

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 x

Filed by a Party other than the Registrant o

Check the appropriate box:

- o Preliminary Proxy Statement
- o **Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**
- o Definitive Proxy Statement
- x Definitive Additional Materials
- o 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):

- x No fee required.
- o 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: _____
 - (2) Aggregate number of securities to which transaction applies: _____
 - (3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined): _____
 - (4) Proposed maximum aggregate value of transaction: _____
 - (5) Total fee paid: _____
- o Fee paid previously with preliminary materials.
- o 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: _____
 - (4) Date Filed: _____

***** Exercise Your *Right* to Vote *****
**Important Notice Regarding the Availability of Proxy Materials for the
Stockholder Meeting to Be Held on June 16, 2011.**

ISIS PHARMACEUTICALS, INC.

ISIS PHARMACEUTICALS, INC.
1896 RUTHERFORD ROAD
CARLSBAD, CA 92008

Meeting Information

Meeting Type: Annual Meeting
For holders as of: April 20, 2011
Date: June 16, 2011 **Time:** 2:00 p.m. PDT
Location: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008

You are receiving this communication because you hold shares in the above named company.

This is not a ballot. You cannot use this notice to vote these shares. This communication presents only an overview of the more complete proxy materials that are available to you on the Internet. You may view the proxy materials online at www.proxyvote.com or easily request a paper copy (see reverse side).

We encourage you to access and review all of the important information contained in the proxy materials before voting.

See the reverse side of this notice to obtain proxy materials and voting instructions.

M35778-P04756

— Before You Vote —
How to Access the Proxy Materials

Proxy Materials Available to VIEW or RECEIVE:

NOTICE AND PROXY STATEMENT ANNUAL REPORT

How to View Online:

Have the information that is printed in the box marked by the arrow → (located on the following page) and visit: www.proxyvote.com

How to Request and Receive a PAPER or E-MAIL Copy:

If you want to receive a paper or e-mail copy of these documents, you must request one. There is NO charge for requesting a copy. Please choose one of the following methods to make your request:

- 1) BY INTERNET: www.proxyvote.com
- 2) BY TELEPHONE: 1-800-579-1639
- 3) BY E-MAIL*: sendmaterial@proxyvote.com

* If requesting materials by e-mail, please send a blank e-mail with the information that is printed in the box marked by the arrow → (located on the following page) in the subject line.

Requests, instructions and other inquiries sent to this e-mail address will NOT be forwarded to your investment advisor. Please make the request as instructed above on or before June 2, 2011 to facilitate timely delivery.

— How To Vote —

Please Choose One of the Following Voting Methods

Vote In Person: Many stockholder meetings have attendance requirements including, but not limited to, the possession of an attendance ticket issued by the entity holding the meeting. Please check the meeting materials for any special requirements for meeting attendance. At the meeting you will need to request a ballot to vote these shares.

Vote By Internet: To vote now by Internet, go to www.proxyvote.com. Have the information that is printed in the box marked by the arrow → available and follow the instructions.

Vote By Mail: You can vote by mail by requesting a paper copy of the materials, which will include a proxy card.

Voting Items

The Board of Directors recommends you vote FOR Proposals 1, 2 and 3:

1. Election of Directors

Nominees:

To be elected for terms expiring in 2014:

- 01) Spencer R. Berthelsen
- 02) B. Lynne Parshall
- 03) Joseph H. Wender

2. To approve the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan.

3. To approve, by non-binding vote, executive compensation.

The Board of Directors recommends you vote for 1 year:

4. To recommend, by non-binding vote, the frequency of executive compensation votes.

The Board of Directors recommends you vote FOR Proposal 5:

5. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2011 fiscal year.

NOTE: Such other business that may be properly presented at the meeting or any adjournment thereof.

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