



Isis Pharmaceuticals Reports That Its Selective CRP Inhibitor Demonstrated Activity in a Phase 1 Study

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Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today the results from a Phase 1 clinical trial in which ISIS-CRPRx produced statistically significant reductions in C-reactive protein (CRP) in the cohort of subjects in the study with elevated CRP. In this study, ISIS-CRPRx was well tolerated at doses up to 600 mg/week. Isis plans to evaluate ISIS-CRPRx in Phase 2 studies in indications that could provide early proof-of-concept in diseases with elevated CRP. Isis plans to initially evaluate ISIS-CRPRx in multiple myeloma and rheumatoid arthritis, before expanding into cardiovascular and other diseases.

"CRP levels are increased in many inflammatory disorders, and excessive amounts of CRP have been linked to multiple clinical conditions, including cardiovascular disease and diabetes," said Paul M. Ridker, M.D., Eugene Braunwald Professor of Medicine at the Brigham and Women's Hospital and Harvard Medical School. "This is the first evaluation of a selective CRP inhibitor and the first such drug shown to be active in man. What this new agent thus provides is a method to directly test whether or not lowering CRP per se might be beneficial for patient care, something that could not be addressed in the past."

The Phase 1 study of ISIS-CRPRx was a blinded, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of ISIS-CRPRx as well as to assess the initial effects of the drug on baseline CRP levels. ISIS-CRPRx was evaluated in single and multiple doses ranging from 50 mg per week to 600 mg per week in 80 healthy volunteers. In all but one cohort, Isis enrolled subjects who had normal (generally undetectable to less than 2 mg/L) CRP levels. In the 600 mg per week multi-dose cohort, Isis enrolled eight subjects with elevated levels of CRP. The subjects enrolled in this cohort had an average CRP level at baseline of approximately 3.0 mg/L. After only three weeks of dosing, the six subjects who received ISIS-CRPRx had an average CRP level of 0.76 mg/L, which is within the normal range of CRP and represents an average reduction of greater than 70 percent compared to placebo. Subjects receiving placebo remained elevated above 3.0 mg/L. In all subjects receiving the drug, it was well tolerated with no serious adverse events.

"This is the first study evaluating the activity of a selective CRP inhibitor, and we are extremely pleased with the activity and safety of ISIS-CRPRx. Based on the substantial reductions in CRP that we observed in the cohort of subjects who had elevated levels of CRP, we expect to see CRP reductions at much lower doses in our Phase 2 studies. In these studies, we will evaluate ISIS-CRPRx in patients with elevated CRP levels in a variety of diseases, including multiple myeloma and rheumatoid arthritis. The results from these initial studies will help us inform the rest of our Phase 2 development program for CRP, in which we will expand into other disease areas," commented Richard Geary, Ph.D., Senior Vice President of Development at Isis. "Chronically elevated levels of CRP have been linked to cardiovascular disease and associated with a worsening of overall outcome in conditions such as end-stage renal disease, suggesting that lowering CRP in these patients could be beneficial."

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 24 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis has designed and executed a patent strategy that has provided the Company with strong and extensive protection for Isis' drugs as well as all aspects of antisense drug discovery, development and manufacturing. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis Pharmaceuticals and the discovery, development and potential of ISIS-CRPRx. 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, 2009 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.

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