

UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549

**SCHEDULE 14A**

Proxy Statement Pursuant to Section 14(a) of  
the Securities Exchange Act of 1934 (Amendment No.        )

Filed by the Registrant

Filed by a Party other than the Registrant

Check the appropriate box:

- Preliminary Proxy Statement
- Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**
- Definitive Proxy Statement
- Definitive Additional Materials
- Soliciting Material Pursuant to §240.14a-12

**Isis Pharmaceuticals, Inc.**

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(Name of Registrant as Specified In Its Charter)

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(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

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- No fee required.
- Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
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On April 29, 2004 the Registrant mailed the following materials to certain of its institutional stockholders and to Institutional Shareholder Services.

April 29, 2004

To whom it may concern:

On April 12, 2004, we filed our proxy statement for the Isis Pharmaceuticals, Inc. 2004 Annual Meeting of Stockholders, which contains a proposed modification to the company's 1989 Stock Option Plan. In this letter, I will discuss the rationale behind the Board of Director's recommendation to amend and restate this plan and how the modifications benefit Isis' stockholders.

Over the course of the company's history, we have consistently designed and responsibly conducted employee equity compensation programs in alignment with stockholders' interests. The proposed amendments to the 1989 Stock Option Plan continue this effort and are aimed to encourage, motivate and inspire our employees for continued company growth, progress and success. As part of our best practices, we observe the majority of the following guidelines on a voluntary basis; however, our goal this year is to formalize a plan to ensure stockholder interests are visibly reflected.

Specifically, the proposed amendment to the 1989 Plan would:

- Prohibit the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders;
- Limit the 1989 Plan to the grant of options and not authorize stock bonuses or restricted stock awards, which is consistent with our current practices;
- Limit the term of each newly granted option to seven years rather than the ten years currently allowed;
- Require that each newly granted option not become fully vested until a date at least two years after the date of grant, except in the case of certain corporate events, although our current practice is to fully vest four years after date of grant;
- Require all options outstanding under the 1989 Plan have an exercise price of not less than 100% of the fair market value of our common stock on the date of grant, which is consistent with our current practices;
- Provide that our Compensation Committee, which is composed entirely of independent directors, will administer the 1989 Plan, which is consistent with our current practices;
- Require that the exercise price for options outstanding under the 1989 Plan can only be paid in cash, which is consistent with our current practices; and
- Extend the term of the 1989 Plan from January 31, 2008 to January 31, 2014.

In addition, the amended plan increases the number of shares reserved for issuance by 3 million shares. This increase ensures we can continue to retain and recruit highly skilled scientists and personnel in the face of intense competition, and grant an appropriate number of stock options to employees and consultants for at least two years. Without the approval of this amendment, we estimate our remaining 1.7 million shares will be depleted by January 2005.

The Isis Board has a noteworthy record of structuring and implementing programs that aim to preserve our highly-qualified employee base in a manner sensitive to stockholder interests. For example, the Board intentionally structured the April 2003 employee stock option exchange program to be in line with best practices and with stockholder interests in mind by making certain that:

- Eligible employees could relinquish a larger number of higher-priced options to receive a smaller number of new lower-priced stock options;

- Vesting for the replacement options restarted on January 1, 2003 (ensuring that the options would provide long-term employee retention value), and
- New options carried a shorter expiration term of approximately five years, minimizing long-term overhang.

This option exchange program provided our employees with meaningful equity incentives, while decreasing the fully diluted shares outstanding and enhancing the alignment of stockholder and employee interests.

