

**UNITED STATES  
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 21, 2004**

**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.)

**2292 Faraday Avenue**

**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))

**Item 1.01 Entry into a Material Agreement.**

On December 21, 2004, Isis Pharmaceuticals, Inc. announced that it had sold a portion of its royalty rights in Macugen® (pegaptanib sodium injection) to Drug Royalty USA, Inc. (DRC) in exchange for aggregate payments of \$24 million over the next three years. Under the terms of the agreement, Isis and DRC will share the royalty rights on Macugen through 2009. After 2009, Isis retains all royalties from Macugen.

In 2001, Eyetech Pharmaceuticals, Inc., the company developing Macugen, licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. Under the license agreement, Isis receives royalties on sales of Macugen and milestones upon the approval of Macugen for new therapeutic indications. Macugen is approved for the treatment of wet age-related macular degeneration and is being investigated in clinical trials for diabetic macular edema.

Under the agreement, through 2009 DRC will receive royalties on the first \$500 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between \$500 million and \$1 billion. Isis retains 90 percent of all royalties on annual sales in excess of \$1 billion and 100 percent of all royalties after 2009.

Isis has retained all milestones payable to Isis by Eyetech under the license agreement. Isis has earned \$6 million in milestones to date from Eyetech in relation to the development of Macugen. Earlier this week, Isis earned a \$3 million milestone payment associated with the marketing clearance of Macugen by the U.S. Food and Drug Administration (FDA) for wet AMD. Also in 2004, Isis earned a \$1 million milestone payment from Eyetech associated with Eyetech's filing of a New Drug Application (NDA) for Macugen for wet AMD.

As part of the sale, Isis agreed to pay DRC liquidated damages if any one of the following events occur during the term of the agreement:

- Eyetech refuses to pay royalties due under the license agreement on the net sales of Macugen;
- Eyetech or Isis, without DRC's prior written consent, terminate their license agreement;
- A judge renders a final *Markman* decision that provides a basis for a dispositive motion on validity or enforceability such that one or more of the patents licensed by Eyetech from Isis are found to be invalid and/or unenforceable;

- Isis is in default under Isis' loan with Silicon Valley Bank (SVB) or under its 5½% convertible promissory notes due 2009; or
- Isis prepays or refinances its loan with SVB or its 5½% convertible promissory notes due 2009 on terms not approved by DRC.

The amount of liquidated damages will be calculated such that DRC will receive a ten per cent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to Isis through the default date *minus* the total of any royalties received by DRC through the default date.

In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, Isis fails to have a minimum liquidity equal to the then outstanding balance on Isis' loan with SVB; *plus* the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; *plus* Isis' cash burn over the most recent three months.

As collateral for Isis' obligations under the sale agreement, Isis granted DRC a first priority security interest in the patents licensed by Isis to Eyetech under the license agreement and in the license agreement itself.

*This report includes forward-looking statements concerning Isis Pharmaceuticals and the potential of the company's intellectual property position and potential future payments to the company related to the success of Macugen. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in Isis' Annual Report on Form 10-K for the year ended December 31, 2003, and quarterly report on Form 10-Q for the quarter ended September 30, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.*

Macugen(R) is a registered trademark of Eyetech Pharmaceuticals, Inc.

#### 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 22, 2004

By: /s/ B. Lynne Parshall  
**B. LYNNE PARSHALL**  
Executive Vice President,  
Chief Financial Officer and Director