

## Isis Pharmaceuticals Reacquires ISIS 113715 Type 2 Diabetes Drug from Merck

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Isis to Initiate Phase I Trials of Antisense Drug for Type 2 Diabetes

CARLSBAD, Calif., Dec. 23 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has reacquired full product rights to ISIS 113715, its preclinical Type 2 diabetes antisense drug candidate, from Merck & Co., Inc. (NYSE: MRK). Isis plans to initiate human clinical trials of ISIS 113715 rapidly in the first half of 2003.

"During the past year, we have compiled a strong preclinical package and are now planning the Phase I clinical trials. We believe this is a compound that can potentially offer distinct advantages over existing treatments and is a significant commercial opportunity for Isis," said Stanley T. Crooke, M.D., Ph.D., Isis' Chairman and CEO. "While we are disappointed that Merck has decided not to invest further in this drug, we are more enthusiastic than ever about the potential of ISIS 113715 as a treatment for Type 2 diabetes."

ISIS 113715, Isis' second-generation antisense inhibitor of PTP-1B, improves the regulation of blood sugar levels in models of Type 2 diabetes. Maintenance of appropriate blood sugar levels is essential to the management of this disease. The following are key findings of the preclinical studies:

- \* ISIS 113715 produced normalization of blood sugar levels in multiple rodent models, which are industry-accepted predictors of probable efficacy in humans.
- \* ISIS 113715 also improved glucose tolerance test results in normal and obese monkeys.
- \* ISIS 113715 did not produce hypoglycemia following administration of doses as high as 20 times greater than the estimated clinical dose.
- \* ISIS 113715 did not cause weight gain, a characteristic of many other Type 2 diabetes treatments. This is an advantageous effect since more than 50% of Type 2 diabetes patients are obese.
- \* ISIS 113715 can be administered once a week or potentially up to once a month by subcutaneous injection.
- \* ISIS 113715 has demonstrated consistent reduction of PTP-1B mRNA and protein levels in liver and fat, key tissues known to be important in the regulation of blood sugar levels.
- \* ISIS 113715 may be a candidate for oral administration, as it is a compound based on Isis proprietary second-generation chemistry (2'-O- methoxyethyl).

ISIS 11375 inhibits expression of the gene encoding PTP-1B, a phosphatase enzyme that acts as an insulin receptor regulator. Insulin receptors are cell surface proteins that notify the cell of when sugar is present in the blood. Antisense inhibition of PTP-1B expression enables insulin receptors to stay active longer, allowing for more sugar uptake into cells, and thereby lowering sugar levels in the bloodstream.

Isis will conduct a live webcast conference call to discuss this news on, Monday, December 23 at 10 a.m. Eastern time. To participate over the Internet go to <http://www.isispharm.com>. A replay of the webcast will be available at this address for up to 30 days.

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. Affinitak™ (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 1000 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 <http://www.isispharm.com>.

This press release contains forward-looking statements concerning the commercial and therapeutic potential of ISIS 113715. 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 and quarterly report on Form 10-Q for the periods ended December 31, 2001 and September 30, 2002, respectively, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

Vitravene® is a registered trademark of Novartis AG.

GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc.

Affinitak™, a trademark of Eli Lilly and Company, is an investigational cancer compound being developed through an alliance between Lilly and Isis Pharmaceuticals, Inc. and marketed globally by Lilly.

