

Isis Pharmaceuticals Retires \$32 Million in Convertible Partner Debt With Low-Interest Five-Year Loan

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CARLSBAD, Calif., Dec. 17 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), announced today that it has retired approximately \$32 million in partner debt using a new five-year, 4% term loan from Silicon Valley Bank. The retired convertible partner debt was due from 2003 to 2005 and carried interest rates ranging from 8.5% to 12%.

"The advanced payments of these notes strengthens Isis' balance sheet by preserving the company's cash balance," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "By refinancing this debt we've taken advantage of historically low interest rates and minimized shareholder dilution."

"Furthermore, this transaction simplifies our debt structure," said Ms. Parshall. "Our debt now consists primarily of this loan, the interest free loan from Eli Lilly and Company, and our publicly traded convertible debt. Our Lilly loan is due in 2005 and is repayable, at Isis' option, in cash or Isis stock at \$40 a share. Our convertible notes are due in 2009."

The retired partner debt was held by Boehringer Ingelheim International GmbH and Elan Corporation plc. As part of its collaboration with Boehringer Ingelheim, Isis borrowed a total of \$23.5 million in principal and interest. The funds were used for Isis' share of collaboration research and development. During Isis' Orasense™ collaboration with Elan, Isis borrowed money under a convertible promissory note, most of which was paid off in 2002 when the collaboration ended. The funds from Elan were used to continue the development of oral formulation technology for 2nd generation antisense drugs and an oral form of ISIS 104838. Isis regained commercial rights to the technology and the product upon termination of the Orasense collaboration. With this low-interest loan, Isis repaid Elan the remaining \$8.1 million of debt.

Isis Pharmaceuticals, Inc., is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has successfully commercialized the world's first antisense product, and has 11 antisense products in development. In the company's GeneTrove™ program, Isis uses antisense technology as a tool to determine the function of genes and uses that information to direct the company's internal drug discovery research and that of its corporate partners. Through its Ibis Therapeutics™ program, Isis is developing a novel diagnostic tool to detect infectious organisms and is focused on the discovery of small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,300 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release contains forward-looking statements concerning the financial position and clinical goals of Isis Pharmaceuticals, Inc. 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 year ended December 31, 2002 and Form 10-Q for the period ended September 30, 2003, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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