
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): **December 11, 2012**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(IRS Employer Identification No.)

2855 Gazelle Court

Carlsbad, CA 92010

(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
 - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
 - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
 - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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Item 1.01. Entry into a Material Definitive Agreement.

On December 11, 2012, Isis Pharmaceuticals, Inc. ("**Isis**") and AstraZeneca announced that they have entered a strategic alliance agreement for the discovery and development of novel generation antisense therapeutics against five cancer targets, which includes a license to develop and commercialize ISIS-STAT3_{Rx}, a drug Isis is currently evaluating in an early clinical trial in patients with advanced lymphomas.

Isis and AstraZeneca filed a press release describing this transaction. A copy of this press release is attached as Exhibit 99.1 to this Current Report and incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated December 11, 2012.

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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: December 11, 2012

By: /s/ B. Lynne Parshall

INDEX TO EXHIBITS

99.1 Press Release dated December 11, 2012.



ISIS PHARMACEUTICALS AND ASTRAZENECA FORM STRATEGIC ALLIANCE ON RNA THERAPEUTICS FOR CANCER

CARLSBAD, Calif., December 11, 2012 — Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) and AstraZeneca announced today a strategic alliance for the discovery and development of novel generation antisense therapeutics against five cancer targets, which includes a license to develop and commercialise ISIS-STAT3_{Rx}, a drug Isis is currently evaluating in an early clinical trial in patients with advanced lymphomas. Antisense therapies target the proteins involved in disease processes by destroying the RNA that is involved in creating these proteins. The Isis discovery platform develops specific therapies that bind to messenger RNA (mRNA) and inhibit the production of disease-causing proteins.

The strategic alliance aims to apply AstraZeneca's experience in developing personalised medicines to enhance the drug discovery and development process for four research programs in the oncology area and to aid in the development of ISIS-STAT3_{Rx} for patient populations that could benefit the most from inhibition of STAT3, a protein that drives cancer growth. The combination of Isis' antisense technology and its new Generation 2.5 chemistry, which increases the potency of its therapeutics, provides AstraZeneca the opportunity to develop drugs that could be much more effective in cancers that are difficult to address with conventional small molecules or antibodies.

"Isis' antisense technology platform allows AstraZeneca to broaden our oncology research efforts beyond traditional drug discovery methods, while at the same time becoming more specific about how we target cancer," said Susan Galbraith, head of the AstraZeneca Oncology Innovative Medicines Unit. "AstraZeneca's expertise in oncology translational science and our global capabilities in development and commercialisation of oncology products and Isis' innovative approach to discovering novel medicines reflect a common goal of bringing new medicines to cancer patients."

"We are excited to collaborate with AstraZeneca, a global leader in oncology, to apply our technology and drug discovery expertise to developing novel anti-cancer agents. We will benefit from AstraZeneca's extensive oncology expertise in the use of novel pre-clinical animal models to validate targets and develop predictive assays to identify which patients would benefit the most from these new targets," said B. Lynne Parshall, chief operating officer and chief financial officer at Isis.

"ISIS-STAT3_{Rx} is our first cancer drug to incorporate our new technology and we are encouraged by the early clinical data we have observed," said Brett Monia, Ph.D., senior vice president, antisense drug discovery at Isis. "While STAT3 is implicated in a number of different cancers, the focus in our ongoing clinical study is to evaluate the effectiveness of our drug in hematologic malignancies, such as lymphoma. We have worked closely with AstraZeneca to design a rapid path to the market for ISIS-STAT3_{Rx} in these patient populations. While working toward this goal, AstraZeneca's resources, expertise and development capabilities also provide us the opportunity to evaluate ISIS-STAT3_{Rx} as a broad-based anti-tumor agent."

Under the terms of the agreement, Isis will receive from AstraZeneca \$31 million in upfront and near term payments, comprising a \$25 million payment on signing followed by a \$6 million payment in the second quarter of 2013 assuming the research program is continuing. In exchange, Isis has granted AstraZeneca an exclusive license to develop and commercialise ISIS-STAT3_{Rx} and a pre-clinical program as well as an option to license products developed under a separate research program. Once licensed, AstraZeneca will be responsible for all further development and commercialization. AstraZeneca will be responsible for all development of ISIS-STAT3_{Rx} other than the conduct of the ongoing clinical trial, which Isis will complete. Isis is eligible to receive further milestone payments subject to achieving certain predefined clinical success criteria for the ISIS-STAT3_{Rx} program and pre-clinical milestones for the other programs. Isis is also eligible to receive downstream development and approval milestone payments, license fees for research program targets as well as royalties on sales from products that are successfully commercialized.

Isis will hold a conference call and live audio webcast today, December 11, 2012 at 8:30 am ET to provide detailed information on its new strategic alliance with AstraZeneca. Interested parties may listen to the call by dialing 866-713-8567 and refer to passcode "ISIS 2012," or access the webcast at www.isispharm.com.

ABOUT ISIS-STAT3_{Rx}

ISIS-STAT3_{Rx} is the first drug in Isis' pipeline that incorporates Isis' Generation 2.5 chemistry, which was developed to increase potency of antisense drugs thereby creating opportunities for drugs like ISIS-STAT3_{Rx} to be more effective in addressing targets in a broader range of tissues, including tumors. ISIS-STAT3_{Rx} is designed to inhibit the production of signal transducer and activator of transcription 3 (STAT3), a protein critical for tumor growth and survival. Because STAT3 is overexpressed in numerous types of cancers, ISIS-STAT3_{Rx} has the potential to be broadly useful for both solid and hematological tumors. Isis recently reported encouraging data from its ongoing Phase 1 study showing that ISIS-STAT3_{Rx} had an acceptable safety profile and treatment with ISIS-STAT3_{Rx} resulted in clear responses in a number of patients with advanced cancer who were refractory to multiple prior chemotherapy treatments. The indication of activity so early in development in a Phase 1 study prompted Isis to initiate a follow up clinical study to evaluate the safety and efficacy of ISIS-STAT3_{Rx} in focused patient populations with lymphomas and other advanced hematologic cancers linked to activation of STAT3 who have failed other treatment options.

ABOUT ASTRAZENECA

AstraZeneca is a global, innovation-driven biopharmaceutical business with a primary focus on the discovery, development and commercialisation of prescription medicines for gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com

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 25 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis'

partner, Genzyme, plans to commercialize Isis' lead product, KYNAMRO™, in the United States and Europe following regulatory approval. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements, including statements regarding Isis' strategic alliance with AstraZeneca, Isis' research and development opportunities in cancer, the development, activity, therapeutic potential and safety of ISIS-STAT3_{RX}, 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 planned commercialization 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, 2011 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.

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

AstraZeneca's Contacts:

Laura Woodin
R&D Media Lead
302 885 1087

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

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