ISIS INITIATES PHASE 1 CLINICAL STUDY OF ISIS-SMN$_{RX}$ IN PATIENTS WITH SPINAL MUSCULAR ATROPHY

U.S. FDA has granted both Fast Track Status and Orphan Drug Designation for ISIS-SMN$_{Rx}$

CARLSBAD, Calif., December 19, 2011 – Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has initiated a Phase 1 study of ISIS-SMN$_{Rx}$ in patients with spinal muscular atrophy (SMA). SMA is a severe motor-neuron disease that is the leading genetic cause of infant mortality. Isis is developing ISIS-SMN$_{Rx}$ as a potential treatment for all Types of SMA.

"SMA is a devastating disease that leads to the loss of motor neurons resulting in muscle weakness and respiratory failure in children. The genetic cause of this disease is well understood, but there are currently no effective disease-modifying therapies. Currently, treatment of SMA is entirely symptomatic and focuses on preserving muscle strength and lung function by physical therapy and assisted ventilation. This supportive approach has improved the natural history of SMA by extending life expectancy, but muscle weakness and atrophy are not affected. A disease-modifying drug like ISIS-SMN$_{Rx}$ that specifically targets the cause of the disease could, for the first time, restore muscle strength and respiratory function and dramatically improve the children's function and quality of life," said Darryl C. De Vivo, M.D, Sidney Carter Professor of Neurology and Pediatrics and Co-Director of the Motor Neuron Center at Columbia University Medical Center.

SMA is a severe genetic disease that affects approximately 30,000 – 35,000 patients in the United States, Europe and Japan. One in 50 people, approximately 6 million people in the United States are carriers of the SMA gene. 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. SMA is caused by a loss of, or defect in, the survival motor neuron 1 (SMN1) gene leading to a decrease in the protein, survival motor neuron (SMN). SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. The severity of SMA correlates with the amount of SMN protein. Infants with Type 1 SMA, the most severe life-threatening form, produce very little SMN protein and have shortened life expectancy. Children with Type II and Type III have greater amounts of SMN protein and less severe, but still life-altering forms of SMA. ISIS-SMN$_{Rx}$ is designed to treat all types of childhood SMA by altering the splicing of a closely related gene (SMN2) that leads to the increased production of fully functional SMN protein.

"Our strategy to treat SMA relies on a simple, powerful antisense method that boosts SMN protein levels by fixing a genetic RNA splicing glitch. Working with Isis, we have successfully redirected splicing to increase functional SMN production. We have thoroughly validated this approach in multiple animal models, observing marked improvement in modifying the disease course in both mild and severe models of SMA," said Adrian Krainer, Ph.D., Professor of Molecular Genetics at Cold

Spring Harbor Laboratory in Long Island, NY. "We look forward to translating this important discovery into an effective treatment for this serious disease."

"SMA represents a serious unmet medical need with no currently available treatments. ISIS-SMN_{Rx} is our first drug to intervene in the splicing of RNA to increase the production of a normal protein, SMN. Together with Dr. Krainer's lab, we have validated the antisense approach to treating this disease and are now advancing this program into clinical studies," said C. Frank Bennett, Ph.D., Senior Vice President of Research at Isis. "We are committed to quickly developing this drug and are finalizing what we believe will be a rapid development path for this drug in all types of SMA. Once we evaluate ISIS-SMN_{Rx} as a single-dose in children with SMA, we will move to multiple-doses in our Phase 1 studies and eventually evaluate the drug in Phase 2 studies in children with SMA, including infants with Type I SMA."

The Phase 1 study of ISIS-SMN_{Rx} is a single-dose, dose-escalation study designed to assess the safety, tolerability and pharmacokinetic profile of the drug in children with SMA between the ages of 2-14 who are medically stable. In this study, ISIS-SMN_{Rx} will be administered intrathecally as a single injection directly into the spinal fluid. Intrathecal administration of an antisense drug, ISIS-$SOD1_{Rx}$, has been shown to be safe and well tolerated in an ongoing Phase 1 study in patients with amyotrophic lateral sclerosis.

