

SCHEDULE 14A INFORMATION

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 / /

Check the appropriate box:

- /X/ 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 Section 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.
- / / 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:

/ / 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:

(4) Date Filed:

PRELIMINARY COPY

ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, CA 92008

NOTICE OF SPECIAL MEETING OF STOCKHOLDERS

TO BE HELD ON JANUARY 12, 2001

TO THE STOCKHOLDERS OF ISIS PHARMACEUTICALS, INC.:

NOTICE IS HEREBY GIVEN that a Special Meeting of Stockholders of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), will be held on Friday, January 12, 2001 at 8:00 a.m. local time at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008, for the following purposes:

1. To approve an amendment to the Company's Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 50,000,000 to 100,000,000 shares.
2. To transact such other business as may properly come before the meeting or any adjournment or postponement thereof.

The foregoing items of business are more fully described in the Proxy Statement accompanying this Notice.

The Board of Directors has fixed the close of business on December 13, 2000 as the record date for the determination of stockholders entitled to notice of and to vote at this Special Meeting and at any adjournment or postponement thereof.

By Order of the Board of Directors

B. Lynne Parshall
Executive Vice President,
Chief Financial Officer and Secretary

Carlsbad, California
December 21, 2000

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE COMPLETE, DATE, SIGN AND RETURN THE ENCLOSED PROXY AS PROMPTLY AS POSSIBLE IN ORDER TO ENSURE YOUR REPRESENTATION AT THE MEETING. A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) IS ENCLOSED FOR THAT PURPOSE. EVEN IF YOU HAVE GIVEN YOUR PROXY, YOU MAY STILL VOTE IN PERSON IF YOU ATTEND THE MEETING. PLEASE NOTE, HOWEVER, THAT IF YOUR SHARES ARE HELD OF RECORD BY A BROKER, BANK OR OTHER NOMINEE AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN FROM THE RECORD HOLDER A PROXY ISSUED IN YOUR NAME.

ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, CA 92008

PROXY STATEMENT
FOR SPECIAL MEETING OF STOCKHOLDERS

January 12, 2001

INFORMATION CONCERNING SOLICITATION AND VOTING

GENERAL

The enclosed proxy is solicited on behalf of the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), for use at a Special Meeting of Stockholders to be held on Friday, January 12, 2001 at 8:00 a.m. local time (the "Special Meeting"), or at any adjournment or postponement thereof, for the purposes set forth herein and in the accompanying Notice of Special Meeting. The Special Meeting will be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008. The Company intends to mail this proxy statement and accompanying proxy card on or about December 21, 2000 to all stockholders entitled to vote at the Special Meeting.

SOLICITATION

The Company will bear the entire cost of solicitation of proxies, including preparation, assembly, printing and mailing of this proxy statement, the proxy card and any additional information furnished to stockholders. Copies of solicitation materials will be furnished to banks, brokerage houses, fiduciaries and custodians holding in their names shares of Common Stock beneficially owned by others to forward to such beneficial owners. The Company may reimburse persons representing beneficial owners of Common Stock for their costs of forwarding solicitation materials to such beneficial owners. Original solicitation of proxies by mail may be supplemented by telephone, telegram or personal solicitation by directors, officers or other regular employees of the Company or, at the Company's request, Georgeson Shareholder Communications, Inc. No additional compensation will be paid to directors, officers or other regular employees for such services, but Georgeson Shareholder Communications, Inc. will be paid its customary fee, estimated to be about \$8,000, if it renders solicitation services.

VOTING RIGHTS AND OUTSTANDING SHARES

Only holders of record of the Company's Common Stock at the close of business on December 13, 2000 will be entitled to notice of and to vote at the Special Meeting. At the close of business on December 13, 2000, the Company had outstanding and entitled to vote _____ shares of Common Stock. Each holder of record of Common Stock on such date will be entitled to one vote for each share held on all matters to be voted upon at the Special Meeting.

All votes will be tabulated by the inspector of election appointed for the meeting, who will separately tabulate affirmative and negative votes, abstentions and broker non-votes. Abstentions and broker non-votes will be counted towards the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes.

