

# Isis Pharmaceuticals Extends Drug Discovery Collaboration With Lilly

August 8, 2005

## Collaboration Adds Cancer Drug Targeting STAT-3

CARLSBAD, Calif., Aug 08, 2005 /PRNewswire-FirstCall via COMTEX/ -- Isis Pharmaceuticals (Nasdaq: ISIS) today announced the extension of its antisense drug discovery collaboration with Eli Lilly and Company (NYSE: LLY). As the initial four-year term of the broad, strategic alliance comes to its pre-planned end, the companies are extending their relationship and will continue to collaborate on mutually agreed targets for approximately 24 months.

"We have benefited from our collaboration with Lilly and together the companies have advanced the technology. Lilly has several antisense drug candidates derived from the collaboration that are in or approaching clinical trials. The goal of this extension is to continue identifying additional candidates for the Lilly pipeline," said Stanley T. Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis Pharmaceuticals.

Isis and Lilly will continue to advance antisense drugs identified during the previous collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis scientists will be supported by collaboration funds, and Lilly scientists will be supported by Lilly. As part of the extension, the companies agree to add a second-generation antisense inhibitor to Lilly's oncology drug discovery and development portfolio, Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis will be entitled to receive milestones and royalties as this antisense inhibitor moves through various stages of development. This activity adds to the two other antisense oncology drugs in development at Lilly, one which is targeted to Survivin and one targeted to eIF-4E. The extended collaboration also provides Lilly access to Isis patents to support Lilly's internal antisense drug discovery program for a limited number of targets.

"Isis is a leader in RNA-based drug discovery and we look forward to continuing our productive collaboration with them," said William W. Chin, M.D., Vice President for Discovery Biology and Clinical Investigation at Lilly.

In connection with the extension, Isis converted the \$100 million interest-free loan provided by Lilly into 2.5 million shares of Isis common stock according to the terms of the original agreement. Lilly has agreed not to sell the conversion shares until the fourth quarter of 2006 (assuming the collaboration is not terminated earlier), in exchange for certain credits against milestones and royalties in the event of a stock price decline.

"The \$100 million loan funded our four-year strategic research collaboration from which two drug candidates emerged. The loan was shown on our books as debt, so we are pleased that we've also substantially improved our balance sheet in this transaction," said B. Lynne Parshall, Isis' Executive Vice President and Chief Financial Officer. "The terms of the collaboration are attractive to both parties and provide Lilly with continuing access to the technology for their own drug discovery efforts while the companies continue to work together on selected targets. We are pleased to contribute new, cutting-edge drug candidates to Lilly's pipeline."

### ABOUT STAT-3

Signal Transducer and Activator of Transcription 3 (STAT-3), is a protein that regulates cell division and growth, and prevents cell death. In preclinical studies, antisense inhibition of STAT-3 significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer. STAT-3 is active in a wide range of cancers, including both solid and hematological cancers. Activated STAT-3 is present in numerous malignancies including head, neck, prostate, breast and lung cancers, and in multiple myeloma, anaplastic lymphoma, chronic myeloid leukemia and melanoma. The control of both the activation and inactivation of STAT-3 are equally important to maintain normal cell growth.

### 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 Isis 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](http://www.isispharm.com).

This press release includes forward-looking statements regarding the extension of Isis' cancer collaboration with Eli Lilly and Company and the development, therapeutic potential and safety of antisense inhibitors for the treatment of cancer. 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

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