
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): **March 31, 2010**

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.)

1896 Rutherford Road

Carlsbad, CA 92008

(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 March 31, 2010, Isis Pharmaceuticals, Inc. ("Isis") and GlaxoSmithKline announced a new strategic alliance that will apply the Isis antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Isis and GlaxoSmithKline 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 March 31, 2010.

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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: March 30, 2010

By: /s/ B. Lynne Parshall

INDEX TO EXHIBITS

99.1 Press Release dated March 31, 2010.



GSK and Isis Pharmaceuticals collaborate on RNA therapeutics for rare and infectious diseases

- GSK has right to license and commercialize compounds at clinical proof-of-concept
- Isis gives GSK access to expertise in discovery and development of anti-RNA therapeutics

LONDON, United Kingdom, and CARLSBAD, Calif., March 31, 2010 — GlaxoSmithKline (NYSE: GSK) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today a new strategic alliance that will apply the Isis antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, Isis will receive an upfront \$35 million payment from GSK and is eligible to receive on average up to \$20 million in milestones per program up to Phase 2 proof-of-concept (PoC). GSK will have the option to license compounds at PoC, and will be responsible for all further development and commercialization. Isis will be eligible to receive license fees and milestone payments, totaling nearly \$1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition, Isis will receive up to double-digit royalties on sales from any product that is successfully commercialized.

“As a platform, the Isis antisense approach offers us an exciting opportunity to target certain severe diseases in a way that has not previously been possible,” said Dr. Patrick Vallance, Senior Vice-President and Head of Drug Discovery at GSK. “Isis Pharmaceuticals is a leader in antisense technology, and this new alliance will enhance our discovery platform in this promising research area.”

Antisense therapies target the proteins involved in disease processes through the RNA that is involved in building these proteins. The Isis discovery platform develops specific therapies that bind to messenger RNA (mRNA) and inhibit the production of disease-causing proteins. Isis recently announced data from a Phase 3 trial in heterozygous familial hypercholesterolemia patients that demonstrated the therapeutic effect of this approach.

This alliance provides GSK with access to Isis’ expertise in drug discovery and development of RNA-targeted therapeutics, with Isis retaining responsibility for the discovery and development of compounds to the alliance targets from inception to PoC.

“We are excited to be working with GSK to apply antisense technology to these new therapeutic areas. We are particularly excited to work on the novel targets GSK brought to the alliance,” said Dr. Stanley T. Crooke, Chairman and Chief Executive Officer of Isis Pharmaceuticals. “This alliance is exactly the type of deal we want to do. We retain control of the discovery and early development of our drugs while working together with a very high-quality partner to maximize the value of the drugs in late-stage development and commercialization.”

Isis will hold a conference call and live audio webcast today, March 31, 2010 at 8:00 a.m. ET to provide detailed information on its new strategic alliance with GSK. Interested parties may listen to the call by dialing 866-783-2137 and refer to passcode “ISIS 2010,” or access the webcast at www.isispharm.com.

About RNA-targeted therapeutics

RNA-targeted therapeutics, or antisense therapies such as oligonucleotides, represent an opportunity for a new drug class. Where most other medicines are small molecules or biologics that target a specific protein in a disease process, antisense therapies prevent protein synthesis by eliminating the mRNA - the template or pattern that guides the production of the protein.

About Isis Pharmaceuticals

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world’s first antisense drug and has 22 drugs in development. Isis’ drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer. Isis’ partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

About GlaxoSmithKline

GlaxoSmithKline — one of the world’s leading research-based pharmaceutical and healthcare companies — is committed to improving the quality of human life by enabling people to do more, feel better and live longer.

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GSK Cautionary statement regarding forward-looking statements

Under the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Factors that may affect GSK's operations are described under 'Risk Factors' in the 'Business Review' in the company's Annual Report on Form 20-F for 2008.

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Isis Safe Harbor Statement

This press release includes forward-looking statements regarding Isis' strategic alliance with GSK, and Isis' research and development opportunities in disease areas including rare and infectious diseases. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs 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 products. 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, 2009, which is on file with the SEC. Copies of this and other documents are available from the Company.

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics Inc.

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