
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): **September 13, 2007**

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.

Isis Pharmaceuticals, Inc. ("Isis") today announced a broad collaboration with Ortho-McNeil, Inc., a Johnson & Johnson company, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including Type 2 diabetes.

Isis 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.

(c) Exhibits.

99.1 Press Release dated September 13, 2007.

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.

INDEX TO EXHIBITS

99.1 Press Release dated September 13, 2007.



**ISIS ENTERS BROAD COLLABORATION WITH ORTHO-MCNEIL, INC. FOR
THE DISCOVERY, DEVELOPMENT AND COMMERCIALIZATION OF
ANTISENSE DRUGS TO TREAT METABOLIC DISEASES**

- *Includes license of two antisense drugs in development targeting glucagon receptor and glucocorticoid receptor*
- *Includes research collaboration to identify antisense drugs to inhibit additional targets to treat metabolic diseases*
- *Conference call webcast Thursday, September 13, 9:45 a.m. EDT at www.isispharm.com*

Carlsbad, Calif., September 13, 2007 – Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced a broad collaboration with Ortho-McNeil, Inc., a Johnson & Johnson company, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including Type 2 diabetes. As part of the collaboration, Isis will grant to Ortho-McNeil worldwide development and commercialization rights to two of its diabetes development candidates, ISIS 325568 and ISIS 377131, which selectively inhibit the production of glucagon receptor (GCGR) and glucocorticoid receptor (GCCR), respectively. Additionally, Ortho-McNeil will provide funding to Isis to support the joint discovery of novel drugs to treat metabolic diseases, including diabetes and obesity. After the initial collaboration phase, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) will continue development of these drugs.

Ortho-McNeil will pay Isis a \$45 million upfront licensing fee, and will provide Isis with research and development funding over the period of the collaboration. In addition to the licensing fee, Isis could receive over \$230 million in milestone payments upon successful development and regulatory approvals of ISIS 325568 and ISIS 377131, as well as royalties on sales. Isis could also receive milestones and royalties on the successful development and regulatory approvals of additional drugs discovered as part of the collaboration. The agreement is subject to clearance under the Hart-Scott-Rodino Antitrust Improvements Act. Prior to closing of the transaction, Isis plans to purchase the equity in Symphony GenIsis, Inc. and reacquire the intellectual property related to the GCGR and GCCR programs as well as regain full ownership of ISIS 301012, the Company's lipid-lowering drug targeting Apolipoprotein B-100.

"We look forward to working with Ortho-McNeil, Inc. and J&JPRD to advance our glucagon receptor and glucocorticoid receptor drugs through the clinic and to develop additional drugs against other promising targets," said Lynne Parshall, J.D., Executive Vice President and Chief Financial Officer, Isis Pharmaceuticals. "This collaboration represents another major step for us in capturing value from our achievements in creating a new drug discovery platform technology and discovering commercially attractive antisense drugs."

"This collaboration has been enabled by the productivity of our metabolic drug discovery program, which has evaluated more than 120 targets in animal models using antisense drugs," said Jeffrey Jonas, M.D., Executive Vice President, Isis Pharmaceuticals. "Both ISIS 325568 and ISIS 377131 have broad and exciting therapeutic profiles that include lowering of blood lipids and body fat, in addition to significant glucose-lowering effects. These drugs have demonstrated robust effects in extremely diabetic and hyperlipidemic animals and have demonstrated a unique and preferential distribution to tissues such as liver and fat, thereby potentially minimizing the systemic side effects that would be expected with traditional approaches against the same gene targets. We are enthusiastic about our research collaboration, which should allow us to discover additional drugs against novel targets, thereby adding to our strong pipeline in this therapeutic area."

About glucagon receptor (GCGR), target of ISIS 325568

Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In Type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of liver GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, is expected to lower blood glucose levels and help control Type 2 diabetes. In preclinical studies, antisense inhibitors of GCGR led to improved glucose control and reduced levels of blood triglycerides without producing hypoglycemia. In addition, treatment with ISIS 325568 led to an increase in circulating glucagon-like peptide, or GLP-1, which is a hormone that helps to preserve pancreatic function, thereby enhancing insulin secretion.

About glucocorticoid receptor (GCCR), target of ISIS 377131

Glucocorticoid hormones have a variety of effects throughout the body, including promoting liver glucose production and fat storage. Although inhibition of GCCR has long been recognized as an attractive strategy for development of therapeutics for Type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged development of traditional drugs. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to antagonize glucocorticoid action primarily in liver and fat tissue. Notably, antisense drugs do not reduce GCCR expression in the central nervous system or adrenal glands – inhibition of GCCR expression in these two organs can lead to systemic side effects. In preclinical studies, Isis has shown that ISIS 377131 has a broad therapeutic profile that includes reduction of blood glucose levels, a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and a reduction in body fat.

Conference Call

At 9:45 a.m. Eastern Time today, September 13, Isis will conduct a live webcast conference call to discuss this transaction. Interested parties may access the webcast at <http://www.isispharm.com> or listen to the call by dialing 800-289-0544. A replay will be available for a limited time at the same address.

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 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing drugs for cancer, and inflammatory and other diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Forward-Looking Statement

This press release includes forward-looking statements regarding Isis' collaboration with Ortho-McNeil, Inc. and its affiliates, and discovery and development of drugs for diabetes and metabolic diseases, including ISIS 325568, ISIS 377131, and drugs against undisclosed additional research targets. 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, including those statements that are described as Isis' goals. 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, 2006, and its quarterly report on Form 10-Q for the quarter ended June 30, 2007, 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, Ibis Biosciences and Ibis T5000 are registered trademarks or trademarks of Isis Pharmaceuticals, Inc.

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