

# Isis Pharmaceuticals Reports Encouraging Data on ISIS-STAT3<sub>RX</sub> in Patients With Cancer

June 3, 2013

## Data presented today at the American Society of Clinical Oncology

CARLSBAD, Calif., June 3, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced that data from the Phase 1 study of ISIS-STAT3<sub>RX</sub> in patients with cancer were presented today at the American Society of Clinical Oncology in Chicago. Results of the initial dose escalation study in patients with metastatic cancer showed that ISIS-STAT3<sub>RX</sub> treatment resulted in partial responses that were durable and prolonged in two out of three patients with diffuse large B-cell lymphoma (DLBCL) who were refractory to prior chemotherapy treatments. Isis and AstraZeneca are currently evaluating ISIS-STAT3<sub>RX</sub> in two clinical studies in patients with advanced lymphoma and metastatic liver cancer.

"STAT3 activation has been shown to be associated with the growth, invasiveness and metastases of many types of cancer making it an attractive anti-cancer target. However, STAT3 has proven to be a difficult target to inhibit. ISIS-STAT3<sub>RX</sub> is one of the new molecules in development that inhibit STAT3," said David S. Hong, M.D., associate professor, department of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center. "Patients with advanced cancer often have failed multiple therapies and have few other chemotherapeutic options. For these patients there is a desperate need for new therapies that can halt their disease progression. The clinical responses observed to date suggest that inhibition of STAT3 could provide benefit to some of these cancer patients. The early clinical data on ISIS-STAT3<sub>RX</sub> is impressive because it suggests that this drug can produce durable responses in patients with advanced cancer who have failed to respond to other therapies."

ISIS-STAT3<sub>RX</sub>, also referred to as AZD9150, is the first drug in Isis' pipeline that incorporates Isis' Generation 2.5 chemistry, which Isis developed to increase potency of antisense drugs, thereby creating opportunities for drugs like ISIS-STAT3<sub>RX</sub> to be effective in more difficult-to-treat cancers, like DLBCL. The open-label, dose-escalation Phase 1 study evaluated ISIS-STAT3<sub>RX</sub> in 15 patients with advanced solid tumors and lymphoma who had relapsed or were refractory to multiple chemotherapy regimens. Signals of tumor responses were observed in four patients, including objective partial responses in two of three patients with DLBCL. One patient with a partial response with DLBCL, who had previously failed ten different chemotherapy regimens, experienced a 50 percent reduction in tumor burden and has maintained a partial response for longer than one year and continues to receive weekly ISIS-STAT3<sub>RX</sub> therapy. Another patient with DLBCL experienced a partial response with a 65 percent reduction in tumor burden and, as a result, was well enough to receive an autologous stem cell transplant. This patient successfully completed a bone marrow transplant and remains disease free. Isis and AstraZeneca are currently evaluating ISIS-STAT3<sub>RX</sub> in two other clinical studies, including a study in patients with advanced lymphomas, like DLBCL, and a study in patients with advanced metastatic hepatocellular carcinoma.

"AstraZeneca's considerable expertise in developing anti-cancer drugs has enabled us to rapidly advance the clinical development of ISIS-STAT3<sub>RX</sub>. We believe that ISIS-STAT3<sub>RX</sub> may be applicable to many different types of cancer. As such, together with AstraZeneca, we plan to evaluate ISIS-STAT3<sub>RX</sub> in a broad Phase 2 program," said Brett Monia, Ph.D., senior vice president, antisense drug discovery at Isis. "We are very pleased and encouraged with the safety and efficacy observed in our initial clinical study of ISIS-STAT3<sub>RX</sub> and look forward to the results from the two ongoing clinical studies in patients, which we plan to report next year."

ISIS-STAT3<sub>RX</sub> is designed to inhibit the production of signal transducer and activator of transcription 3 (STAT3), a protein critical for tumor cell growth and survival. In addition, STAT3 is an important mediator of signaling in the JAK2/STAT3 pathway, which has been previously shown to be an important target for drug development. Because STAT3 is activated in numerous types of cancer, ISIS-STAT3<sub>RX</sub> has the potential to be broadly useful for both solid and hematologic tumors. ISIS-STAT3<sub>RX</sub> has been shown to reduce STAT3 levels in preclinical tumor models and produce anti-tumor activity. Inhibition of STAT3 has also been shown to block the induction of tumor-associated cytokines involved in the progression of cancer, such as IL-6, IL-1, TGF, and IL-10, which could serve as important biomarkers in clinical studies.

### Conference Call

At 2:00 p.m. Eastern Time today, June 3, 2013, Isis will conduct a live webcast conference call to discuss recent highlights from its cancer franchise, including the addition of ISIS-AR<sub>RX</sub> to its cancer franchise and data from the Phase 1 study of ISIS-STAT3<sub>RX</sub> that was presented today at the American Society of Clinical Oncology. Interested parties may listen to the call by dialing 866-652-5200, or access the webcast at [www.isispharm.com](http://www.isispharm.com). A webcast replay will be available for a limited time at the same address.

### ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 28 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO™, in the United States for the treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

### ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' strategic alliance with AstraZeneca, the development, activity, therapeutic potential and safety of ISIS-STAT3<sub>RX</sub>, and the therapeutic benefit of antisense drugs that incorporate Isis' Generation 2.5 chemistry. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, 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 in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2012, and its most recent quarterly report on Form 10-Q, which are on file

with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. KYNAMRO™ is a trademark of Genzyme Corporation.

**Isis Pharmaceuticals' Contacts:**

D. Wade Walke, Ph.D.

Executive Director, Corporate Communications and Investor Relations

760-603-2741

Amy Blackley, Ph.D.

Associate Director, Corporate Communications

760-603-2772

SOURCE Isis Pharmaceuticals, Inc.