

Isis Pharmaceuticals Expands Therapeutic Potential of Antisense Technology To Cardiovascular Disease

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MONTREAL, May 21 /PRNewswire-FirstCall/ -- ISIS 147764, an antisense inhibitor of ApoB-100, normalized or lowered cholesterol levels in animal models of cardiovascular disease, according to data presented at the 11th International Congress on Cardiovascular Pharmacology in Montreal, Canada. The data reported are the first to emerge from Isis' newly established cardiovascular drug discovery program and demonstrate the expanding therapeutic potential of antisense technology into cardiovascular disease. ApoB-100 is the carrier of LDL cholesterol, the "bad" lipid involved in heart disease. ISIS 147764 is being developed by Isis Pharmaceuticals, Inc. (Nasdaq: ISIS).

"ApoB-100 is an exciting target for lowering cholesterol, and we believe our work in cardiovascular disease is further evidence of the remarkable efficiency of antisense drug discovery," said C. Frank Bennett, Isis' Vice President, Antisense Research. "Over 15 months, three scientists have explored more than 20 cardiovascular gene targets in vitro and have evaluated many of these genes in animal models. Our cardiovascular research team is focused on advancing many new, more potent and highly specific cholesterol-lowering drugs as potential candidates for clinical study."

ApoB-100 is a target that has been of interest to the pharmaceutical industry for many years, but has been considered "undruggable" by traditional approaches. ApoB-100 resides in fat, and is therefore difficult for conventional drugs to access.

In the study, treatment with a second-generation antisense inhibitor of ApoB-100 for 6 weeks in mouse models of dyslipidemia caused a dose-dependent reduction in all components of cholesterol commonly measured in monitoring heart disease. These animals were obese and had high cholesterol. Total cholesterol, very low density lipoprotein (VLDL), high density lipid (HDL) and low density lipid (LDL) levels were measured before, during and after treatment with ISIS 147764. As a result of treatment, a 50% reduction of total cholesterol was observed in addition to a 15% reduction in VLDL and an 88% decrease in LDL. Significant reductions in triglyceride levels were also observed. Further, the decrease in cholesterol correlated with a decrease in both ApoB-100 protein and RNA levels in the liver, demonstrating an antisense mechanism of action. No adverse events or toxicities were noted.

ISIS 147764 was discovered through Isis' evaluation of the effects of antisense inhibition of multiple enzymes in the lipid-synthesis pathway. This drug is the first potential development candidate to emerge from the company's cardiovascular research program.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene® (formivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline, with two in late-stage development and six in Phase II human clinical trials. Affinitac™ (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of more than 900 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isispharm.com.

This press release contains forward-looking statements concerning the potential profile of ISIS 147764 and the potential and prospects of Isis' cardiovascular drug discovery program. Any statement describing a goal, expectation, intention or belief of the company 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 financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the company's Annual Report on Form 10-K for the period ended December 31, 2001, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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