
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): **April 7, 2005**

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 April 7, 2005, Isis Pharmaceuticals, Inc. (the "Company") amended its Rights Agreement with American Stock Transfer and Trust Company dated December 8, 2000 (the "Rights Agreement") to include a three-year independent director evaluation provision (the "TIDE Provision").

The TIDE Provision requires an independent committee of the Company's Board of Directors to review the Rights Agreement every three years and evaluate whether the Rights Agreement still is in the Company's and its stockholders' best interests.

Item 9.01. **Financial Statements and Exhibits.**

(c) Exhibits.

99.1 Amendment No.1 to Rights Agreement dated April 7, 2005.

2

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: April 7, 2005

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Executive Vice President,

INDEX TO EXHIBITS

99.1 Amendment No. 1 to Rights Agreement dated April 7, 2005.

AMENDMENT NO. 1 TO RIGHTS AGREEMENT

This Amendment No.1 to Rights Agreement, effective as of April 7, 2005 (“Amendment No.1”), between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the “Company”), and **AMERICAN STOCK TRANSFER & TRUST COMPANY** (the “Rights Agent”), provides as follows:

WHEREAS, the Company and the Rights Agent are parties to a Rights Agreement dated as of December 8, 2000 (the “Rights Agreement”), specifying the terms of the Rights (as defined therein);

WHEREAS, the Company and the Rights Agent now desire to amend the Rights Agreement in order to provide for a three-year independent director evaluation of the Rights, as provided herein.

NOW, THEREFORE, in consideration of the premises and mutual agreements herein set forth, the parties hereby agree as follows:

1. **Amendment and Restatement of Section 28: “Determination and Actions by the Board Of Directors, Etc.”** Section 28 of the Rights Agreement is hereby amended, restated and replaced in its entirety by the following:

SECTION 28. DETERMINATION AND ACTIONS BY THE BOARD OF DIRECTORS, ETC.

(a) For all purposes of this Agreement, any calculation of the number of Common Shares outstanding at any particular time, including for purposes of determining the particular percentage of such outstanding Common Shares or any other securities of which any Person is the Beneficial Owner, shall be made in accordance with the last sentence of Rule 13d-3(d)(1)(i) of the General Rules and Regulations under the Exchange Act as in effect on the date of this Agreement. The Board of Directors shall have the exclusive power and authority to administer this Agreement and to exercise all rights and powers specifically granted to the Board, or the Company, or as may be necessary or advisable in the administration of this Agreement, including without limitation, the right and power to (i) interpret the provisions of this Agreement, and (ii) make all determinations deemed necessary or advisable for the administration of this Agreement (including a determination to redeem or not redeem the Rights or to amend this Agreement). All such actions, calculations, interpretations and determinations (including, for purposes of clause (y) below, all omissions with respect to the foregoing) which are done or made by the Board in good faith, shall (x) be final, conclusive and binding on the Rights Agent and the holders of the Rights, and (y) not subject the Board to any liability to the holders of the Rights.

(b) It is understood that the TIDE Committee (as described below) of the Board of Directors shall review and evaluate this Agreement in order to consider whether the maintenance of this Agreement continues to be in the best interests of the Company, its stockholders and other relevant constituencies of the Company at least once every three years, or sooner than that if any Person shall have made a proposal to the Company or its stockholders, or taken any other action that, if effective, could cause such Person to become an Acquiring Person hereunder, if a majority of the members of the TIDE Committee shall deem such review and evaluation appropriate after giving due regard to all relevant circumstances. Following each such review, the TIDE Committee shall communicate its conclusions to the full Board of Directors, including any recommendation in light thereof as to whether this Agreement should be modified or the Rights should be redeemed. The TIDE Committee shall be comprised of members of the Board of Directors who are not officers, employees or Affiliates of the Company and shall be the Nominating, Governance and Review Committee of the Board of Directors (or any successor committee) as long as the members of such committee meet such requirements.

(c) The TIDE Committee and the Board of Directors, when considering whether this Agreement should be modified or the Rights should be redeemed, shall have the power to set their own agenda and to retain at the expense of the Company their choice of legal counsel, investment bankers and other advisors. The TIDE Committee and the Board of Directors, when considering whether this Agreement should be modified or the Rights should be redeemed, shall have the authority to review all information of the Company and to consider any and all factors they deem relevant to an evaluation of whether this Agreement should be modified or the Rights should be redeemed.

2. **No Other Amendments.** Except as expressly amended hereby, the terms of the Rights Agreement will remain in full force and effect in all respects.
3. **Governing Law.** This Agreement and each Right Certificate issued hereunder shall be deemed to be a contract made under the laws of the State of Delaware and for all purposes shall be governed by and construed in accordance with the laws of such state applicable to contracts to be made and performed entirely within such state.
4. **Counterparts.** This Amendment No.1 may be executed in any number of counterparts, and each of such counterparts will for all purposes be deemed to be an original, and all such counterparts will together constitute but one and the same instrument.

IN WITNESS WHEREOF, the parties hereto have caused this Amendment No.1 to be executed by their duly authorized representatives as of the date first above written.

AMERICAN STOCK TRANSFER & TRUST

/s/ Herbert J. Lemmer

Herbert J. Lemmer

Vice President

ISIS PHARMACEUTICALS, INC.

/s/ B. Lynne Parshall

