ISIS 301012 Produces Significant and Durable Reductions in Cholesterol in Humans

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CARLSBAD, Calif., June 9 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today final data from a clinical trial in which ISIS 301012 produced rapid, dose-dependent, and prolonged reductions of its target, ApoB-100, with concomitant reductions in low density lipoprotein (LDL or "bad" cholesterol), very low density lipoprotein (VLDL) and total cholesterol levels. These reductions occurred after only one month of dosing, and lasted more than 100 days. 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.

"ISIS 301012 is already showing the potential for an attractive profile, validating what we saw in pre-clinical studies, and we are excited about moving it forward in clinical development," said Mark Wedel, MD, JD, Isis' Vice President of Clinical Research and Chief Medical Officer. "ApoB-100 has been of great interest in the cardiovascular community because of its critical role in cholesterol transport, and is a molecular target uniquely approachable with antisense technology. This unique means of lowering LDL cholesterol may enable more people than ever before to reach their recommended target levels of LDL with drug treatment."

The goal of this placebo-controlled, dose-escalation Phase 1 study was to measure the safety and pharmacokinetic profile of ISIS 301012, and its ability to reduce several components of cholesterol important in the management of cardiovascular disease. The study enrolled 36 volunteers with elevated cholesterol, and tested ISIS 301012 doses of 50mg, 100mg, 200mg and 400mg. After an initial single dose for safety evaluation, subjects received a three dose loading regimen, followed by a once weekly subcutaneous dose for three weeks.

Study Highlights:
-- ISIS 301012 produced the following results:

-- Average reductions in ApoB-100 from 30% (50mg) to 52% (400mg). Effects of 200mg ISIS 301012 observed on Day 39 (14 days after the last dose) on ApoB-100 differed from placebo by P=0.006.

-- Average reductions in LDL from 17% (50mg) to 48% (400mg). Effects of 200mg ISIS 301012 observed on Day 39 on LDL differed from placebo by P=0.002.

-- Average reductions in total cholesterol from 16% (50mg) to 40% (400mg). Effects of 200mg ISIS 301012 observed on Day 39 on total cholesterol differed from placebo by P=0.0006.

-- Effects of the 100mg dose group were also highly statistically significant.

-- The minimum active dose in the study was 50mg per week.

-- ISIS 301012's onset of action was rapid, with reductions in ApoB-100 and lipids observed immediately after the loading regimen.

-- Reductions in ApoB-100 and associated decreases in LDL, VLDL, and total cholesterol were prolonged and lasted longer than 100 days in some subjects in the 100mg and 200mg groups. In contrast, placebo-treated volunteers demonstrated negligible ApoB-100 or lipid reductions during the study.

-- No treatment-related serious adverse events have been reported.

-- The most commonly reported side effect was mild, dose-related skin reactions at the site of subcutaneous injections, which did not interfere with continued treatment and were comparable in frequency and similar in degree to skin reactions observed with other subcutaneously administered drugs.

"In this study, we saw in normal volunteers remarkable pharmacology consistent with an antisense mechanism. The long duration of effect suggests that ISIS 301012 may be administered as infrequently as once a quarter," said Dr. Wedel. "Next, we want to determine the optimal dose and schedule and evaluate it in combination with statins and other agents. The goal for this drug is that it be used in combination with currently available therapeutics in patients who remain at risk despite statin therapy. We will first develop ISIS 301012 in familial hypercholesterolemia (FH), a genetic disorder. Individuals with the disorder have incredibly high lipid levels and, as a consequence, die very early of cardiovascular disease. FH patients are not

adequately controlled on currently available lipid-lowering medications such as statins, and many of these patients end up requiring apheresis. This relatively short term opportunity will be pursued while developing the drug for less severe forms of FH as well as the traditional polygenic hypercholesterolemia."

Additional phase 2 trials will commence in the second-half of 2005 to explore ISIS 301012 as a monotherapy to optimize dose and schedule, as a combination to statins, and in patients with FH. An oral formulation of ISIS 301012 is currently in phase 1 studies.

ABOUT CARDIOVASCULAR DISEASE

The American Heart Association estimates that nearly 105 million American adults have borderline high cholesterol and approximately 46.5 million have levels of 240 or above. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. According to the National Institutes of Health, cardiovascular disease is the leading cause of death in the U.S.

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 system that has the potential to revolutionize the identification of 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 http://www.isispharm.com .

This press release includes forward-looking statements regarding the development, therapeutic potential and safety of the oral and subcutaneous formulations of ISIS 301012 targeting ApoB-100 and in treating high cholesterol and cardiovascular disease. Any statement describing our 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. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. 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 on Form 10-K for the year ended December 31, 2004, and 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.

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