REVOCABILITY OF PROXIES

Any person giving a proxy pursuant to this solicitation has the power to revoke it at any time before it is voted. It may be revoked by filing with the Secretary of the Company at the Company's principal executive office, 2292 Faraday Avenue, Carlsbad, California 92008, a written notice of revocation or a duly executed proxy bearing a later date, or it may be revoked by attending the meeting and voting in person. Attendance at the meeting will not, by itself, revoke a proxy.

STOCKHOLDER PROPOSALS

The deadline for submitting a stockholder proposal for inclusion in the Company's proxy statement and form of proxy for the Company's 2001 annual meeting of stockholders pursuant to Rule 14a-8 of the Securities and Exchange

Commission (the "SEC") is December 25, 2000. Stockholders wishing to submit proposals or director nominations that are not to be included in such proxy statement and proxy must also do so by December 25, 2000. Stockholders are also advised to review the Company's Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

PROPOSAL 1

APPROVAL OF INCREASE IN NUMBER OF AUTHORIZED SHARES OF COMMON STOCK

The Board of Directors has adopted, subject to stockholder approval, an amendment to the Company's Restated Certificate of Incorporation to increase the Company's authorized number of shares of Common Stock from 50,000,000 shares to 100,000,000 shares.

The additional Common Stock to be authorized by adoption of the amendment would have rights identical to the currently outstanding Common Stock of the Company. Adoption of the proposed amendment and issuance of the Common Stock would not affect the rights of the holders of Common Stock or the Company's Series A Preferred Stock or Series B Preferred Stock, except for effects incidental to increasing the number of shares of the Company's Common Stock outstanding, such as dilution of the earnings per share and voting rights of current holders of the Company's Common Stock. If the amendment is adopted, it will become effective upon filing of a Certificate of Amendment of the Company's Restated Certificate of Incorporation with the Secretary of State of the State of Delaware. The complete text of the Certificate of Amendment to the Restated Certificate that would be filed with the Secretary of State of the State of Delaware is set forth in Exhibit A to this Proxy Statement. However, the text of the Certificate of Amendment is subject to revision to include such changes as may be required by the Secretary of State of the State of Delaware and as the Board deems necessary and advisable to effect the proposed amendment of the Company's Restated Certificate of Incorporation.

In addition to the 39,001,173 shares of Common Stock outstanding at October 31, 2000, the Company has reserved 3,516,908 shares of Common Stock for possible issuance under a Form S-3 shelf registration statement currently on file with the Securities and Exchange Commission. Also as of October 31, 2000, there were 7,934,467 shares of Common Stock issuable upon exercise of outstanding options granted under the Company's stock option plans and 1,340,088 shares of Common Stock subject to future issuance under the Company's equity plans. The Company has also issued warrants and convertible debt which, on October 31, 2000, would have been exercisable and convertible into an aggregate of 3,994,759 shares of Common Stock. In addition, the Company has outstanding 129,568 shares of Series A Preferred Stock and 12,497 shares of Series B Preferred Stock which is convertible into Common Stock on March 31, 2001 and June 30, 2002, respectively. The Preferred Stock converts into Common Stock at a premium to market at the time of conversion. If the Company's preferred stock were convertible on October 31, 2000, it would convert into an aggregate of 1,791,844 shares of Common Stock on such date.

Although at present the Board of Directors has no other plans to issue the additional shares of Common Stock, it desires to have the shares available to provide additional flexibility to the Company for business and financial purposes in the future. The additional shares may be used, without further stockholder approval, for various purposes including, without limitation, raising capital, providing equity incentives to employees, directors or consultants, establishing strategic relationships with other companies and expanding the Company's business or product lines through the acquisition of other businesses or products.

The additional shares of Common Stock that would become available for issuance if the proposal were adopted could also be used by the Company to oppose a hostile takeover attempt or delay or prevent changes in control or management of the Company. For example, without further stockholder approval, the Board could strategically sell shares of Common Stock in a private transaction to purchasers who would oppose a takeover or favor the current Board. Although this proposal to increase the authorized Common Stock has been prompted by business and financial considerations and not by the threat of any hostile takeover attempt, nor is the Board currently aware of any such attempts directed at the Company, nevertheless, stockholders should be aware that approval of this proposal could facilitate future efforts by the Company to deter or prevent changes in control of the Company, including transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices.