"SMA is a heartbreaking disease. Children with SMA are bright and engaging, but often never achieve the simplest motor milestones like walking, crawling, and sitting up. Many do not live to reach kindergarten. In milder cases, SMA patients inexorably grow weaker and experience the loss of the few abilities they did acquire. In addition to motor losses, SMA patients young and old are at constant risk of tragic consequences from simple respiratory infections that you and I take in stride," said Karen S. Chen, Ph.D., Chief Scientific Officer at the SMA Foundation. "If you consider that this is the normally bleak clinical outlook for these patients, you can understand why the ISIS-SMN_{Rx} trial represents such a watershed moment for SMA. The landmark science behind ISIS-SMN_{Rx} is compelling and it has a chance to fill the therapeutic void for SMA and transform the hopes and futures of thousands of patients and families."

"We are very pleased to see the great milestone of a disease-modifying drug treatment advancing into clinical trials in SMA patients," said Kenneth Hobby, President of Families of SMA. "Our community has worked for a long time to reach the goal of moving specific therapies for SMA from the bench and into the clinic. This has been made possible by close interactions between basic researchers, families, clinicians, and industry. Families of SMA applauds ISIS for investing in and leading drug developments efforts for this devastating, orphan disease."

"We see real promise in therapeutic strategies for SMA that increase production of the SMN protein," said Muscular Dystrophy Association Executive Vice President Research and Medical Director Valerie

Cwik, M.D. “We’re delighted ISIS Pharmaceuticals is moving forward with a Phase 1 dose-escalation study of its antisense drug in children with SMA.”

Isis acknowledges support from the following organizations for this program: Muscular Dystrophy Association， SMA Foundation, Families of SMA and intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

The United States Food and Drug Administration granted Orphan Drug Designation with Fast Track Status to ISIS-SMN_{Rx} for the treatment of patients with SMA.

For more information on the Phase 1 study of ISIS-SMN_{Rx} please visit: www.clinicaltrials.gov.

About Splicing

Splicing is a normal mechanism that the cell uses in order to produce many different, but closely related proteins from a single gene by varying the processing of the RNA. It is estimated that of the approximately 25,000 genes in the human genome, approximately 90% have alternative splice forms. In some cases, alternative splicing of RNA results in the production of proteins that are involved in disease. These diseases are referred to as splicing diseases and include SMA, cystic fibrosis and Duchenne’s muscular dystrophy.

ABOUT COLD SPRING HARBOR LABORATORY

Founded in 1890, Cold Spring Harbor Laboratory (CSHL) has shaped contemporary biomedical research and education with programs in cancer, neuroscience, plant biology and quantitative biology. CSHL is ranked number one in the world by Thomson Reuters for impact of its research in molecular biology and genetics. The Laboratory has been home to eight Nobel Prize winners. Today, CSHL's multidisciplinary scientific community is more than 350 scientists strong and its Meetings & Courses program hosts more than 11,000 scientists from around the world each year. Tens of thousands more benefit from the research, reviews, and ideas published in journals and books distributed internationally by CSHL Press. The Laboratory's education arm also includes a graduate school and programs for undergraduates as well as middle and high school students and teachers. CSHL is a private, not-for-profit institution on the north shore of Long Island. For more information, visit www.cshl.edu.

ABOUT THE UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

The University of Massachusetts Medical School attracts more than $300 million in research funding annually, and its innovative programs are the centerpiece of the Massachusetts Life Sciences Initiative. Consistently ranked by *U.S.News & World Report* as one of the leading medical schools in the nation for primary care education, UMMS is a leader in health sciences education, research and public service and home to 2006 Nobel Laureate Craig C. Mello, PhD, co-discoverer of RNA interference. UMMS is the academic partner of UMass Memorial Health Care. To learn more, visit www.umassmed.edu.

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 28 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic and severe and rare/neurodegenerative diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, mipomersen, following regulatory approval, which is expected in 2012. 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 the discovery, development and potential of drugs for severe and rare diseases, and the development, activity, therapeutic potential and safety of ISIS-SMN_{Rx}. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of mipomersen, 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, 2010 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, including Regulus Therapeutics Inc., its jointly owned subsidiary.

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