ISIS 301012 Continues to Produce Attractive Lipid Reduction

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ISIS 301012 Treatment Produced 60% Reduction in apoB-100 and 54% Reduction of LDL

CARLSBAD, Calif., Aug. 4 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today data from an additional Phase 1 301012 study in which ISIS 301012 produced rapid reductions of its target, apoB-100, with concomitant reductions in low density lipoprotein (LDL or "bad" cholesterol). Less than one month following dosing, healthy volunteers achieved a median reduction of 60% in apoB-100 and a median reduction of 54% in LDL. In the study, six healthy volunteers with mildly elevated cholesterol levels were treated with approximately 350 mg/week of ISIS 301012 for one month. No treatment-related serious adverse events were reported. Lowering cholesterol levels is a key component in the management of coronary artery disease. ISIS 301012 selectively targets apoB-100, the protein component of LDL cholesterol. The data will be presented by Mark Wedel, MD, JD, Vice President of Clinical Research and Chief Medical Officer of Isis Pharmaceuticals, at the Southeast Lipid Association 8th Annual Scientific Forum in Pinehurst, North Carolina.

"We continue to be very encouraged by the rapid, significant reduction of lipids observed with ISIS 301012. The data from this study are consistent with data from our earlier Phase 1 301012 study, further demonstrating the ability of ISIS 301012 to lower cholesterol. The long duration of effect was also similar to what we observed in our earlier study," Dr. Wedel said. "With statin-like lipid reductions via a non-statin mechanism, ISIS 301012's attractive profile continues to show significant promise as an alternative for patients who are not tolerating statin therapy or as add-on therapy for the lowering of cholesterol in patients failing to reach their therapeutic target. As such, it has the potential to address a substantial market opportunity since cardiovascular disease is one of the leading causes of death in the world."

In June of this year, Isis announced positive results from a Phase 1 study of ISIS 301012 in which ISIS 301012 produced rapid, dose-dependent, and prolonged reductions of its target, apoB-100, with concomitant reductions in LDL, very low density lipoprotein and total cholesterol levels. ISIS 301012 produced average reductions in apoB-100 from 30% (50mg) to 52% (400mg), average reductions in LDL from 17% (50mg) to 48% (400mg), and average reductions in total cholesterol from 16% (50mg) to 40% (400mg).

Isis plans to commence a series of Phase 2 trials in the second-half of 2005 to optimize dose and schedule of ISIS 301012 as monotherapy, to explore pharmacology in combination with statins and to study the effects of ISIS 301012 in patients with familial hypercholesterolemia (FH). FH is a genetic disorder characterized by lethally high lipid levels. An oral formulation of ISIS 301012 is currently in Phase 1 studies. Isis plans to report data from the oral study in the second half of 2005.

ABOUT CARDIOVASCULAR DISEASE

According to the World Health Organization, heart disease and stroke kill 17 million people a year, which is almost one-third of all deaths globally. By 2020, heart disease and stroke will become the leading cause of both death and disability worldwide, with the number of fatalities projected to increase to over 20 million a year and by 2030 to over 24 million a year.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. 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 11 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the development, therapeutic potential and safety of ISIS 301012 targeting apoB-100 and in treating high cholesterol and cardiovascular disease. Any statement describing Isis' goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. 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 products. 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, 2004, and its quarterly report on Form 10-Q for the quarter ended March 31, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.
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