
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 20, 2006

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 April 20, 2006, Isis Pharmaceuticals, Inc. ("Isis") amended its 2002 Non-Employee Directors' Stock Option Plan to add a provision that expressly prohibits repricing options under the plan without first obtaining stockholder approval. A copy of the amendment is attached to this Report as Exhibit 99.1.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

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 20, 2006

By: /s/ B. Lynne Parshall

B. LYNNE PARSHALL

Executive Vice President,

Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1 Amendment to 2002 Non-Employee Directors' Stock Option Plan dated April 20, 2006.

**AMENDMENT TO
ISIS PHARMACEUTICALS, INC.
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
ADOPTED BY THE BOARD OF DIRECTORS APRIL 20, 2006**

This Amendment to the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "Amendment"), is effective as of April 20, 2006.

A. WHEREAS, the Board of Directors of Isis approved an amendment to the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "NED"), as more fully described below.

NOW THEREFORE, the NED is hereby amended as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the NED.

ARTICLE 1. AMENDMENT

1.1 Addition of New Section 12(e). A new Section 12(e) is hereby added to the NED as follows:

"(e) **Option Repricing Prohibited.** The Board will not have the authority, at any time, without obtaining the approval of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, to (1) reduce the exercise price of any Options under the Plan that are currently outstanding; or (2) cancel any outstanding Options under the Plan and grant in substitution therefore new Options under the Plan at a lower exercise price (including entering into any "6 month and 1 day" cancellation and re-grant scheme), regardless of whether or not the cancelled Options revert to and again become available for issuance under the Plan. This Section 12(e) may not be amended without the affirmative vote of the holders of a majority of the shares present or represented and entitled to vote at a duly convened meeting of the stockholders of the Company. Notwithstanding the foregoing, this paragraph will not be construed to apply to "issuing or assuming a stock option in a transaction to which section 424(a) applies," within the meaning of Section 424 of the Code."

1.2 Except as specifically provided in this Amendment, all other terms and conditions of the NED will remain in full force and effect.