive neurological disease resulting in deterioration in mental abilities and physical control. HD is referred to as a triplet repeat disorder, and is one of a large family of genetic diseases in which certain gene sequences are mistakenly repeated. In HD, the gene that encodes for the HTT protein contains a trinucleotide sequence that is repeated in the gene more than 36 times. The resulting HTT protein is toxic and gradually damages neurons in the brain. Symptoms of HD usually appear between the ages of 30 to 50 years, and continually worsen over a 10 to 25 year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there is no effective disease modifying treatment, and current approaches only focus on managing the severity of some disease symptoms.

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 Roche, the development, activity, therapeutic potential, commercial potential and safety of ISIS-HTT_{Rx}. 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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