Alicaforsen (ISIS 2302) Improves Potential for Responses and Remissions

October 21, 2002

in Patients With Crohn's Disease

Isis to Provide Conference Call Update on Clinical Programs, Including Status

of the Two Phase III Trials of Affinitac That Remain Blinded

SEATTLE, Oct. 21 /PRNewswire-FirstCall/ -- Results of an open-label Phase II clinical trial of alicaforsen (ISIS 2302) in patients with Crohn's disease show that the antisense drug may produce clinical disease remissions when patients receive appropriate doses of the drug. Thirteen of 22 patients (59 percent) achieved a response as defined by a 70 point reduction in Crohn's Disease Activity Index (CDAI) score. Nine of the thirteen responders, 41 percent of the total patients in the trial, achieved a clinical remission. Clinical remission was defined as a CDAI score of less than or equal to 150, with no increase in the use of corticosteroids or immunosuppressives, or need for surgery for Crohn's disease. Findings from the Phase II study were presented at the 67th Annual Scientific Meeting of the American College of Gasteroenterology yesterday. Alicaforsen is an antisense inhibitor of Intercellular Adhesion Molecule-1 (ICAM-1) that is being developed by
Isis Pharmaceuticals, Inc., (Nasdaq: ISIS). The company is currently conducting two, 150-patient Phase III clinical trials of alicaforsen in patients with Crohn's disease. The trials are taking place in the U.S., Canada and Europe.

While this is a relatively small, uncontrolled trial, these data are compelling as they demonstrate that alicaforsen, at the doses used in this study, appears to have a beneficial effect on patients with Crohn's disease by inducing remissions, said Charles F. Barish, M.D., of Wake Research Associates in Raleigh, North Carolina, and lead clinical investigator of the Phase II study. Further, these findings support the continued clinical development of alicaforsen in Crohn's disease and corroborate the dosing regimen that is currently being studied in Phase III clinical trials.

The randomized, uncontrolled, efficacy, pharmacokinetic and safety study enrolled 22 patients with a mean baseline CDAI score of 304. The drug was administered at fixed doses designed to approximate

4 -5 mg/kg of ideal body weight three times a week for four weeks by intravenous infusion. The doses studied were approximately 2.5 times greater than those previously studied. Patients responding to treatment were followed for six to twelve months. All patients in the study remained on their Crohn's disease medications, including corticosteroids and immunosuppressives, during the treatment period. However, tumor necrosis factor alpha (TNF-alpha) treatments, including infliximab, were discontinued for more than 3 months prior to patients' starting the trial.

Summary of Key Alicaforsen (ISIS 2302) Findings:

Remission and response rates

In the study of 22 patients, 17 were evaluable for response. Patients were considered evaluable for response if they received more than three infusions of alicaforsen.

-- 59% of the total patients (13 of 22) and 76% of evaluable patients

(13 of 17) achieved a response.

-- 41% of the total patients (nine of 22) and 53% of evaluable patients

(nine of 17) experienced a clinical remission.

-- Five of the nine patients with clinical remission achieved a complete

clinical remission, as they were corticosteroid and

immunosuppressive-free after treatment with alicaforsen.

-- Four of five patients previously treated with infliximab responded to

alicaforsen treatment. Three of these achieved clinical remission.

Pharmacokinetics

-- The pharmacokinetic properties of alicaforsen observed in the study are

consistent with previous trial experience, where distribution of drug

predominately occurs in lean body tissue and not to fat tissue.

Safety

-- Infusion related reactions such as fever, chills and nausea were

observed in several patients and caused some to discontinue treatment

early. The symptoms were managed with Tylenol® (acetaminophen) and

corticosteriods.

-- This experience was used to design the Phase III clinical trials to

avoid infusion-related events. In the Phase III study, patients

receive doses of Tylenol and corticosteroids with initial doses of

alicaforsen.

With this Phase II trial, we have gained valuable experience with alicaforsen in Crohn's disease and we are optimistic about the potential of this late-stage compound, said F. Andrew Dorr, M.D., Isis' Vice President and Chief Medical Officer. The results of this study are supportive of the Phase III trials in progress in Crohn's disease.

ICAM-1 is one of a family of molecules (known as Cellular Adhesion Molecules, or CAMs) that can be found on the surface of virtually every cell in the body, including cells that line the gastrointestinal tract. CAMs are important to many human body functions such as, 1) organ/tissue development and maintenance, 2) movement or travel of immune and inflammatory cells to sites of inflammation, 3) initiation and transmission of immune responses, and 4) wound healing.

Webcast Conference Call

Isis will conduct a live webcast conference call to discuss the data described in this press release and provide an update on the company's late-stage clinical programs on Monday, October 21, at 5:30 pm Eastern time.

Clinical Program Update: Affinitac

Included in the discussion will be the status of the two ongoing randomized, controlled Phase III trials of Affinitac in patients with non-small cell lung cancer, each of which remain blinded.

-- The most advanced Phase III trial, which is studying the effects of

Affinitac in combination with carboplatin and paclitaxel, completed

enrollment of 600 patients in January 2002. Eli Lilly and Company and

Isis expect to report the results of this trial in early 2003 and file

a new drug application (NDA) based on a single study if the data are

sufficiently positive.

-- The second Phase III trial, being conducted by Lilly, is studying the

effects of Affinitac in combination with Gemzar and cisplatin. Lilly

has decided to add a third treatment arm to this study to more fully

evaluate the dosing schedules available to Affinitac. The dosing

schedule used in this new treatment arm is identical to that being

evaluated in the ongoing Phase III trial of Affinitac in combination

with carboplatin and paclitaxel. Lilly plans to enroll approximately

1000 patients in total in this second Phase III trial. If the results

of this trial are used in a two-study NDA, Lilly anticipates its

submission in the late-2004 to 2005 timeframe, pending the progress of

enrollment.

Other Program Update

-- We will review upcoming newsflow opportunities for ISIS 14803 in

hepatitis C, ISIS 104838 oral formulation development and ISIS 2503 in

pancreatic cancer.

To participate in the webcast conference call over the Internet, go to our website at www.isispharm.com or to www.firstcallevents.com/service /ajwz368358248gf12.html . 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® (formivirsen), 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 six in Phase II human clinical trials. Affinitac™ (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III trials 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 1000 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 discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isispharm.com .

This press release contains forward-looking statements about the potential of the investigational compound alicaforsen (ISIS 2302) in the treatment of

Crohn's disease and plans for and prospects of Affinitac, each of which is the subject of two ongoing Phase III trials. 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 and quarterly report on Form 10-Q for the periods ended December 31, 2001 and June 30, 2002, respectively, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

Affinitac™, 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.

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