Isis Pharmaceuticals Updates Operating Plan For 2003

April 2, 2003

Company Implements Employee Stock Option Exchange Program and Provides Financial Guidance for the Year

CARLSBAD, Calif., April 2 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its updated operating plan and the implementation of an employee stock option exchange program and provided financial guidance for 2003. The operating plan enables the company to continue to aggressively develop its antisense drugs and maintain the company's leadership position in RNA-based technology while sustaining its strong cash position.

The modified operating plan reflects the impact of the results of the Phase 3 trial of Affinitak™ in patients with non-small cell lung cancer, which were not sufficient to support a single-study new drug application. Therefore, Isis will not receive revenue in 2003 from Affinitak success milestones, as the opportunity for the commercialization of this drug has been delayed. Isis is implementing expense reduction measures, including a modest reduction in workforce, to ensure the company has resources to maintain its business momentum through 2006 or longer.

Operating Plan
Isis' 2003 operating plan is based upon the following factors:
-- Strong financial position
The company ended 2002 with $289 million in cash and has over $100 million in committed cash from existing partners through 2005. Therefore, cash plus cash commitments total nearly $400 million. Isis' debt is favorably structured, with high conversion prices and long-term maturity dates.

-- Effective management of resources
The company is implementing a number of cost containment measures, including a reduction of its workforce by 9%. A significant number of the positions affected were in support of the commercialization and manufacture of Affinitak. There will be a one-time charge associated with this restructuring.

-- Focus on advancement of pipeline to key development milestones
The company's pipeline is comprised of two drugs in Phase 3 clinical trials, five products in Phase 2 and several in Phase 1 and preclinical development, all of which have significant commercial potential. The size and diversity of its pipeline provides Isis with many opportunities for clinical success. A list of upcoming clinical goals is included later in this release.

"We are very enthusiastic about the potential of our product pipeline, and we have taken appropriate steps to manage our resources in a manner that will enable us to reach many key drug development milestones in the near-term," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "We are also excited about the progress in our antisense drug discovery programs with both Lilly and Amgen."

Employee Stock Option Exchange Program

Isis plans to implement an employee stock option exchange program to ensure that it maintains one of the company's key assets, its employee base, in a manner that is sensitive to shareholder interests. The program will allow employees to elect to surrender higher-priced options, granted prior to January 5, 2002, in exchange for a lesser number of lower-priced options.

Key features of the program include:
-- Facilitation of employee retention
-- Exercise price of replacement options is the greater of $5 or the closing price of Isis' common stock on the day of the grant, projected to be on or around April 29, 2003.
-- Vesting of options restarts upon exchange.

-- Potential for reducing number of shares outstanding
-- The exchange of eligible options will be made according to a

variable exchange ratio based on the price of the original options. The exchange ratios range from a three-to-one (3:1) ratio for original options priced greater than $20, to a one-and-a-half-to-one (1.5:1) ratio for original options priced in the range of equal-to-or-greater-than $5 to less than $10.

-- Should Isis exchange all the outstanding eligible options subject to the offer, it would grant replacement options to purchase approximately 3.6 million shares of its common stock in exchange for the return of stock options to purchase approximately 6.5 million shares.

"Isis employees have significant expertise in RNA-based drug discovery and development. Retaining our people is paramount to the success of the company, our drugs and antisense technology," Ms. Parshall continued. "We believe this stock option exchange program will assist us in continuing long-term employee incentive in a manner that has the potential to reduce total shares outstanding."

The replacement options will be treated as variable awards and thus will subject the company to non-cash compensation charges in accordance with variable accounting rules.

Financial Guidance

-- Isis' projected operating loss for 2003 is in-line with the company's objective to end the year with more than three years of cash Based on Isis' expense management measures, its anticipation for reduced revenue from the delay of Affinitak commercialization, and its commitment to aggressively develop its pipeline, the company expects its loss from operations for 2003 to be in the mid-$70 million range, excluding current year restructuring charges and non-cash compensation expenses associated with the employee option exchange program. With reasonable assumptions for new sources of revenue and cash, the company believes it has sufficient resources to fund activities through 2006 or longer. In this timeframe, Isis expects to advance multiple products to key clinical milestones.

