



Isis Pharmaceuticals Updates Positive Clinical Data on Multiple Antisense Drugs

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Company Summarizes Encouraging Study Results on Four Antisense Drugs Presented at Recent Scientific Meetings in the Third Quarter 2003

CARLSBAD, Calif., Oct. 27 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced positive data from clinical trials of four antisense drugs for the treatment of four diseases. Final results from Phase 2 studies of ISIS 104838 in patients with rheumatoid arthritis and ISIS 14803 for the treatment of the hepatitis C virus (HCV) were presented last weekend at the 67th Annual Meeting of the American College of Rheumatology (ACR) and the 54th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), respectively. Updated results of a Phase 2 study of alicaforsen (ISIS 2302) in patients with pouchitis were presented at the 67th Annual Scientific Meeting of the American College of Gastroenterology (ACG) and results from a Phase 1 study involving ISIS 113715 for type 2 diabetes were reported at the Nucleic Acid World Summit in September.

"The recent positive results from multiple drugs in a variety of diseases demonstrate antisense technology's broad applicability, and add to the growing body of evidence that antisense drugs are active in man," said Jon T. Holmlund, M.D., Isis' Vice President, Development.

"We are particularly enthusiastic about the data from our proprietary second-generation drugs, ISIS 104838 and ISIS 113715, as they are showing early, encouraging activity as predicted by animal models," said Dr. Holmlund. "The targets for these drugs, TNF-alpha mRNA and PTP-1b mRNA, are attractive because they have endpoints that can be readily measured in clinical trials and provide evidence of pharmacologic activity early in clinical development. For example, data from the biomarker trial of ISIS 104838 clearly demonstrate reduction of target by an antisense drug in patients' synovium, a target tissue in rheumatoid arthritis. Additionally, normal volunteers receiving ISIS 113715 required less insulin to normalize glucose after a glucose challenge. Isis' proprietary second-generation antisense drugs represent a significant advance as they are more potent, safer and dosed less frequently than antisense drugs based on earlier chemistries."

CLINICAL DATA SUMMARY

Second-Generation Compounds Advance:

Phase 2a Biomarker Trial of ISIS 104838 in Patients with Rheumatoid Arthritis

ISIS 104838 accumulated in synovial tissue in a dose-dependant manner, reducing TNF-alpha mRNA levels in patients with rheumatoid arthritis (RA) who received 300 mg of the second-generation antisense drug, according to final results from the 20-patient Phase 2a study.

This trial was designed to evaluate the ability of ISIS 104838 to reach synovial tissue and reduce the level of TNF-alpha mRNA in synovium, the lining surrounding joints that is inflamed in patients with RA. In the randomized trial, patients received six doses of 100 mg or 300 mg of ISIS 104838 or placebo over one month. Synovial tissue lining patients' knees or wrists was biopsied at the start of the trial and at the end of the treatment period. Key findings from the trial include:

- * ISIS 104838 accumulated in synovium, a fundamental target tissue in RA, and the amount of drug in tissue correlated with dose.
- * Subcutaneous injections were as effective at producing accumulation in the target tissue as intravenous infusions, demonstrating the feasibility of self-administration.

- * As concentrations of ISIS 104838 in synovial tissue increased, the amount of TNF-alpha mRNA in synovium decreased.

- * Patients treated with the 300 mg dose experienced a greater reduction in swollen and tender joints compared to placebo treated patients
 - ISIS 104838 treated patients achieved a 35% decrease in mean swollen joints at the end of the treatment period (Day 29) and a 28% decrease at the end of treatment follow up (Day 85), compared to baseline. Placebo-treated patients experienced a 25% decrease in mean swollen joints at Day 29 and a 16% decrease at Day 85, compared to baseline.
 - Similarly, ISIS 104838 treated patients experienced a 26% decrease in mean tender joints at the end of the treatment period (Day 29) and a 18% decrease at the end of treatment follow up (Day 85), compared to baseline. Placebo treated patients experienced a 19% decrease in mean tender joints at Day 29 and a 1% increase at Day 85, compared to baseline.
 - These findings suggest an early placebo response following intensive treatment visits that waned by the end of follow up, as well as a drug response that continued through the end of the follow up period.

