Alicaforsen (ISIS 2302) Improves Clinical Symptoms of Pouchitis Patients

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Results Support Antisense Drug Development Program in Inflammatory Bowel Disease

ORLANDO, Fla., May 21 /PRNewswire-FirstCall/ -- Patients with pouchitis experience an improvement in clinical disease symptoms after receiving treatment with alicaforsen (ISIS 2302), an antisense inhibitor of the inflammatory target Intercellular Adhesion Molecule-1 (ICAM-1), according to results of an open-label, uncontrolled Phase II clinical trial. Improvements in endoscopic scores observed in the trial suggest there is long-term benefit of ICAM-1 inhibition in the treatment of pouchitis, an inflammatory bowel disease (IBD). Philip B. Miner, Jr., M.D., of The Oklahoma Foundation for Digestive Research, and principal investigator of the Phase II study, presented findings from the study yesterday at the 2003 Digestive Disease Week (DDW) meeting. Alicaforsen is being developed by Isis Pharmaceuticals, Inc., (Nasdaq: ISIS). The company has a broad development program for alicaforsen in IBD, including Phase III clinical trials in patients with Crohn's disease, and Phase II studies in patients with ulcerative colitis.

The study was designed to evaluate both the efficacy and the safety of alicaforsen. The trial enrolled 12 patients with pouchitis. Patients received 240 mg of alicaforsen nightly for six weeks by enema administration, and will be followed for up to one year. Results from the first eight patients and one month of follow-up were reported at DDW. The primary endpoint of the trial was improvement in the Pouchitis Disease Activity Index (PDAI), a commonly used 18-point system that evaluates patients' symptom score, endoscopy and histology (each category is scored on a 0-6 scale). To date, clinical evaluation and endoscopy have been performed at baseline and at weeks 3, 6 and 10, and histologic assessment was done at baseline and at weeks 6 and 10.

DATA HIGHLIGHTS

-- Mean PDAI for all patients in the study decreased from a baseline value of 11.1 to 6.3 at week 10 (p=0.008), with no change in histology score.
-- Patients in the trial experienced a significant improvement in mean endoscopic scores after 3 weeks of treatment (from baseline value of 5.0 to 2.6 at week 3, p=0.03) with sustained improvement of at least 1 month after completion of treatment (1.6 at week 10, p=0.008).
-- Clinical benefit was also observed when evaluating the clinical PDAI (clinical symptom score and endoscopy). Mean clinical PDAI score decreased rapidly from a baseline value of 8.8 to 4.8 (p=0.008)at 3 weeks and was maintained through week 10.
-- No significant adverse events were observed.

"The effects observed in this trial are dramatic and impressive. While this is a small patient group, the efficacy demonstrated by alicaforsen suggests that patients with disease in ileal pouches can experience meaningful improvement in their condition with nightly alicaforsen enemas," said Dr. Miner. "Further, these data support the theory that ICAM-1 inhibition by alicaforsen can be of benefit to patients with IBD conditions, and provide additional evidence of the drug's potential value in ulcerative colitis and Crohn's disease."

ABOUT POUCHITIS

According to the Crohn's and Colitis Foundation of America, pouchitis is an Inflammatory Bowel Disease. When patients with ulcerative colitis or familial polyposis syndromes have a colectomy to manage their disease, a surgeon may create a continent ileostomy or an ileal pouch. An ileal pouch is created by the removal of the colon and rectum and the formation of an internal pouch from the small bowel, which is joined to the anal muscles. The surgical construction of an ileal pouch connected to the anal canal has revolutionized the treatment of patients requiring a total colectomy. Unfortunately, inflammation in the pouch often causes symptoms of pain, urgency and bleeding as troublesome as the original disease.

ABOUT ALICAFORSEN

Alicaforsen (ISIS 2302) is an antisense inhibitor of ICAM-1, a molecule that plays a key role in a wide range of inflammatory and autoimmune conditions such as pouchitis, ulcerative colitis and Crohn's disease. In pouchitis specifically, ICAM-1 influences lymphocyte function, pivotal in cell trafficking, and is over-expressed in pouchitis. ICAM-1 is part of a molecular family (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 inflamed gastrointestinal (GI) tract. Alicaforsen (ISIS 2302) is also being studied in an intravenous formulation for Crohn's disease and an enema formulation for ulcerative colitis.

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 13 antisense products in its development pipeline with two in late-stage development and five in Phase II human clinical trials. Affinitak™, an inhibitor of PKC-alpha, is in Phase III development for non-small cell lung cancer and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in two Phase III trials for Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of more than 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 development of a diagnostic tool to detect biological agents and 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

pouchitis, ulcerative colitis and Crohn's disease and the potential of Isis' drug development 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. 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 Isis' Annual Report on Form 10-K and quarterly report on Form 10-Q for the periods ended December 31, 2002 and March 31, 2003, respectively, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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