ISIS Reports Phase 1 Data Demonstrating ISIS-TTRRx Produces Significant Reductions in TTR Protein

January 5, 2012

CARLSBAD, Calif., Jan. 5, 2012 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today results from a Phase 1 study with ISIS-TTRRx. The results demonstrated that treatment with ISIS-TTRRx produced dose-dependent statistically significant reductions of greater than 80 percent in transthyretin (TTR) protein. In this study, ISIS-TTRRx was generally well tolerated with no significant adverse events. ISIS-TTRRx is an antisense drug in development with GlaxoSmithKline (GSK) for the treatment of TTR amyloidosis, a severe and rare genetic disease characterized by progressive dysfunction of peripheral nerve and/or heart tissues. Isis and GSK are planning to begin a clinical study on ISIS-TTRRx this year designed to achieve an efficient route to registration.

"TTR amyloidosis is a fatal disease that affects approximately 50,000 patients worldwide. Patients with familial amyloid polyneuropathy, or FAP, experience TTR build up in their peripheral nerves and experience the loss of motor functions, such as walking. These patients also experience the accumulation of TTR amyloid in the heart, causing familial amyloid cardiomyopathy (FAC), and in their intestinal tract, which prevents the proper absorption of nutrients, leading to death. Since current treatments are highly limited, there is a great need to develop a drug that can reduce TTR levels thereby preventing, and potentially reversing, progression of this disease," said Merrill D. Benson, M.D., Professor of Medical Genetics at Indiana University.

"Currently the most effective way to retard progression of FAP is a liver transplant. However, many patients with FAP are unable to receive a liver transplant due to availability of a donor liver or the patient's diminished health. In the small number of patients who do receive a transplant, their quality of life is substantially compromised. Although, liver transplant replaces mutant TTR, amyloid formation continues due to accumulation of normal TTR protein," said Richard Geary, Ph.D., Senior Vice President of Development at Isis. "ISIS-TTRRx blocks the production of both normal and mutant TTR, thereby preventing further amyloid accumulation, which may prevent, and potentially reverse, disease progression."

The Phase 1 study of ISIS-TTRRx was a blinded, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of ISIS-TTRRx in healthy volunteers. ISIS-TTRRx was evaluated in single and multiple doses ranging from 50 mg per week up to 400 mg per week. After only four weeks of dosing, subjects in the 200 mg and 400 mg multiple-dose cohorts displayed a mean reduction of 44 percent and 81 percent in TTR levels, respectively. ISIS-TTRRx was generally well tolerated in all subjects.

"In this study, we observed substantial dose-dependent reductions in TTR protein of greater than 80 percent. Based on the mechanism of action and the early data we have presented, we believe that ISIS-TTRRx could provide benefit to patients with FAP," said Brett Monia, Ph.D., Senior Vice President, Drug Discovery and Corporate Development of Isis. "Together with our partner GSK, we are finalizing the development plan for ISIS-TTRRx, which is intended to achieve an efficient route to registration. Our next clinical study for ISIS-TTRRx will begin in 2012 and evaluate the effects of the drug on disease progression and other measures of disease burden/improvements on quality of life in patients with FAP."

ABOUT ISIS-TTRRx
Transthyretin amyloidosis is a genetic disease in which the patient inherits a mutant gene that produces a misfolded form of TTR, which progressively accumulates in tissues, impairing their function. In patients with transthyretin amyloidosis, both the mutant and normal forms of TTR can build up as fibrils in tissues, including heart, peripheral nerves, and the gastrointestinal tract. The presence of TTR aggregates interferes with the normal functions of these tissues, and as the TTR protein aggregates enlarge more tissue damage occurs and the disease worsens. There are two common types of transthyretin amyloidosis, familial amyloid cardiomyopathy, or FAC, which affects more than 40,000 patients worldwide, and FAP, which affects more than 10,000 patients worldwide. Patients with FAC have TTR build up in the heart muscle and succumb to heart failure five to six years after symptom onset. Patients with FAP have TTR build up in peripheral nerve tissue leading to the loss of nerve function and wasting. ISIS-TTRRx is an investigational drug that is designed to inhibit the production of all forms of TTR, and could offer an alternative approach to treat all types of transthyretin-related amyloidosis.

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 Isis' collaboration with GlaxoSmithKline, the discovery, development and potential of drugs for severe and rare diseases, and the development, activity, therapeutic potential and safety of ISIS-TTRRx. 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.

SOURCE Isis Pharmaceuticals, Inc.

CONTACT: Kristina Lemonidis, Director, Investor Relations, +1-760-603-2490, or Amy Blackley, Ph.D., Assistant Director, Corporate Communications, +1-760-603-2772