First Drug From Isis Pharmaceuticals and Lilly's Drug Discovery Alliance Enters Phase 1 Clinical Trials in Cancer

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Isis Earns Milestone Payment From Lilly

CARLSBAD, Calif., Nov. 17 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that LY2181308, the first antisense drug to emerge from its drug discovery alliance with Eli Lilly and Company (NYSE: LLY), has moved into Phase 1 clinical trials in cancer patients, marking a significant milestone in the partnership. For the accomplishment of this milestone, Isis earned a $1.5 million payment from Lilly. This is the second milestone Isis has achieved in the development of this second-generation antisense drug, which was licensed to Lilly in April 2003, and the third milestone achieved in the collaboration overall. Recently, Isis announced that Lilly licensed a second anti-cancer drug LY2275796 for clinical development. The companies' oncology collaboration, initiated in June 2002 and extended earlier this year, is part of the companies' broad, strategic alliance to discover antisense drugs.

"Moving LY2181308 into clinical trials is an important event for the Isis-Lilly collaboration. It demonstrates that we are realizing the goal of the partnership, which is to discover new RNA-based drugs for cancer as well as for inflammatory and metabolic diseases," said C. Frank Bennett, Ph.D., Isis' Vice President, Antisense Research. "LY2181308 is the first drug to successfully inhibit survivin, a molecule that has received considerable attention in the cancer community and the pharmaceutical industry."

LY2181308 was selected by Lilly for clinical trials based on compelling preclinical data. Specifically, it has:

- Demonstrated consistent activity in human xenograft tumor models and multiple cancer cell lines derived from the lung, colon, breast, prostate, ovary, cervix, skin and brain;
- Produced anti-tumor activity in animals that is associated with selective inhibition of survivin protein expression with no effects on other anti-apoptotic proteins;
- Shown additive effects with several chemotherapeutic agents, and
- Confirmed an antisense mechanism of action for the drug in cell culture and in animals.

LY2181308 targets survivin, a molecule that supports the survival of cells that would normally die through programmed cell death or apoptosis. Survivin helps in the abnormal growth of cancer cells, and is abundant in many types of cancers, including colon, brain, lung, skin and others, but nearly nonexistent in normal cells and tissues.

"Lilly has made a substantial commitment to antisense through our broad research partnership, the largest RNA-based drug discovery alliance in the industry. We are pleased that this collaboration is successfully producing new drugs for Lilly's high quality and innovative product portfolio," continued Dr. Bennett. "We will continue to apply the strength of our technology, experience and expertise in multiple antisense mechanisms, including RNase H, siRNA and RNA splicing, and advanced chemistries to discover additional antisense drugs that can add significant value to Lilly's pipeline."

ISIS' ANTI-CANCER DRUG DISCOVERY AND DEVELOPMENT PARTNERSHIPS

The entry of LY2181308 into the clinic further strengthens Isis' robust cancer franchise that is supported through both strategic partnerships and internal research and development. In addition to Isis' drug discovery partnership with Lilly, the company has several ongoing collaborations that are focused on identifying new antisense drugs for the treatment of a variety of tumors.

With Isis' assistance, OncoGenex Technologies is developing OGX-011, an inhibitor of clusterin. Clusterin is a cell survival protein that, when overproduced, prevents cancer cell death and counters the effectiveness of standard anti-tumor treatments.

OGX-011 is a second-generation antisense drug being developed to sensitize tumors resistant to existing treatments such as chemotherapy, hormone ablation therapy and radiation therapy. The companies have reported results from a Phase 1 study showing that once-weekly intravenous administration of OGX-011 is well-tolerated, achieves excellent drug concentration in target tissue, and produces up to a 91% dose-dependent down-regulation of its target, clusterin, in prostate cancer.

In 2003, Isis and OncoGenex expanded their antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug candidate, OGX-225. The compound is the first bi-specific antisense inhibitor, a single-stranded antisense drug designed to inhibit the production of two proteins simultaneously, to enter preclinical development. OGX-225 targets both insulin-like growth factor binding protein-5 (IGFBP-5) and insulin-like growth factor binding protein-2 (IGFBP-2), two molecules involved in the development of metastatic disease in hormone-regulated tumors such as prostate and breast.

Isis is also working with Ercole Biotech, a company focused on discovering antisense drugs that regulate alternative RNA splicing. Through this collaboration, Ercole received a license to Isis' Bcl-x preclinical antisense drug. This drug inhibits the production of splice variants of the Bcl-x gene, which is involved in the regulation of apoptosis, or programmed cell death.

Additionally, Isis continues its internal drug discovery efforts in oncology, recently adding ISIS 345794 to its clinical development pipeline. ISIS 345794 is a second-generation antisense drug that targets STAT-3, a protein known to be an important transcription factor that turns on genes required for the division, growth and death of cells. Activation of STAT-3 is known to contribute to the formation and development of tumors.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases, and cancer. Through its Ibis Therapeutics® program, Isis is developing a biosensor to identify infectious organisms, and is discovering 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 1,400 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis' collaborations with Eli Lilly and Company, OncoGenex Technologies and Ercole Biotech and the development, therapeutic potential and safety of LY2181308, LY2275796, OGX-011, OGX-225, ISIS 345794 and an antisense inhibitor of Bcl-x in treating cancer. Any statement describing our 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' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press 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 Isis' Annual Report on Form 10-K for the year ended December 31, 2003, and quarterly report on Form 10-Q for the quarter ended September 30, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

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