- * ISIS 104838 was well tolerated.

Nathan Wei, M.D., Clinical Director of the Arthritis and Osteoporosis Center of Maryland and the study's lead investigator, presented these results at ACR on Saturday, October 25th.

A 160-patient Phase 2 placebo-controlled, dose ranging trial of ISIS 104838 in rheumatoid arthritis is currently in progress. The company plans to report results from this trial by the end of the year.

Randomized, Double-blind Phase 1 Healthy Volunteer Trial of ISIS 113715

for Type 2 Diabetes

In a Phase 1 study, ISIS 113715 decreased the amount of insulin necessary to normalize blood glucose. ISIS 113715 is an inhibitor to protein tyrosine phosphatase (PTP-1B), a target which has long been pursued and found to be an "undruggable" target using traditional drug discovery methods.

Twenty healthy volunteers received ISIS 113715 or a placebo by parenteral administration for one week in the dose-escalation trial. The pharmacologic activity of the two highest doses of ISIS 113715, 5.0 mg/kg and 7.5 mg/kg, was assessed with a glucose tolerance test. This test measures the ability of insulin to normalize blood glucose after the subject is given a significant dose of glucose, a procedure known as a glucose challenge.

All volunteers that received ISIS 113715 (6 of 6) experienced the desired effect, increased insulin sensitivity, meaning that less insulin was required to normalize blood glucose. In contrast, insulin sensitivity was unchanged in placebo treated volunteers (2 of 2). Subjects treated with ISIS 113715 did not experience hypoglycemia, or excessively low blood sugar, which is an adverse effect observed with many currently available treatments for type 2 diabetes. ISIS 113715 was well tolerated. These findings are consistent with data from Isis' robust preclinical experience, which includes data from multiple animal models of diabetes and normal non-human primates.

These results were presented at the Nucleic Acid World Summit in Boston in mid-September.

Isis is initiating Phase 2 clinical trials in type 2 diabetes patients.

"Based on the cumulative data to date, both alicaforsen and ISIS 14803 have the potential to benefit patients with unmet medical needs," said Mark Wedel, M.D., Isis' Vice President, Development and Chief Medical Officer. "We are particularly encouraged by the significance of activity and the prolonged duration of response produced by alicaforsen in patients with pouchitis. Prolonged response has been observed in studies of alicaforsen in ulcerative colitis and Crohn's disease, and is an attribute that has the potential to differentiate alicaforsen from other treatments."

- * Open-label Uncontrolled Phase 2 Trial of Alicaforsen Enema in Patients with Chronic, Unremitting Pouchitis
Pouchitis patients treated with alicaforsen enema in this Phase 2 trial experienced a sustained improvement of up to nine months, based on endoscopic scores that measured the physical signs of inflammation in the lower bowel. The patients enrolled in the trial had failed treatment with a wide variety of alternative therapies. Alicaforsen (ISIS 2302) is an antisense inhibitor of the inflammatory target Intercellular Adhesion Molecule-1 (ICAM-1). These results suggest there is long-term benefit of ICAM-1 inhibition in the treatment of pouchitis, an inflammatory bowel disease (IBD).

In the study, patients received 240 mg of alicaforsen enema nightly for six weeks, and continue to be followed for up to one year. 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). Clinical evaluation and endoscopy were performed at baseline and at weeks 3, 6 and 10, and histologic assessment was done at baseline and at weeks 6 and 10. Results from the 12 patients having up to nine months of follow-up are:

- * Patients showed improvement in their disease as measured by PDAI and clinical PDAI
 - Mean PDAI for all patients in the study decreased from a baseline value of 11.4 to 6.8 after six weeks of treatment. Remission is traditionally defined by a value less than 7. This result was statistically significant ($p=0.001$).
 - 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 9.0 to 4.4 ($p=0.002$) at 6 weeks and was maintained through week 10.
- * The most significant improvement was measured by endoscopic analysis of inflamed tissue. Patients experienced a significant improvement in mean endoscopic scores after 6 weeks of treatment (from baseline value of 5.3 to 2.6, $p=0.0005$) with sustained improvement of up to nine months.
- * Alicaforsen enema was well tolerated.