The affirmative vote of the holders of a majority of the shares of the Common Stock will be required to approve this amendment to the Company's Restated Certificate of Incorporation. As a result, abstentions and broker non-votes will have the same effect as negative votes.

THE BOARD OF DIRECTORS RECOMMENDS
A VOTE IN FAVOR OF PROPOSAL 1

SECURITY OWNERSHIP OF
CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table sets forth certain information regarding the ownership of the Company's Common Stock as of October 31, 2000 by: (i) each director of the Company; (ii) the Company's Chief Executive Officer and its other four most highly compensated executive officers; (iii) all executive officers and directors of the Company as a group; and (iv) all those known by the Company to be beneficial owners of more than five percent of its Common Stock.

BENEFICIAL OWNER	BENEFICIAL OWNERSHIP (1)	
	NUMBER OF SHARES	PERCENT OF TOTAL (2)
Citigroup Inc. (3) 153 Greenwich Street New York, NY 10043	3,986,883	10.2
Novartis Pharma AG (4) Lichtstrasse 35 CH-4002, Basel SWITZERLAND	2,354,150	6.0
Stanley T. Crooke (5)	1,314,931	3.3
Christopher F. O. Gabrieli (6)	1,256,349	3.2
Alan C. Mendelson (7)	40,027	*
William R. Miller (8)	60,000	*
B. Lynne Parshall (9)	283,976	*
Mark B. Skaletsky (10)	47,000	*
Joseph H. Wender (11)	71,000	*
C. Frank Bennett (12)	91,130	*
F. Andrew Dorr (13)	36,259	*
David J. Ecker (14)	167,679	*
All directors and executive officers as a group (11 persons)(15)	3,524,460	8.8

* Less than one percent.

(1) This table is based upon information supplied by officers, directors and principal stockholders and Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, the Company believes that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.

- (2) Applicable percentages are based on 39,001,173 shares of Common Stock outstanding on October 31, 2000, adjusted as required by rules promulgated by the SEC.
- (3) Includes _____ shares of Common Stock held by Salomon Smith Barney Holdings Inc., a wholly-owned subsidiary of Citigroup Inc. Also includes _____ shares of Common Stock held by Salomon Brothers Holding Company Inc., a wholly-owned subsidiary of Salomon Smith Barney Holdings, Inc., and _____ shares of Common Stock held by Salomon Smith Barney Inc., a wholly-owned subsidiary of Salomon Brothers Holding Company Inc.
- (4) Includes 2,219,000 shares of Common Stock held by Novartis Pharma AG, 38,053 shares of Common Stock held by Novartis Pharmaceuticals Corporation, and 97,097 shares of Common Stock held by Genetic Therapy Inc. Novartis Pharmaceuticals Corporation and Genetic Therapy Inc. are Delaware corporations and are directly or indirectly wholly-owned subsidiaries of Novartis Pharma AG.
- (5) Includes 281,483 shares of Common Stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before December 30, 2000 and 16,207 shares of Common Stock issuable upon exercise of options held by Rosanne Crooke, Mr. Crooke's wife, that are exercisable on or before December 30, 2000. Dr. Crooke disclaims beneficial ownership of the shares of Common Stock issuable upon exercise of options held by his wife.
- (6) Includes 759,566 shares of Common Stock held of record by Bessemer Venture Partners II ("BVP II"), 329,479 shares of Common Stock held of record by Bessemer Venture Partners III ("BVP III") and 740 shares of Common Stock held of record by the Gabrieli Family Foundation ("GFF"). Mr. Gabrieli is a Manager of Deer II & Co. LLC and of Deer III & Co. LLC, the General Partners of BVP II and BVP III, respectively, and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to BVP II and BVP III except to the extent of his respective interests therein. Mr. Gabrieli is a trustee of GFF and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to GFF. Also includes 50,500 shares of Common Stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before December 30, 2000.
- (7) Includes an aggregate of 620 shares of Common Stock held in trust by Mr. Mendelson's wife for his sons and 25,000 shares of Common Stock issuable upon exercise of options held by Mr. Mendelson that are exercisable on or before December 30, 2000. Mr. Mendelson disclaims beneficial ownership of the shares of Common Stock held in trust by his wife for his sons.
- (8) Includes 18,000 shares of Common Stock issuable upon exercise of options held by Mr. Miller that are exercisable on or before December 30, 2000.
- (9) Includes 265,110 shares of Common Stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before December 30, 2000, and an aggregate of 18,554 shares of Common Stock issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before December 30, 2000.
- (10) Includes 25,000 shares of Common Stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before December 30, 2000.
- (11) Includes 40,000 shares of Common Stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before December 30, 2000.
- (12) Includes 91,007 shares of Common Stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before December 30, 2000.
- (13) Includes 36,259 shares of Common Stock issuable upon exercise of options held by Dr. Dorr that are exercisable on or before December 30, 2000.
- (14) Includes 33,840 shares of Common Stock held in the Ecker Family Revocable Trust of which Dr. Ecker is a trustee, 2,491 shares of Common Stock owned by his daughter, and 2,891 shares of Common Stock owned by his son. Also includes 128,457 shares of Common Stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before December 30, 2000.
- (15) Includes shares of Common Stock described in the notes above, as applicable.

