



Isis Initiates Phase 1 Study of ISIS-PTP1BRx to Treat Type 2 Diabetes

July 21, 2011

CARLSBAD, Calif., July 21, 2011 /PRNewswire via COMTEX/ --

Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has initiated a Phase 1 clinical study for ISIS-PTP1BRx, an antisense drug for the treatment of type 2 diabetes targeting protein tyrosine phosphatase-1B, PTP-1B. ISIS-PTP1BRx is designed to increase the body's sensitivity to the natural hormone insulin, resulting in better glucose control for patients with type 2 diabetes. Because of its unique mechanism ISIS-PTP1BRx has the potential to contribute to the treatment of type 2 diabetes without causing weight gain or hypoglycemia. The reductions in LDL-C produced by PTP-1B inhibition should also provide an added benefit to patients.

"We are developing ISIS-PTP1BRx for patients whose glucose is inadequately controlled by insulin or oral therapies. Having demonstrated the attractive profile of a PTP-1B inhibitor with ISIS 113715, we are now proceeding with the development of a more potent PTP-1B inhibitor," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Disorders and Translational Medicine at Isis. "We believe that ISIS-PTP1BRx could be a safer insulin sensitizer. The only class of insulin sensitizers currently available also broadly affects the transcription of multiple genes, which leads to side effects. Some of these side effects, such as increases in LDL-C, weight gain, and thinning of bones are particularly problematic in diabetics. Because ISIS-PTP1BRx selectively reduces only the PTP-1B protein, a mechanism distinct from current insulin sensitizers, it is unlikely to have those side effects."

Earlier Phase 2 studies of ISIS 113715 provided evidence of the therapeutic potential of inhibiting PTP-1B. In those studies, PTP-1B inhibition improved glucose control and reduced LDL-C in both newly diagnosed diabetic patients and in patients who were taking sulfonylureas. Those studies also showed that PTP-1B inhibition did not cause weight gain, another substantial advantage in the treatment of diabetic patients who are frequently obese and at high cardiovascular risk. The data from these studies support the development of ISIS-PTP1BRx and should allow a very rapid route to clinical proof-of-concept.

ISIS-PTP1BRx has the potential to be broadly useful in combination with most of the other commonly used drugs to treat patients with diabetes, including insulin, GLP-1 agonists, and more traditional drugs like metformin. The initial clinical development plan for ISIS-PTP1BRx will focus on treating diabetic patients who are inadequately controlled on insulin, helping them utilize insulin more efficiently; and patients who are beginning to fail oral therapies, extending the time they have before becoming dependent on insulin.

ABOUT ISIS-PTP1BRx

ISIS-PTP1BRx is an antisense drug that targets PTP-1B, a phosphatase that negatively regulates insulin receptor signaling and is responsible for turning off the activated insulin receptor. Reducing PTP-1B enhances insulin activity. Scientists have long recognized PTP-1B as an attractive target to treat diabetes, but due to structural similarities among closely related proteins, pharmaceutical companies have had difficulty identifying small molecule drugs with sufficient specificity to be safe. ISIS-PTP1BRx selectively inhibits the production of PTP-1B without affecting other closely related proteins that, when inhibited, could lead to unwanted side effects. ISIS-PTP1BRx may offer new treatment to patients who do not respond adequately to currently available therapies such as glitazones, sulfonylureas, metformin, and GLP-1 based therapies, and has the potential to be used in combination with such other therapies.

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 24 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, a sanofi company, plans to commercialize Isis' lead product, mipomersen, 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 development, activity, therapeutic potential and safety of Isis' antisense inhibitors of PTP-1B including ISIS-PTP1BRx and planned commercialization of mipomersen. 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, 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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