Isis Pharmaceuticals Reports Positive Phase 2 Data for ISIS-FXI Rx in the Prevention of Venous Thrombosis in Patients Undergoing Total Knee Replacement Surgery

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Seven-fold lower incidence of VTEs in patients treated with ISIS-FXIRx compared to enoxaparin

CARLSBAD, Calif., May 22, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive top-line data from a Phase 2 comparator-controlled study evaluating the incidence of venous thrombolic events (VTE) in patients treated with ISIS-FXI$_{Rx}$ undergoing total knee replacement surgery, or total knee arthroplasty (TKA). ISIS-FXI$_{Rx}$ inhibits the production of Factor XI, a coagulation factor that plays a key role in thrombosis. In this study with a data cutoff of May 7, 2014, ISIS-FXI$_{Rx}$-treated patients experienced a dose-dependent decrease in VTEs. Patients treated with 300 mg of ISIS-FXI$_{Rx}$ experienced a seven-fold ($p<0.0001$) lower incidence of VTEs compared to patients treated with enoxaparin. Patients treated with 200 mg of ISIS-FXI$_{Rx}$ had comparable incidence of VTEs compared to patients treated with enoxaparin. Patients treated with ISIS-FXI$_{Rx}$ and enoxaparin experienced a very low rate of bleeding with ISIS-FXI$_{Rx}$-treated patients experiencing numerically fewer bleeding events compared to patients treated with enoxaparin. Isis plans to report the full data at an upcoming scientific meeting.

"Thrombosis is the leading cause of morbidity and mortality worldwide. Although warfarin and oral Factor Xa and thrombin inhibitors are effective, there are limitations that preclude their use in a number of indications. In addition, bleeding remains a concern because there are no specific antidotes for the new oral anticoagulants. As such, there remains a significant unmet need for safer and more effective anticoagulants," said Jeffrey Weitz, M.D., professor of medicine and biochemistry, McMaster University, Ontario, Canada. "This study is the first to evaluate a Factor XI lowering strategy in humans and the results validate Factor XI as a novel target for effective antithrombotic therapy. The data show that compared with enoxaparin, ISIS-FXI$_{Rx}$ can significantly lower the risk of venous thromboembolism after elective knee replacement surgery. The incidence of venous thromboembolism with ISIS-FXI$_{Rx}$ are numerically lower than those observed with new oral anticoagulants in this setting. Therefore, ISIS-FXI$_{Rx}$ has the potential to be a best-in-class antithrombotic drug and could be useful in many different therapeutic settings."

"Genetic and preclinical studies clearly suggest that reducing Factor XI should be a more effective means of reducing thrombogenic events than reducing other coagulation factors, and could be associated with very low bleeding risk. In fact, in head-to-head comparisons in animal models, we have shown that inhibiting Factor XI was more effective and produced less bleeding than achieved with warfarin or Factor Xa inhibitors. The results from this Phase 2 study support this attractive profile," said Brett Monia, Ph.D., senior vice president, antisense drug discovery at Isis. "TKA results in a high incidence of VTEs. By evaluating our drug in this therapeutic setting, we have been able to directly compare the activity and safety of ISIS-FXI$_{Rx}$ to enoxaparin, a commonly prescribed anticoagulant. These data suggest that ISIS-FXI$_{Rx}$ has a low bleeding risk and is a more effective antithrombotic agent than enoxaparin. Given the mechanism of Factor XI inhibition, we believe that this drug could be used broadly to prevent VTE in many different therapeutic settings as well as other therapeutic indications requiring safe and effective thromboprophylaxis. We believe based on this robust data package that ISIS-FXI$_{Rx}$ represents a significant licensing opportunity."

The Phase 2 study of ISIS-FXI$_{Rx}$ in approximately 300 patients was a global, multi-center, open-label, comparator-controlled study in patients undergoing TKA. The study compared the safety and activity of ISIS-FXI$_{Rx}$ to enoxaparin. Patients in the ISIS-FXI$_{Rx}$-treated cohorts received either 200 mg or 300 mg of ISIS-FXI$_{Rx}$ for six weeks prior to TKA surgery and a dose six hours and three days after surgery. Patients in the enoxaparin cohort received 40 mg of enoxaparin the evening before TKA surgery, six to eight hours after surgery and daily for at least eight days after surgery. VTEs and bleeding events were evaluated by a blinded independent adjudicated committee.

ISIS-FXI$_{Rx}$ was well tolerated in the study. There were no observed differences in safety compared to the enoxaparin group. There were no flu like symptoms, and injection site reactions were infrequent and mild. There have been no drug-related serious adverse events reported to date.

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 32 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. 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, commercial potential and safety of ISIS-FXI$_{Rx}$. 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, 2013, 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.

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