

Antisense Drug Targeting Survivin Inhibits Growth Of Tumors In Animal Models

November 20, 2003

Data Support Clinical Development

Eli Lilly and Company and Isis Pharmaceuticals Report Preclinical Data at AACR-NCI-EORTC International Conference

INDIANAPOLIS & CARLSBAD, Calif.--(BUSINESS WIRE)--Nov. 20, 2003-- Eli Lilly and Company (NYSE:LLY) and Isis Pharmaceuticals, Inc. (Nasdaq:ISIS) today announced LY2181308 a second-generation antisense drug that targets survivin, inhibited tumor growth in animal models. Antitumor activity was associated with significant reduction of survivin expression in tumors, evidence that the drug was working through an antisense mechanism. These data were presented yesterday at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston. Survivin is a molecule that promotes cell survival. These cells would otherwise undergo programmed cell death, a natural process in the cell life cycle. Survivin is expressed in a vast majority of cancers, but not in normal tissue.

"These are among the first reported data to demonstrate antitumor activity in vivo using a drug that specifically inhibits survivin expression. As an antisense drug, LY2181308 binds to survivin RNA, enabling it to inhibit the production of a target considered undruggable by traditional protein-binding approaches," said Dr. Richard Gaynor, vice president for cancer research and clinical investigation at Lilly. "The over expression of survivin in a wide variety of tumors makes it an exciting target for drug development. We look forward to the advancement of this novel compound for the treatment of cancer."

"These results broaden the extensive preclinical package Isis and Lilly have developed for LY2181308 by demonstrating potent antitumor activity in animals. We are enthusiastic about this survivin antisense drug, the first product to be selected for clinical development from our broad-antisense drug discovery collaboration with Lilly. We believe antisense drugs have the potential to benefit patients with cancer and numerous other diseases," said Frank Bennett, Vice President Antisense Research for Isis.

LY2181308 demonstrated consistent activity in both human xenograft tumor models and multiple cancer cell lines derived from the lung, colon, breast, prostate, ovary, cervix, skin and brain, according to data presented by Dr. Bharvin K. R. Patel, research scientist at Lilly, in a poster entitled "Antisense Inhibition of Survivin Expression as a Cancer Therapeutic." Inhibition of survivin by LY2181308 produced the following results:

- Inhibition of tumor growth as demonstrated in animal models
- Antitumor activity associated with selective inhibition of survivin protein expression and with no effects on other anti-apoptotic proteins
- Induction of programmed cell death as evidenced by:
 - multinucleated cells in both animal models and cell lines
 - induction of Cyclin B1 expression in the tumors in animal models
 - cell cycle arrest at G2/M phase of the cell division cycle, and
 - concentration-dependent increase in caspase-3 activity in tumor cells

Lilly licensed LY2181308 from Isis as a part of the cancer drug discovery collaboration the companies previously initiated. The oncology relationship builds on a broad, ongoing strategic alliance established by Isis and Lilly to discover antisense drugs in the areas of inflammatory and metabolic diseases.

About Antisense

Antisense inhibitors work at the molecular level by binding to messenger RNA to interrupt the process by which disease-related proteins are produced. Antisense drugs can be designed to treat a wide range of diseases. Due to their gene selectivity, they have the potential to be highly effective and less toxic than traditional small molecule drugs.

About Lilly

Lilly, a leading innovation-driven corporation is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Indiana, Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

About Isis

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 regarding Isis Pharmaceuticals and its partnership with Eli Lilly and Company, and the potential of the companies' antisense drug discovery partnerships, and the therapeutic potential and safety of LY2181308. Any statement describing a goal, expectation, intention or belief of Isis or Lilly 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 the research of Lilly or Isis research and development programs are described in additional detail in the companies' Annual Reports on Form 10-K, for the period ended December 31, 2001,

and subsequent quarterly reports on Form 10-Q which are on file with the U.S. Securities and Exchange Commission, copies of which are available from both companies. The companies undertake no duty to update forward-looking statements.

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Contact:

317-276-6987 - Asia Martin (Lilly)

760-603-3880 - Karen Lundstedt (Isis)