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

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Seven-fold lower incidence of VTE in patients treated with ISIS-FXI Rx compared with enoxaparin
Data published in New England Journal of Medicine and featured at the American Society of Hematology annual meeting
Isis to host a webcast at 9:00 a.m. ET on Monday, December 8, 2014

CARLSBAD, Calif., Dec. 7, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today final data from its Phase 2 comparator-controlled study evaluating the incidence of venous thromboembolic events (VTE) in patients treated with ISIS-FXI$_{Rx}$ undergoing total knee replacement surgery, or total knee arthroplasty (TKA). ISIS-FXI$_{Rx}$ is designed to reduce the production of Factor XI, a coagulation factor that plays a key role in thrombosis. These data were published in *The New England Journal of Medicine* and will be presented at the 56th American Society of Hematology meeting as a late-breaking oral presentation on Tuesday, December 9, 2014.

"Thrombosis is the leading cause of morbidity and mortality worldwide. Although warfarin and oral Factor Xa and thrombin inhibitors are effective, they have limitations that restrict or prevent their use in several indications. Furthermore, despite the benefit of existing anticoagulants, there is a risk of bleeding when they are administered in therapeutic doses. Consequently, 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. "Because Factor XI is involved in the propagation of clots, but not in their initiation, we hypothesized that reducing Factor XI activity would decrease the risk of deep vein thrombosis after knee replacement surgery without increasing the risk of bleeding. This concept is supported by evidence from patients with congenital Factor XI deficiency; such patients are at reduced risk for venous thrombosis and do not suffer from spontaneous bleeding. The results of this study are important for two reasons. First, these results support the important biological role that Factor XI plays in the development of blood clots after surgery. Second, the results showed that lowering the levels of Factor XI with ISIS-FXI$_{Rx}$ was associated with a reduction in clotting without increasing the risk of bleeding. Therefore, for the first time, we have results that dissociate the antithrombotic effect from bleeding risk."

In the paper and presentation titled 'Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis' the authors report that ISIS-FXI$_{Rx}$-treated patients experienced a dose-dependent decrease in venous thromboembolic events. Patients treated with 300 mg of ISIS-FXI$_{Rx}$ experienced a seven-fold lower rate of VTE as compared with those treated with enoxaparin (4.2% and 30.4%, respectively; $p<0.001$). Patients treated with 200 mg of ISIS-FXI$_{Rx}$ had a rate of VTE comparable to that in patients treated with enoxaparin (26.9% and 30.4%, respectively). The rate of VTE in patients given enoxaparin is within the range documented in previous studies in this therapeutic setting. ISIS-FXI$_{Rx}$ treatment was associated with a dose-dependent and sustained reduction in Factor XI activity that correlated with the lower rate of VTE. The rate of bleeding was low with ISIS-FXI$_{Rx}$ and enoxaparin.

"This study is the first to evaluate a Factor XI lowering therapeutic strategy in patients and the results validate Factor XI as a novel target for antithrombotic therapy. These data show that ISIS-FXI$_{Rx}$ significantly lowered the risk of venous thromboembolism following a highly thromboembolic event, elective knee replacement surgery. The rate of VTE with ISIS-FXI$_{Rx}$ in this Phase 2 study is lower than that observed in the previous studies with the new oral anticoagulants in this surgical setting. These data suggest that ISIS-FXI$_{Rx}$ has the potential to be a best-in-class antithrombotic drug and could be useful in many different therapeutic settings, including patients at high-risk for thrombosis and high risk of bleeding" said Harry Buller, M.D., Ph.D., professor of medicine, department of vascular medicine academic medical center in Amsterdam, Netherlands.

"TKA is associated with a high incidence of postoperative VTE. By evaluating our drug in this therapeutic setting, we were able to directly compare ISIS-FXI$_{Rx}$ with enoxaparin, a commonly prescribed anticoagulant. In this study, the lower incidence of thromboembolic events with ISIS-FXI$_{Rx}$ compared with enoxaparin, combined with the low rate of bleeding, support the concept that ISIS-FXI$_{Rx}$ has the potential to provide a breakthrough therapeutic opportunity for the treatment of thrombosis. By reducing Factor XI activity, we believe that ISIS-FXI$_{Rx}$ could be used to prevent thrombosis in many different therapeutic settings" said Sanjay Bhanot, M.D. Ph.D., vice president, clinical development and translational medicine at Isis Pharmaceuticals. "Given the limitations of currently prescribed anticoagulants, there are many patients who need a safer anticoagulant. We plan to conduct additional Phase 2 studies in patients with the greatest unmet needs, including patients with atrial fibrillation who also have end-stage renal disease. These patients are at the highest risk of stroke, but because the risk of bleeding in these patients is so high, they are rarely prescribed anticoagulants. ISIS-FXI$_{Rx}$ has the potential to change this."

"Our plan is to bring in a partner for later-stage development and commercialization of this program. We have already had considerable interest from potential partners," said Lynne Parshall, chief operating officer at Isis Pharmaceuticals. "Our goal is to identify a partner who has experience with development and commercialization of drugs in this therapeutic area; one who can help us optimize the opportunities this drug represents."

The Phase 2 study of ISIS-FXI$_{Rx}$ in 293 patients undergoing TKA was a global, multi-center, open-label, comparator-controlled study comparing ISIS-FXI$_{Rx}$ with enoxaparin. Patients in the ISIS-FXI$_{Rx}$-treated groups received either 200 mg or 300 mg of ISIS-FXI$_{Rx}$ for six weeks prior to TKA surgery and six hours and three days after surgery. Patients in the enoxaparin group received 40 mg of enoxaparin the evening before surgery, and once daily thereafter for at least eight days. All patients underwent mandatory bilateral venography to detect deep vein thrombosis. Venograms and suspected bleeding events were evaluated by a blinded independent adjudication committee.

In this study, ISIS-FXI$_{Rx}$ was well tolerated. There were no observed differences in safety outcomes compared with enoxaparin. In particular, 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.

The Phase 2 study was published ahead of print and on-line in *The New England Journal of Medicine* on Sunday, December 7, 2014.

Investor Event

At 9:00 a.m. Eastern Time, December 8, 2014, Isis will conduct a webcast to discuss ISIS-FXI$_{Rx}$ data presented at the ASH. A live audio webcast of the presentation will be available on the "Investors & Media" section of the Company's website, www.isispharm.com. Interested parties may listen to the call by dialing 877-443-5662. A replay will be available for a limited time. The slides presented at the ASH meeting will be available on Isis' website at www.isispharm.com on Tuesday, December 9, 2014.

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 34 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 has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include a ISIS-APOCIII$_{Rx}$, a drug Isis is developing to treat patients with severely high triglycerides, such as patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. 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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