



Isis Pharmaceuticals Reports Clinical Data Showing Blunting of Severe Increases in CRP Following Endotoxin Challenge With ISIS-CRP Rx

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Up to 63% Reduction in CRP Response with ISIS-CRP Rx Treatment

CARLSBAD, Calif., March 13, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that ISIS-CRP_{Rx} selectively reduced severe elevations in C-reactive protein (CRP) in humans. Data from a Phase 1 clinical study showed that ISIS-CRP_{Rx} produced statistically significant, dose-dependent reductions in CRP response following an endotoxin challenge, which produces immune responses similar to those seen with bacterial infections. In this study, significant reduction of the endotoxin-induced CRP response was achieved in the healthy volunteers treated with ISIS-CRP_{Rx}, with no changes in other important immune modulators, such as TNF-alpha, IL-6, and other cytokines and chemokines. Selective reduction of CRP could offer a safer approach to treating patients who have chronic inflammatory diseases, such as rheumatoid arthritis, by potentially lowering the risk of infections, a common side effect of other anti-inflammatory drugs, such as TNF-alpha inhibitors. A Phase 2 study of ISIS-CRP_{Rx} in patients with rheumatoid arthritis is currently underway with data anticipated in the middle of this year.

"The study illustrates the considerable specificity of antisense technology to target a single component of a complex immunologic response," said Dr. Paul Ridker of the Brigham and Women's Hospital and the Harvard Medical School. "Thus, the approach shown to be effective here provides an opportunity to evaluate the role of CRP in different inflammatory disorders."

"This study is the first clinical demonstration of selective blunting of severe increases in CRP. The fact that reductions in CRP can be achieved without affecting any other key inflammatory markers supports a potentially valuable profile for CRP inhibition in inflammatory diseases. The selectivity of ISIS-CRP_{Rx} could translate into significant therapeutic benefit, especially in patients who, due to their disease, need to selectively reduce inflammation without suppressing critical immune system functions," said Richard Geary, Ph.D., senior vice president of development at Isis.

The Phase 1 study was a randomized, placebo-controlled, dose-response study designed to assess the effects of ISIS-CRP_{Rx} pretreatment on CRP levels following an endotoxin challenge in 30 healthy subjects. ISIS-CRP_{Rx} was administered six times over the course of 22 days (days 1, 3, 5, 8, 15 and 22) at a dose of 400 mg or 600 mg. At day 26, all subjects were administered an endotoxin challenge. Key inflammatory markers were measured just prior to and after the challenge. In this study, ISIS-CRP_{Rx} blunted severe increases in CRP levels by 63% (p=0.0011) in the 600 mg cohort and 36% (p=0.023) in the 400 mg cohort compared to placebo subjects at the time of peak CRP response (24 hours post challenge). No changes in other inflammatory markers were observed. Subjects receiving placebo had a mean baseline level of CRP of 1 mg/L and experienced robust, acute increases of CRP levels of greater than 30 times normal levels after the endotoxin challenge, which returned to baseline after 72 hours. ISIS-CRP_{Rx} was well tolerated with no serious adverse events observed and no dose limiting toxicities.

"ISIS-CRP_{Rx} is the first drug to selectively reduce CRP protein in humans. CRP levels are frequently elevated in many inflammatory diseases, and patients with chronic elevation of CRP have increased disease burden and worse outcomes. As such, we believe that ISIS-CRP_{Rx} could provide patients with therapeutic benefit in numerous diseases with large commercial opportunities," said Stanley T. Crooke, M.D., Ph.D., chief executive officer and chairman at Isis.

ISIS-CRP_{Rx} is currently being evaluated in a Phase 2 study in patients with rheumatoid arthritis, an autoimmune disease where CRP is chronically elevated. In these patients, the degree of CRP elevation correlates with the severity of inflammation. ISIS-CRP_{Rx} is also being evaluated in a Phase 2 study in patients with atrial fibrillation, a condition that involves an irregular and often rapid heart rate. In patients with atrial fibrillation, elevated levels of CRP are associated with an increase in the severity of atrial fibrillation episodes. By selectively lowering CRP in these diseases, ISIS-CRP_{Rx} could provide significant therapeutic benefit to these patients. Isis plans to report data from the rheumatoid arthritis study in the middle of this year and from the atrial fibrillation study in the first half of 2014.

"Our Phase 2 program is designed to show benefit in diseases where elevated levels of CRP are predictive of disease severity, like atrial fibrillation and rheumatoid arthritis. If positive, data from one or both of these studies will be evidence of the large potential of this drug in a variety of inflammatory diseases and conditions," concluded Dr. Crooke.

ABOUT ISIS-CRP_{Rx}

ISIS-CRP_{Rx} is an antisense drug that is designed to inhibit the production of C-reactive protein (CRP). For many years, CRP has been used as a clinical biomarker of disease activity with an inflammatory component, such as cardiovascular disease, Crohn's

disease, rheumatoid arthritis and end-stage renal disease. Elevated levels of CRP have been linked to coronary artery disease and a growing body of evidence from clinical trials implicated CRP in cardiovascular disease progression. Although CRP's active participation in these diseases remains to be determined, several lines of evidence support a causal role of CRP in disease, suggesting that it may be therapeutically beneficial to decrease CRP levels.

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, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO™, in the United States for the treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets, including Europe. 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-CRP_{Rx}. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, 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, which is on file with the SEC. Copies of this 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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