

## Isis Pharmaceuticals and Eli Lilly and Company Renegotiate Affinitak(TM) Manufacturing Relationship

June 5, 2003

CARLSBAD, Calif., June 5 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that the company and Eli Lilly and Company have reached a mutually beneficial renegotiation of their manufacturing relationship. Lilly has waived repayment of the \$21 million manufacturing loan it provided Isis to build the Affinitak™ manufacturing facility. Lilly has also agreed to allow Isis to use the facility to manufacture other drugs, including drugs in Isis' pipeline and drugs arising out of research collaborations with partners, such as the broad antisense drug discovery collaboration with Lilly. In exchange, Isis has agreed to release Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from Isis and the obligation to pay for the costs of maintaining an idle manufacturing suite.

Isis built a state-of-the-art, commercial scale manufacturing facility, initially dedicated to Affinitak and financed with the loan from Lilly. Isis completed this facility in February 2003. The facility is fully qualified and is capable of producing hundreds of kilograms per year of antisense drugs.

"The manufacturing facility created through our partnership with Lilly is an important strategic asset for Isis as we advance the development of our 13 antisense products and drugs from our collaborators, including Lilly," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "This resolution to our manufacturing commitment enables Isis to maximize the value of the facility. The transaction demonstrates the strong partnership between the companies, which is further evidenced in the continued progress of our broad collaboration to discover antisense drugs."

"Our financial strength is enhanced by this agreement, as our long-term debt will be reduced," said Ms. Parshall. "The transaction is essentially neutral in terms of its impact on our profit-and-loss statement and cash balance."

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® (fomivirsen), 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 five in Phase II human clinical trials. Affinitak™ (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III development 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 1,200 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 diagnosis of infectious organisms and the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

This press release contains forward-looking statements concerning Isis' manufacturing capabilities, the potential for our products in our pipeline, and the potential value of the company's drug discovery technology platform. 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 on Form 10-Q for the period ended March 31, 2003, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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

Vitravene® is a registered trademark of Novartis AG.

SOURCE Isis Pharmaceuticals, Inc.