SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): **January 5, 2004**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

2292 Faraday Avenue
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Item 5. Other Events.

On January 5, 2003, Isis Pharmaceuticals, Inc. (the "Company") announced 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=0.05). Response to ISIS 104838 treatment was measured by the American College of Rheumatology (ACR 20) response criteria, a widely used index of RA severity.

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 in 2003, 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.

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.

This report on Form 8-K 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 and on Form 10-Q for the fiscal year ended December 31, 2002, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the Company.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: January 7, 2004

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Executive Vice President,
Chief Financial Officer and Director