Philip B. Miner, Jr., M.D., of The Oklahoma Foundation for Digestive Research, and principle investigator of the Phase 2 study presented these findings at ACG in Baltimore on October 15th.

Isis is evaluating alicaforsen in Phase 3 studies for the treatment of Crohn's disease and Phase 2 studies in patients with ulcerative colitis, with results from the trials expected in the second half of 2004.

* Phase 2 Single-Agent Study of ISIS 14803 in Drug-Resistant, Genotype 1 HCV Patients

ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log dose-dependent reductions in plasma virus levels in patients with HCV, according to final results of a Phase 2 study. The majority of patients participating in the three-month study were HCV genotype 1, the most common and difficult to treat form of HCV, and all but four had been previously treated with interferon.

Two doses and two treatment schedules of ISIS 14803 were evaluated in this trial. A total of 43 patients were enrolled, and all patients initially received 2.5 mg/kg of ISIS 14803 three times a week for two weeks. Patients then received 4 mg/kg or 6 mg/kg of ISIS 14803 either once weekly or twice weekly for 10 weeks by intravenous infusion.

- Five of 17 patients receiving 6 mg/kg of ISIS 14803 twice a week experienced viral titer reductions of 1.0 - 3.8 logs; three patients experienced a greater than 3.0 log reduction.
- Based on these data, a dose of 6 mg/kg twice weekly will be studied in further clinical trials.
- In the trial, decreases in viral titers were accompanied by asymptomatic transient increases in alanine aminotransferase (ALT) levels. These data suggest that ALT elevations may correlate with antiviral activity of ISIS 14803.

Stuart C. Gordon, M.D., of William Beaumont Hospital, Royal Oak, Michigan, and first author of the Phase 2 study, presented these data at the AASLD in Boston on Saturday, October 25th.

Isis will conduct a live webcast conference call to discuss this press release on Monday, October 27 at 10:00 am Eastern time. To participate over the Internet, go to www.isispharm.com or to <http://www.firstcallevnts.com/service/ajwz392433780gf12.html>. A replay of the webcast will be available at this address for up to 30 days.

About Rheumatoid Arthritis

According to the Arthritis Foundation, RA affects 2.1 million Americans, mostly women. RA is a systemic disease that affects the entire body and is one of the most common forms of arthritis. RA is characterized by the inflammation of the membrane lining the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and cause damage to bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

About Type 2 Diabetes

According to the American Diabetes Association, diabetes affects nearly 17 million people and type 2 diabetes constitutes 90 percent of those cases.

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 Hepatitis C

According to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), HCV is one of the most important causes of chronic liver disease in the U. S. It accounts for approximately 20% of acute viral hepatitis, 60% to 70% of chronic hepatitis,

and 30% of cirrhosis, end-stage liver disease, and liver cancer. Nearly four million Americans, or 1.8% of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. There are at least six major genotypes and more than 50 subtypes of HCV. Genotypes 1a and 1b are the most common in the U.S. Genotypes 2 and 3 are present in approximately 30% of patients. There is little difference in the severity of disease or outcome of patients infected with different genotypes. However, patients with genotypes 2 and 3 are more likely to respond to interferon and ribavirin. HCV causes an estimated 8,000 to 10,000 deaths annually in the U.S.

About Isis Pharmaceuticals, Inc.

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 concerning the development and therapeutic potential and safety of ISIS 104838, ISIS 113715, alicaforsen and ISIS 14803. 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 on Form 10-Q for the period ended June 30, 2003, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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