



ISIS Initiates Phase 1 Clinical Trial of ISIS-SOD1Rx in Patients With ALS

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Isis' first drug to treat neurodegenerative disease enters clinical trials

CARLSBAD, Calif., March 5, 2010 /PRNewswire via COMTEX/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has initiated a Phase 1 study of ISIS-SOD1Rx in patients with an inherited, aggressive form of Lou Gehrig's disease also known as familial amyotrophic lateral sclerosis (ALS). Approximately 20 percent of all familial ALS cases are caused by a mutant form of superoxide dismutase, or SOD1. ISIS-SOD1Rx is an antisense drug designed to inhibit the production of SOD1. The ALS Association and the Muscular Dystrophy Association are providing funding for the development of ISIS-SOD1Rx.

"There is a desperate need for new and more substantive treatments for ALS patients. The mission of the Northeast ALS Consortium is to help advance new therapeutic options for patients with ALS, and I am very pleased to be a co-chair on this important study evaluating ISIS-SOD1Rx in people with familial ALS," said Merit Cudkowicz, M.D., Co-Chair of the Northeast ALS Consortium and a Professor of Neurology at the Massachusetts General Hospital of Harvard Medical School.

"It is evident that certain cases of familial ALS are related to mutant forms of SOD1. Therefore, the selective inhibition of SOD1 production could provide a way to improve the outcomes of these patients with ALS," said Timothy Miller, M.D., Ph.D., Assistant Professor of Neurology at Washington University School of Medicine and Director of the Christopher Wells Hobler Laboratory for ALS Research at the Hope Center for Neurological Disorders. "This is the first study to administer an inhibitor of SOD1 directly into the central nervous system. Having been involved with Isis in the research and now the clinical development of ISIS-SOD1Rx, I am looking forward to co-chairing this study with Dr. Cudkowicz and the Northeast ALS Consortium."

"ISIS-SOD1Rx is our first antisense drug to enter clinical trials to treat a neurodegenerative disease and our first antisense drug to be administered directly into the central nervous system. Based on our earlier preclinical studies, we believe that ISIS-SOD1Rx could offer an effective treatment for patients with familial ALS," said C. Frank Bennett, Ph.D., Senior Vice President of Research at Isis Pharmaceuticals. "This study is the first step in demonstrating the applicability of antisense drugs to treat severe neurodegenerative diseases. We also continue to advance our earlier-stage programs toward human studies."

The Phase 1 study of ISIS-SOD1Rx is a placebo-controlled, dose-escalation study designed to assess the safety, tolerability and pharmacokinetic profile of ISIS-SOD1Rx in patients with familial ALS that is caused by mutations within the SOD1 gene. The study consists of four cohorts with eight patients each. In this study, ISIS-SOD1Rx will be administered intrathecally using an external pump to deliver the drug directly into the spinal fluid during a single, 12-hour infusion. The study will be conducted in multiple centers within the United States.

"This therapy will be the first treatment for ALS that is specifically aimed at the target, SOD1, known to cause ALS. The development of new treatments for ALS is an extremely challenging and costly process. The ALS Association has been pleased to co-fund this study and partner with Isis on this extremely promising treatment approach. It is only through the support of our generous donors that this type of advancement is made possible," commented Lucie Bruijn, Ph.D., Chief Scientist, The ALS Association.

"This is a watershed moment," said R. Rodney Howell, M.D., Chairman of the MDA Board of Directors. "More than 30 people with familial ALS caused by mutations in the SOD1 gene soon will receive infusions of a SOD1 inhibitor directly into their central nervous systems." Dr. Howell added that "MDA has invested more than \$270 million fighting ALS, and it's exciting to see an excellent dose-escalation study get underway to assess the safety of ISIS-SOD1Rx."

ABOUT ISIS-SOD1Rx

ISIS-SOD1Rx is designed to inhibit the production of SOD1. In preclinical studies, Isis, in collaboration with Timothy Miller, Don Cleveland (University of California, San Diego), and Richard Smith (Center for Neurological Study) were able to lower production of SOD1 with ISIS-SOD1Rx in neurons and surrounding cells and prolong life in rats that showed many symptoms of ALS. In December 2007, the FDA granted ISIS-SOD1Rx Orphan Drug designation for the treatment of ALS. Because antisense drugs do not cross the blood-brain barrier, a small pump administers the drug directly into the central nervous system infusing the drug into the cerebral spinal fluid. Clinicians call this type of administration intrathecal infusion. As part of Isis' alliance with Genzyme, Genzyme has a right of first negotiation to license ISIS-SOD1Rx from Isis.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 22 drugs in development. Isis' drug

development programs are focused on treating cardiovascular, metabolic and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis' discovery and development of drugs for neurodegenerative diseases, and the development, activity, therapeutic potential and safety of ISIS-SOD1Rx in the treatment of ALS. 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 products. 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, 2009, which is on file with the SEC. Copies of this 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, including Regulus Therapeutics Inc.

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