
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 7, 2008**

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 January 7, 2008, Isis Pharmaceuticals, Inc. ("Isis") and Genzyme Corporation ("Genzyme") announced a major strategic alliance in which Genzyme will develop and commercialize mipomersen. Mipomersen, formerly ISIS 301012, is a lipid-lowering drug targeting apolipoprotein B-100. As part of the strategic relationship, Genzyme has exclusively licensed mipomersen from Isis and will also have preferred access to future Isis drugs for central nervous system and certain rare diseases.

Genzyme will pay Isis \$150 million to purchase five million shares of Isis common stock for \$30 per share ("the Shares") upon Hart-Scott-Rodino clearance. Upon completion of final contracts, Genzyme will pay Isis a \$175 million up-front mipomersen license fee. In addition to this initial \$325 million, Isis has the potential to receive significant milestone payments for mipomersen, which is currently in phase 3 trials. Once the product is launched, the two companies will share profits.

Isis will transition development responsibility for mipomersen to Genzyme over the next two years, and Isis will fund a portion of development costs over that time. Genzyme will take over full development and commercialization responsibilities thereafter.

In addition to the up-front payment, Isis also has the opportunity to receive from Genzyme up to \$825 million in development and regulatory milestone payments plus up to \$750 million in commercial milestone payments.

Genzyme and Isis will share mipomersen profits 50/50 when annual worldwide revenues reach \$2 billion or more. The profit share begins with a 70/30 Genzyme/Isis split and reaches 50/50 on a sliding scale as annual revenues ramp up to \$2 billion.

Closure of the transaction is subject to clearance under the Hart-Scott-Rodino Antitrust Improvements Act.

Item 3.02. Unregistered Sales of Equity Securities.

The information set forth in Item 1.01 is incorporated herein by this reference.

The Shares will be issued only to an accredited investor, as such term is defined in Rule 501 of Regulation D promulgated under the Securities Act of 1933, as amended (the "Securities Act"). The Shares have not been registered under the Securities Act or any state securities laws. Isis relied on the exemption from the registration requirements of the Securities Act set forth in Section 4(2) thereof and the rules and regulations promulgated thereunder. Isis has agreed to file a registration statement for the resale of the Shares. Neither this current report on Form 8-K nor any of the exhibits attached hereto is an offer to sell or the solicitation of an offer to buy shares of common stock or other securities of Isis.

THIS REPORT INCLUDES FORWARD-LOOKING STATEMENTS REGARDING ISIS' STRATEGIC ALLIANCE WITH GENZYME CORP., THE DEVELOPMENT AND COMMERCIALIZATION POTENTIAL OF MIPOMERSEN FOR CARDIOVASCULAR DISEASE, AND ISIS' RESEARCH AND DEVELOPMENT OPPORTUNITIES IN DISEASE AREAS INCLUDING CNS AND CERTAIN RARE 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, 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 SEPTEMBER 30, 2007, WHICH ARE ON FILE WITH THE SEC. COPIES OF THESE AND OTHER DOCUMENTS ARE AVAILABLE FROM THE COMPANY.

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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: January 7, 2008

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

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