

Isis Pharmaceuticals Initiates Phase II Clinical Trial of ISIS 104838, A TNF-Alpha Inhibitor, in Rheumatoid Arthritis

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CARLSBAD, Calif., March 13 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc., (Nasdaq: ISIS) announced today it has initiated a Phase II clinical trial of ISIS 104838, an antisense inhibitor of tumor necrosis factor-alpha (TNF-alpha), in rheumatoid arthritis (RA). The Phase II clinical trial will evaluate the safety and efficacy of ISIS 104838 in RA when administered by subcutaneous injection (SQ) for three months. This is the second Phase II study of ISIS 104838 in RA currently in progress. TNF-alpha is a naturally occurring cytokine that is involved in the development and progression of many inflammatory diseases, including RA.

The double-masked, placebo-controlled, randomized Phase II study is planned to enroll 160 people with RA at 25 sites in the U.S. and Canada. Three dosing regimens will be examined in this study: ISIS 104838 injections twice a week, once a week or once every other week. The primary endpoint in the study is improvement in American College of Rheumatology (ACR) response criteria, which measures improvement in patient- and professional-reported disease severity and activity.

"We are pleased to begin the second study of ISIS 104838 in people with rheumatoid arthritis, and to move forward with the clinical development of our new generation of antisense drugs. The initial Phase II trial, which began last November, is studying ISIS 104838 drug concentrations in tissue and blood as well as the drug's ability to reduce TNF-alpha levels. This new trial will be the first to provide efficacy information about ISIS 104838 in RA. We will use the combined results from the two studies to direct our future development plans with this drug," said F. Andrew Dorr, M.D., Isis Vice President and Chief Medical Officer.

Isis' first Phase II clinical trial of ISIS 104838 is evaluating the biological effect of TNF-alpha inhibition by ISIS 104838 in 20 RA patients over a four-week treatment period. Oral formulations of ISIS 104838 are being developed in parallel by Orasense™ Ltd., a joint venture between Isis and Elan Corporation plc.

ISIS 104838 is a product of Isis' proprietary second-generation chemistry called 2'-O-methoxyethyl. Phase I trials of intravenous infusion and SQ administration of ISIS 104838 demonstrated enhanced tolerability, duration of effect and dosing convenience compared with first-generation drugs. In June 2001, Isis initiated a Phase II clinical trial of topical ISIS 104838 in psoriasis. Currently, Isis has six second-generation products in its development pipeline to treat RA, diabetes, diabetic retinopathy, psoriasis, multiple sclerosis and cancer.

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 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 commercialized its first product, Vitravene® (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 12 products in its development pipeline, with two in late-stage development and six in Phase II human clinical trials. LY900003 (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 nearly 900 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.

This press release contains forward-looking statements concerning the development and potential of the investigational compound ISIS 104838 in the treatment of rheumatoid arthritis. Any statement describing an 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 10Q, for the period ended September 30, 2001, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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