



Isis Reports Positive Phase 1 Data Demonstrating ISIS-FXIRx Reduces Factor XI Activity Without Bleeding

December 12, 2011

CARLSBAD, Calif., Dec. 12, 2011 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive results from a Phase 1 study with ISIS-FXIRx. The results demonstrated that treatment with ISIS-FXIRx produced dose-dependent statistically significant reductions of up to 78 percent in Factor XI activity. ISIS-FXIRx was safe and well tolerated with no increase in bleeding. These data were presented today at the 2011 American Society of Hematology (ASH) Annual Meeting in San Diego.

"High levels of Factor XI increase the risk of thrombosis, aberrant blood clot formation that is responsible for most heart attacks and strokes and is the number one cause of death and disability in the United States and worldwide. Elevated levels of Factor XI also increase the risk of venous thrombosis, a common problem after surgery, particularly major orthopedic procedures, such as knee or hip replacement. Although currently available anticoagulants (blood thinners) reduce the risk of these complications, they are associated with increased bleeding that can be fatal," said Jeffrey Weitz, M.D., F.A.C.P., F.R.C. P.(C), Professor of Medicine at McMaster University and Executive Director of the Thrombosis and Atherosclerosis Research Institute. "Factor XI is a unique target for new blood thinning therapies because Factor XI plays a key role in clot formation, but its inhibition does not induce bleeding. Consequently, Factor XI-targeted therapy holds the promise of reducing thrombosis with a potentially better safety profile than currently available anticoagulants."

In the oral presentation titled "ISIS-FXIRx, A Novel and Specific Antisense Inhibitor of Factor XI, Significantly Reduces FXI Antigen and Activity and Increases aPTT Without Causing Bleeding in Healthy Volunteers" Dr. Sanjay Bhanot presented the results of a Phase 1 study evaluating ISIS-FXIRx in healthy volunteers. This Phase 1 study was a double blind, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of ISIS-FXIRx and to assess the initial effects of the drug on Factor XI activity as measured with an assay that employs activated partial thromboplastin time (aPTT), a common measure of clotting time. ISIS-FXIRx was evaluated in single and multiple doses ranging from 50 mg per week up to 300 mg per week.

The study produced the following results:

- Robust, sustained, statistically significant reductions of up to 78 percent and 85 percent in Factor XI protein levels in the 200 mg and 300 mg dose cohorts, respectively. ($p < 0.0001$)
- Robust, sustained, statistically significant reductions of up to 71 percent and 78 percent in Factor XI activity in the 200 mg and 300 mg dose cohorts, respectively. Reductions in activity were accompanied by aPTT prolongation, consistent with preclinical data. ($p < 0.0001$)

ISIS-FXIRx demonstrated a good safety profile and was well tolerated in all subjects with no clinically significant changes in hematology, electrolytes, liver or kidney function. The most common adverse event was a low incidence of mild injection site reactions.

"Although there are a number of anti-coagulants on the market, there is still a substantial need for new and safer drugs. If the activity of ISIS-FXIRx observed in this Phase 1 study is also seen in patients, particularly without an increase in bleeding, this drug could offer a significant improvement over current standard-of-care, since most anti-coagulants result in increase in bleeding. Humans who are deficient in Factor XI have been shown to have a lower incidence of thromboembolic events. Thus, ISIS-FXIRx could also be particularly useful for patients with atrial fibrillation and acute coronary syndrome for the prevention of heart attacks and stroke," said Harry Buller, Ph.D., M.D., Professor of Medicine at Academic Medical Center in Netherlands.

Also at ASH this year, Isis' scientists presented new data in non-human primates demonstrating that a 50 percent or greater decrease in Factor XI activity produced potent anti-thrombotic effects with no bleeding. These data are consistent with previously reported preclinical data in multiple models of venous and arterial thrombosis, in which antisense inhibition of Factor XI produced robust anti-thrombotic effects. In addition, Isis' scientists presented data from experimental surgery models in non-human primates with ISIS-FXIRx. In this study, treatment with ISIS-FXIRx produced a dose-dependent reduction of Factor XI activity of greater than 80 percent after four weeks of treatment with no bleeding. Furthermore, inhibition of Factor XI did not increase bleeding parameters in experimental surgery models compared to control. In contrast, in the same study, treatment with Enoxaparin produced statistically significant increases in bleeding time and loss of blood volume. These data further support the anti-thrombotic potential of reducing levels of Factor XI without an increased risk of bleeding.

"We are very encouraged with the robust and sustained reductions in Factor XI activity we observed in our Phase 1 study with no increase in bleeding even in subjects who reached undetectable levels of Factor XI. In addition, these results are consistent with our preclinical studies in which we observed potent, anti-thrombotic activity without bleeding," said Sanjay Bhanot M.D., Ph.D., Vice President, Clinical Development and Translational Medicine at Isis. "The increase in bleeding associated with currently available anticoagulants prohibits their wide-spread use in patients who are at high bleeding risk. We believe that the safety profile we have seen to date for ISIS-FXIRx, coupled with its robust anti-thrombotic activity indicate that our drug could have a significant impact in reducing aberrant blood clot formation. We plan to initiate a proof-of-concept Phase 2 study evaluating the effects of ISIS-FXIRx in patients who are undergoing total knee replacement surgery in 2012."

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 25 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, activity, therapeutic potential and safety of ISIS-FXIRx. 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.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

SOURCE Isis Pharmaceuticals, Inc.

Kristina Lemonidis, Director, Investor Relations, +1-760-603-2490, or Amy Blackley, Ph.D., Assistant Director, Corporate Communications, +1-760-603-2772, both of Isis Pharmaceuticals, Inc.