

Isis Pharmaceuticals Reports Positive Data from Phase 2 Trial Of ISIS 104838 in Rheumatoid Arthritis

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CARLSBAD, Calif., Jan. 5 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today reported data from a Phase 2 clinical trial which demonstrate that ISIS 104838, an antisense TNF-alpha inhibitor, produced a statistically significant disease response in patients with rheumatoid arthritis (RA). In the randomized, placebo-controlled trial, 157 evaluable RA patients received subcutaneous injections of either placebo or one of three dose regimens of 200 mg of ISIS 104838: every other week, once weekly or twice weekly. Patients receiving the once- and twice- weekly doses experienced similar responses to treatment, with 41% of evaluable patients achieving a 20% decrease in disease activity. In comparison, 23% of placebo-treated patients achieved a 20% decrease ($p=0.04$). Response to ISIS 104838 treatment was measured by the American College of Rheumatology (ACR 20) response criteria, a widely used index of RA severity.

"We are pleased with the activity ISIS 104838 demonstrated in this trial," said Jon T. Holmlund, M.D., Vice President, Development. "The responses in the trial were continuing to increase at the conclusion of 3 months of treatment. Therefore, we believe longer dosing or higher doses of ISIS 104838 may significantly enhance activity."

"Our Phase 2 data suggest that ISIS 104838 has the potential to offer several important competitive advantages over protein-based drugs, particularly with regard to side effect profile and cost. Moreover, as we develop our oral form of ISIS 104838, we look forward to the opportunity to dramatically increase patient convenience and the market potential," said Dr. Holmlund. "We are aggressively advancing the development of ISIS 104838 for the treatment of rheumatoid arthritis as an alternative to currently available drugs."

Isis plans to initiate additional Phase 2 trials to further explore dose, schedule and treatment duration of ISIS 104838 in patients with RA. The company is engaged in ongoing trials to optimize oral formulations for ISIS 104838 and other second-generation antisense drugs.

In total, 176 patients with RA enrolled in the study. The primary endpoint in the study was improvement in ACR 20 at day 85. Results from the total patient group and evaluable patients were comparable. The nineteen patients excluded from evaluation were evenly distributed across the study's four dose groups.

Additional highlights from the trial are as follows:

- * Significantly more patients dropped out of the placebo group due to progression of their RA than the two highest ISIS 104838 dose groups ($p=0.05$) □
- * Each of the two highest ISIS 104838 dose groups independently showed improvement in ACR 20 scores at day 85
 - * 40% of evaluable patients who received ISIS 104838 once a week ($p=0.09$) and 41% who received the drug twice a week ($p=0.08$) experienced improved ACR 20 scores, compared to 23% of placebo patients □
- * Patients receiving the two highest doses of ISIS 104838 experienced a greater improvement over baseline in the number of swollen and tender joints than patients in the placebo group
- * ISIS 104838 produced an acceptable safety profile in the Phase 2 trial
 - * No drug-related serious adverse events were reported
 - * The most frequent adverse event was injection site reaction. The reactions were generally considered mild in nature and occurred principally in the first month of treatment and with similar frequency as reported for protein therapeutics.

These Phase 2 results add to Isis' strong portfolio of data demonstrating activity of ISIS 104838. Another component of this data package is the Phase 2 biomarker study which evaluated the biological effect of TNF-alpha inhibition by ISIS 104838 in 20 RA patients over a four-week treatment period. As reported earlier this year, ISIS 104838 accumulated in synovial tissue in a dose-dependent manner, reducing TNF-alpha mRNA levels in patients with RA who received 300 mg of the second-generation antisense drug (see company press release from September 18, 2003). The synovium, the lining surrounding joints, is inflamed in patients with RA.

Isis will conduct a live webcast conference call to discuss this press release on Monday, January 5 at 10:00 am Eastern time. To participate over the Internet, go to www.isispharm.com or to <http://www.firstcallevents.com/service/ajwz395550818gf12.html> . A replay of the webcast will be available at this address for up to 30 days.

ABOUT ISIS 104838

ISIS 104838 is an antisense inhibitor of TNF-alpha, and a product of Isis' proprietary second-generation chemistry, called 2'-O-methoxyethyl. Based on clinical and preclinical data, second-generation drugs offer: increased potency over first-generation antisense drugs; a decreased side effect profile; enhanced subcutaneous administration; enhanced patient convenience and the potential for oral delivery.

ABOUT RHEUMATOID ARTHRITIS

According to the Arthritis Foundation, RA affects 2.1 million Americans, predominately 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 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, 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 September 30, 2003, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company. GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc.

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