"We recognize that the most direct route to generating value for shareholders is through the commercialization of antisense drugs, and we continue to execute plans to accomplish this objective," concluded Ms. Parshall.

Clinical Development Goals

Isis will continue to advance the development of its large product pipeline. The drug development goals for the 2003-2004 timeframe are as follows:

First Half 2003

-- Report results from Phase 2 study of alicaforsen enema in UC/pouchitis at the upcoming Digestive Diseases Week (DDW) meeting
-- Report results from Phase 2 studies of ISIS 2503 at an upcoming meeting of the American Society of Clinical Oncology (ASCO)
-- Initiate Phase 2 trials of ISIS 14803 in combination with current therapy in hepatitis C (HCV)
-- Initiate a Phase 1 study of ISIS 113715 for Type 2 diabetes
-- Initiate Phase 1 trials of at least one additional preclinical drug (Isis or partner)
-- Add cardiovascular compound to development pipeline

Second Half 2003

-- Report results of ISIS 104838 Phase 2 studies in rheumatoid arthritis
-- Report final results of ongoing Phase 2 study of ISIS 14803 in HCV
-- Report results of Phase 1 trial of ISIS 113715 in Type 2 diabetes; initiate Phase 2 trial
-- Complete trials to optimize oral solid dosage form of second-generation antisense drugs

First Half 2004
-- Complete enrollment of Phase 3 studies and report performance of alicaforsen in Crohn's disease
-- Complete enrollment of Phase 2 studies and report performance of alicaforsen in ulcerative colitis
-- Report results of Phase 2 trial of ISIS 113715 in Type 2 diabetes
-- Report results of Phase 2 studies of ISIS 14803 in combination with current therapy in HCV
-- Initiate clinical trials of Isis' first antisense drug for cardiovascular disease, an inhibitor of ApoB-100

Webcast Conference Call

Isis will conduct a live webcast conference call to discuss this press release on Wednesday, April 2 at 10 a.m. Eastern time. To participate over the Internet go to www.isispharm.com . A replay of the webcast will be available at this address for up to 30 days.

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 12 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 a Phase III trial 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 nearly 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 .

ISIS PHARMACEUTICALS, INC. HAS NOT COMMENCED THE OFFER TO EXCHANGE THAT IS REFERRED TO IN THIS COMMUNICATION. UPON THE COMMENCEMENT OF THE OFFER TO EXCHANGE, ISIS WILL FILE WITH THE SECURITIES AND EXCHANGE COMMISSION A COMPLETED SCHEDULE T/O AND RELATED EXHIBITS AND DOCUMENTS, INCLUDING THE OFFER TO EXCHANGE. ALL ISIS OPTIONHOLDERS ELIGIBLE TO PARTICIPATE IN THE OFFER TO EXCHANGE ARE STRONGLY ENCOURAGED TO READ THE SCHEDULE T/O AND RELATED EXHIBITS AND DOCUMENTS, INCLUDING THE OFFER TO EXCHANGE, WHEN THESE BECOME AVAILABLE. THESE DOCUMENTS WILL CONTAIN IMPORTANT INFORMATION ABOUT THE OFFER TO EXCHANGE. THE SCHEDULE T/O AND RELATED EXHIBITS AND DOCUMENTS WILL BE AVAILABLE WITHOUT CHARGE AT THE SECURITIES AND EXCHANGE COMMISSION WEBSITE AT WWW.SEC.GOV AND WILL BE AVAILABLE WITHOUT CHARGE FROM ISIS TO ALL ISIS OPTIONHOLDERS ELIGIBLE TO PARTICIPATE IN THE OFFER TO EXCHANGE.

This press release includes forward-looking statements concerning the financial position of Isis Pharmaceuticals, the therapeutic and commercial potential of compounds developed by the company and the potential value of the company's drug discovery programs. 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, including those statements that are described as Isis' 2003 drug development, research and financial goals within the body of this press release. 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 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 the company's Annual Report on Form 10-K for the period ended December 31, 2002, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

SOURCE Isis Pharmaceuticals, Inc.