

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

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.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

- No fee required.
- Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
 - (1) Title of each class of securities to which transaction applies:

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- Fee paid previously with preliminary materials.
- Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.
 - (1) Amount Previously Paid:

 - (2) Form, Schedule or Registration Statement No.:

 - (3) Filing Party:

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On April 22, 2004 the Registrant posted the following materials on its website.

April 22, 2004

Dear Stockholders,

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. Furthermore, we continually design our employee incentive plans with our stockholders' interests in mind.

Our commitment to operating under these standards is reflected in the company's Institutional Shareholder Services (ISS) Corporate Governance Quotient (CGQ) score. Isis outperformed 84% of the companies in the Pharmaceuticals & Biotechnology group. Examples of recently implemented corporate governance initiatives include the following:

1. Introduced a corporate governance section to the company's website, which includes detailed information regarding board composition, committees, meetings and compensation.
2. Adopted a Code of Ethics that highlights our ethical and legal requirements for our officers, directors and employees.
3. Adopted new policies and procedures designed to ensure complete, fair and accurate public disclosures.
4. Reviewed the composition of our board of directors and its committees to ensure a majority of the board is composed of independent directors and that each committee is composed entirely of independent directors. Furthermore, as part of each board meeting, the independent directors meet in executive session without the presence of employee directors.
5. Increased the authority of our audit committee to appoint and dismiss the company's auditors, pre-approve the services provided by our auditors and review and approve all related party transactions. In addition, the audit committee is responsible for overseeing the internal controls over financial reporting established by management and the process by which management satisfies itself that they are working effectively.
6. Increased responsibility of the nominating, governance and review committee to annually evaluate the adequacy of Isis' corporate governance guidelines and recommend any changes to the Board for approval.

In addition to corporate governance, we also have initiated efforts to encourage and motivate our employees to inspire continued company growth, progress and success. For instance, in April 2003 Isis' board of directors authorized an employee stock option exchange program to ensure that we maintained our highly-qualified employee base. In a manner sensitive to stockholder interests, the board structured the exchange program such that:

- Eligible employees could relinquish a larger number of higher-priced options to receive a smaller number of lower-priced new 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 5 years, minimizing long-term overhang.

This option exchange program created an opportunity to provide our employees with meaningful equity incentives while decreasing the fully diluted shares outstanding and enhancing the alignment of stockholder and employee interests.

A third example of our commitment to these principles is our proposed modifications to the 1989 Stock Option Plan, which are detailed in this year's proxy statement for the 2004 Annual Meeting of Stockholders. Isis' Board of Directors recommends we amend and restate the 1989 Plan to further bring stockholder and employee interests in line. As part of our best practices, we already follow most of the following guidelines; however, our goal is to formalize a plan to ensure stockholders' interests are visibly reflected.

I'd now like to describe how stockholder approval of these amendments would affect the 1989 Plan. It 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 7 years rather than the 10 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.

The amended plan also would increase the number of shares reserved for issuance under the plan by 3 million shares, allowing us to continue to retain and recruit highly skilled scientists and personnel in the face of intense competition. Without the amendment, we only have 1.7 million shares remaining under the 1989 Plan, which we estimate will be depleted by January 2005. Approving the additional 3 million requested shares will ensure that we can continue to grant an appropriate number of stock options to employees and consultants for at least two years. It is important to remember that all of Isis' management and employees have stock options or own shares in the company. We are dedicated to making Isis a continuous success, which in turn, generates value for stockholders.

Our Board of Directors believes that the proposed amendment and restatement of the 1989 Plan is in the best interests of Isis and our stockholders for the reasons stated above. **Therefore, the Board unanimously recommends a vote "for" approval of the amendment and restatement of the 1989 plan.**

Your vote on each of the proposals outlined in the proxy *is* important to the growth of Isis. Click here to learn more about how to cast your *vote*. We encourage you to take the time to review the proxy in detail and send in your vote via mail, internet or phone.

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 hope to see you at

our Annual Meeting of Stockholders on May 26, 2004. The meeting will be held at the company's headquarters in Carlsbad, California and will begin at 2:00 P.M. Pacific Time. This event is a great opportunity to meet Isis' management and employees, as they will showcase the company's latest advances in RNA-based product discovery and development.

Thank you for your continued support.

Sincerely,

/s/ B. LYNNE PARSHALL
B. Lynne Parshall
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.

Voting Rights and Outstanding Shares

We will begin mailing this Proxy Statement and accompanying proxy card on or about April 16, 2004 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on March 29, 2004 are entitled to vote at the Annual Meeting. On this record date, we had 55,999,594 shares of our Common Stock outstanding.

Each share of our Common Stock that you own entitles you to one vote. The proxy card indicates the number of shares of our Common Stock that you own. Votes will be counted by the inspector of election appointed for the meeting, who will separately count "For" and (with respect to proposals other than the election of directors) "Against" votes, abstentions and broker non-votes. Abstentions will be counted towards the vote total for each proposal, and will have the same effect as "Against" votes. Broker non-votes have no effect and will not be counted towards the vote total for any proposal. If your shares are held by your broker as your nominee (that is, in "street name"), you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. This year, Proposal 2 is a non-discretionary item.

You may vote in one of the following ways:

- Attend the 2004 Annual Meeting and vote in person;
- Complete, sign, date and return the enclosed proxy card; or
- Vote by telephone or the Internet by following the instructions included with your proxy card.

General Information for all Shares Voted via the Internet or by Telephone

Votes submitted via the Internet or by telephone must be received by 12:00 midnight, Eastern Daylight Time, on May 25, 2004. Submitting your proxy via the Internet or by telephone will not affect your right to vote in person should you decide to attend the Annual Meeting.

We provide Internet proxy voting to allow you to vote your shares on-line, with procedures designed to ensure the authenticity and correctness of your proxy vote instructions. However, please be aware that you must bear any costs associated with your Internet access, such as usage charges from Internet access providers and telephone companies.

For Shares Registered in Your Name

If you are a stockholder of record, you may go to <http://www.voteproxy.com> to vote your shares by means of the Internet. The votes represented by such proxy will be generated on the computer screen and you will be prompted to submit or revise your votes as desired. If you are using a touch-tone telephone you may also vote your shares by calling 1-800-PROXIES (1-800-776-9437) and following the recorded instructions. Please have your proxy card available at the time you are voting.

For Shares Registered in the Name of a Broker or Bank

Most beneficial owners whose stock is held in street name receive instructions for voting their shares from their bank, broker or other agent, rather than our proxy card.

A number of brokers and banks are participating in a program provided through ADP Investor Communication Services that allows proxies to vote shares to be granted by means of the telephone and Internet. If your shares are held in an account with a broker or bank participating in the ADP Investor Communication Services program, you may vote your shares online or via telephone (have the

voting form in hand) and call the number or go to the website indicated on the form and follow the instructions.

Revocability of Proxies

Once you have submitted your proxy by mail, Internet or telephone, you may revoke it at any time before we exercise it. You may revoke your proxy in any one of four ways:

- You may send in by mail another proxy marked with a later date;
- You may revoke it via the Internet;
- You may notify our Secretary in writing that you wish to revoke your proxy before the Annual Meeting takes place; or
- You may vote in person at the Annual Meeting. *Attendance* at the meeting *will not*, by itself, revoke a proxy.

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