OTHER MATTERS

The Board of Directors knows of no other matters that will be presented for consideration at the Special Meeting. If any other matters are properly brought before the meeting, it is the intention of the persons named in the accompanying proxy to vote on such matters in accordance with their best judgment.

By Order of the Board of Directors

B. Lynne Parshall
Executive Vice President,
Chief Financial Officer and Secretary

December 21, 2000

EXHIBIT A

CERTIFICATE OF AMENDMENT OF
RESTATED CERTIFICATE OF INCORPORATION OF
ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on December 8, 2000 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 115,000,000 shares, consisting of 100,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this ____ day of _____, 2001.

By:

Stanley T. Crooke
Chairman of the Board of Directors
and Chief Executive Officer

ISIS PHARMACEUTICALS, INC.
PROXY SOLICITED BY THE BOARD OF DIRECTORS
FOR THE SPECIAL MEETING OF STOCKHOLDERS TO BE HELD ON JANUARY 12, 2001

The undersigned hereby appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as attorneys and proxies of the undersigned, with full power of substitution, to vote all of the shares of stock of Isis Pharmaceuticals, Inc. (the "Company") which the undersigned may be entitled to vote at the Special Meeting of Stockholders of the Company to be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008 on Friday, January 12, 2001 at 8:00 a.m., and at any and all continuations and adjournments thereof, with all powers that the undersigned would possess if personally present, upon and in respect of the following matters and in accordance with the following instructions, with discretionary authority as to any and all other matters that may properly come before the meeting.

UNLESS A CONTRARY DIRECTION IS INDICATED, THIS PROXY WILL BE VOTED FOR PROPOSAL 1 AS MORE SPECIFICALLY DESCRIBED IN THE PROXY STATEMENT. IF SPECIFIC INSTRUCTIONS ARE INDICATED, THIS PROXY WILL BE VOTED IN ACCORDANCE THEREWITH.

(Continued on other side)

PLEASE DATE, SIGN AND MAIL YOUR PROXY CARD BACK AS SOON AS POSSIBLE!

SPECIAL MEETING OF STOCKHOLDERS
ISIS PHARMACEUTICALS, INC.

January 12, 2001

PLEASE DETACH AND MAIL IN THE ENVELOPE PROVIDED

Please mark your
/ X / votes as in this
example

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSAL 1

	FOR	AGAINST	ABSTAIN
Proposal 1: Amendment of the Certificate of Incorporation to increase the Company's authorized common stock from 50,000,000 shares to 100,000,000 shares	/ /	/ /	/ /

PLEASE VOTE, DATE AND PROMPTLY RETURN THIS PROXY IN THE ENCLOSED RETURN ENVELOPE WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES.

SIGNATURE _____ DATE _____ SIGNATURE _____ DATE _____
(SIGNATURE IF HELD JOINTLY)

NOTE: Please sign exactly as your name appears hereon. If the stock is registered in the names of two or more persons, each should sign. Executors, administrators, trustees, guardians and attorneys-in-fact should add their titles. If signer is a corporation, please give full corporate name and have a duly authorized officer sign, stating title. If signer is a partnership, please sign in partnership name by authorized person.