



Second-Generation Antisense Drug ISIS 104838 Reduces TNF-alpha In Rheumatoid Arthritis Patients

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Isis Pharmaceuticals Highlights Upcoming Presentation of Trial Results At the 67th Annual Meeting of the American College of Rheumatology

CARLSBAD, Calif., Sept. 18 /PRNewswire-FirstCall/ -- ISIS 104838 reduced TNF-alpha mRNA levels in synovial tissue and stabilized levels of TNF-alpha in blood, according to interim results of a Phase 2a clinical trial in rheumatoid arthritis (RA) patients receiving 300 mg of the second-generation antisense drug. Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that the final results and additional data analyses of this first randomized, placebo- controlled Phase 2a clinical trial of its proprietary second-generation antisense drug for RA will be presented at the 67th Annual Meeting of the American College of Rheumatology (ACR), October 23-28 in Orlando, FL. The Phase 2a trial was designed to evaluate the ability of ISIS 104838 to reach synovial tissue and reduce the level of TNF-alpha in blood and in synovial tissue, the lining surrounding joints that is inflamed in patients with RA. The study also evaluated the pharmacological effect of TNF-alpha inhibition by ISIS 104838 in patients with RA.

The abstract of the Phase 2a trial, entitled "Synovial Biomarker Study of ISIS 104838, An Antisense Oligodeoxynucleotide Targeting TNF-alpha, in Rheumatoid Arthritis," is currently available to the public on ACR's website at www.rheumatology.org and contains interim data available at the time of abstract submission.

In the randomized trial, patients received either 100 mg (low dose) or 300 mg (high dose) of ISIS 104838 or placebo. Patients received six doses of ISIS 104838 over one month by subcutaneous injection or intravenous infusion. Synovial tissue lining patients' knees or wrists was biopsied at the start of the trial and at the end of the treatment period. At the time of the abstract, data were available for 15 patients.

Data highlights of the abstract follow:

- Concentrations of ISIS 104838 in synovial tissue increased linearly with dose, with no significant difference between subcutaneous and intravenous administration.
- A greater decrease in TNF-alpha mRNA expression was observed in synovial tissue of patients receiving the high dose of ISIS 104838 than in synovium of patients receiving the low dose of ISIS 104838 or placebo. □
- Mean TNF-alpha levels in plasma of ISIS 104838 high dose-treated patients were stable at the end of treatment, while mean plasma TNF-alpha levels in placebo-treated patients increased.
- ISIS 104838 high dose-treated patients achieved a 42% decrease in mean swollen joints at the end of the treatment period (Day 29) and a 33% decrease at the end of treatment follow up (Day 85), compared to baseline. Placebo-treated patients experienced a 21% decrease in mean swollen joints at Day 29 and an 8% decrease at Day 85 compared to baseline, suggesting an early placebo response following intensive treatment visits that later waned.

- Similarly, ISIS 104838 high dose-treated patients experienced a 27% decrease in mean tender joints at the end of the treatment period (Day 29) and a 22% decrease at the end of treatment follow up (Day 85). Placebo-treated patients experienced a 26% decrease in mean tender joints at Day 29 and a 3% decrease at Day 85, compared to baseline. □
- Four of five (80%) of patients receiving the 300 mg dose of ISIS 104838 achieved a 20% improvement in American College of Rheumatology (ACR) response criteria by the end of the treatment period compared to four of six (66%) placebo patients. ACR response criteria measures improvement in patient- and professional-reported disease severity and activity.
- ISIS 104838 was well tolerated.

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 in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and causes 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.

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 1,200 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release contains forward-looking statements concerning development and therapeutic potential and safety of ISIS 104838. 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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