Furthermore, Isis has an option budget. This is an important tool used to balance our equity compensation objectives with stockholder interests and minimize potential dilution. Each year the Compensation Committee approves a budget that establishes the number of stock options available for grant to employees. The option budget is a "net" budget, which means that if options expire or otherwise terminate without being exercised, the Common Stock not purchased pursuant to such options is added to the budget. Over the past three years, the average option budget set by the Compensation Committee has been less than 2.6% of our outstanding Common Stock. According to the Radford Surveys 2003 Biotechnology Annual Trend Report, the average net annual burn rate (gross number of options granted over the year, net of cancellations, expressed as a percentage of total issued and outstanding shares) was 3.7% in 2001, 3.2% in 2002 and 2.8% in 2003. Isis' net burn rate was below average each year with net burn rates of 2.5% in 2001, 2.8% in 2002 and (1.8%) in 2003.

Because we have consistently granted options within the option budget and below the Radford average, we believe the above-average potential dilution attributable to our stock option plans is related to the extensive period of time that our management team and employees typically hold options. On average, Isis employees hold options for approximately 6.2 years. We believe this is for two reasons. First, it represents their confidence in the technology and company, and positive expectations of improved stockholder value over the long-term. Second, Isis has a very low turnover rate so unlike former-employees who are forced to sell options before they expire as a result of their departure from the company, our continuing employees choose to hold their options with the hope of maximizing returns. We believe these two positive factors contribute to the majority of the potential dilution attributable to our stock option plans.

These programs are examples of how we continue to align employee and stockholder interests. Throughout our history, we have made significant efforts to be a leader in proactively implementing best practices and we are further formalizing these efforts with our latest corporate governance initiatives and proposed policies. We believe these efforts provide stockholders with increased insight into the company and its practices. At Isis, we are committed to operating under high legal and ethical standards. Adhering to these principles is important to the company, our employees and our stockholders. We are dedicated to making Isis a continuous success, which in turn, generates value for stockholders.

Sincerely,

B. Lynne Parshall  
Isis Pharmaceuticals  
Executive Vice President, CFO and Secretary

ON APRIL 12, 2004, ISIS PHARMACEUTICALS, INC. FILED WITH THE SECURITIES AND EXCHANGE COMMISSION A DEFINITIVE PROXY STATEMENT FOR THE 2004 ANNUAL MEETING OF STOCKHOLDERS, WHICH WAS MAILED ON OR ABOUT APRIL 16, 2004 TO STOCKHOLDERS ELIGIBLE TO VOTE AT THE 2004 ANNUAL MEETING. THE PROXY STATEMENT INCLUDES A DETAILED DESCRIPTION OF THE PROPOSED AMENDMENT AND RESTATEMENT OF THE ISIS PHARMACEUTICALS 1989 STOCK OPTION PLAN. ALL ISIS STOCKHOLDERS ELIGIBLE TO VOTE AT THE 2004 ANNUAL MEETING ARE STRONGLY ENCOURAGED TO READ THE DEFINITIVE PROXY STATEMENT WHICH IS AVAILABLE WITHOUT CHARGE AT THE SECURITIES AND EXCHANGE COMMISSION WEBSITE AT *WWW.SEC.GOV* AND IS AVAILABLE WITHOUT CHARGE FROM ISIS TO ALL ISIS STOCKHOLDERS ELIGIBLE TO VOTE AT THE 2004 ANNUAL MEETING.

On April 29, 2004 the Registrant emailed the following message to its employees.

By now, as Isis shareholders, you have received your invitation and proxy for Isis' 2004 annual meeting of stockholders.

I wanted to highlight Proposal 2 which is an amendment and restatement of the 1989 Stock Option Plan to, among other things, increase the number of shares of Common Stock authorized for issuance under the 1989 Plan by 3 million shares..

Our management and Board of Directors believe that stock options are a key aspect of our ability to attract and retain qualified employees. If our stockholders do not approve the share increase, we may be unable to continue to grant options at competitive levels. Without these additional shares, we expect that the current shares available for grant under the 1989 Plan will not be sufficient to maintain our option grant practices for new employees, and for promotions and merit awards for current employees after January 2005.

Your vote is very important, so whether or not you plan to attend the annual meeting on Wednesday, May 26, please complete your proxy and submit it as soon as possible. If you have misplaced your proxy, please contact Linda Powell.

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