

SCHEDULE 14A INFORMATION
(Rule 14a-101)

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 sec.240.14a-11(c) or sec.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)(4) 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:

ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CA 92008

NOTICE OF
1999 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 1999 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Friday, May 21 at 2 P.M. In addition to covering the formal items on the agenda, we will review the major developments of the past year and answer your questions.

This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. The Proxy Statement explains the matters we will discuss in the meeting, and provides general information about Isis Pharmaceuticals.

Your vote is very important. Whether or not you plan to attend the meeting, please complete, date, sign and return the enclosed proxy as soon as possible to ensure your representation at the meeting. We have provided a postage-paid envelope for your convenience. If you plan to attend the meeting and prefer to vote in person, you may still do so even if you have already returned your proxy.

PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR NOMINEE.

We look forward to seeing you at the meeting.

Sincerely,

B. Lynne Parshall
Secretary

ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CA 92008

NOTICE OF 1999 ANNUAL MEETING OF STOCKHOLDERS

Date: Friday, May 21, 1999

Time: 2:00 P.M.

Place: Isis Pharmaceuticals
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Stockholders,

At our 1999 Annual Meeting, we will ask you to:

- o Elect two Directors to serve for a three-year term;
- o Ratify the selection of Ernst & Young LLP as independent auditors for 1999;
- o Transact any other business that may properly be presented at the Annual Meeting.

If you were an Isis stockholder of record at the close of business on March 29, 1999, you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CA 92008

PROXY STATEMENT

INFORMATION ABOUT THE 1999 ANNUAL MEETING AND VOTING

GENERAL

The enclosed proxy card has been sent to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, so you may vote at the 1999 Annual Meeting of Stockholders. This Proxy Statement summarizes the information you will need to know to vote in an informed manner.

VOTING RIGHTS AND OUTSTANDING SHARES

We will begin mailing this Proxy Statement and accompanying proxy card on or about April 12, 1999 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on March 29, 1999 are entitled to vote at the Annual Meeting. On this record date, we had 27,327,345 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. The inspector of election will separately tabulate affirmative and negative votes, abstentions and broker non-votes. Abstentions will count as a cast vote that has the same effect as a negative vote. The inspector of election will count broker non-votes towards a quorum, but not towards whether the stockholders have approved a proposal.

You may vote in one of two ways:

- o Attend the 1999 Annual Meeting and vote in person, or
- o Simply complete, sign and return the enclosed proxy card.

SOLICITATION

We will pay all the costs associated with soliciting these proxies. In addition to mailing proxy-soliciting material, our directors and employees may also solicit proxies in person, by telephone or by other electronic means of communication. We will ask banks, brokerage houses, fiduciaries, and custodians to forward the proxy material to their principals and to obtain authority to execute proxies. We will then reimburse them for expenses.

REVOCABILITY OF PROXIES

Once you have returned your proxy, you may revoke it at any time before we exercise it. You may revoke your proxy in any one of three ways:

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

STOCKHOLDER PROPOSALS

If you have a proposal you would like to be presented at the 2000 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 14, 1999 to be included in the proxy statement.

PROPOSAL 1

ELECTION OF DIRECTORS

INFORMATION ABOUT OUR BOARD OF DIRECTORS

The Board is divided into three classes, each consisting as nearly as possible of one-third of the total number of directors. Presently, the Board has eight members, so two classes consist of three directors, and one class consists of two directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to replace the directors whose term has expired.

During the course of a term, the Board may elect a new director to fill any vacant spot (including a vacancy caused by an increase in the size of the Board). The new director will finish out the term of the director he or she replaced.

INFORMATION ABOUT THE 1999 ELECTIONS

The Board has nominated two directors for election at the 1999 Annual Meeting. Each of the nominees currently serves as one of our directors. If re-elected, each will serve until the 2002 annual meeting or until his successor is elected and has qualified.

Our stockholders elect directors by a plurality of the votes of the shares present in person or represented by proxy at the meeting and entitled to vote in the election of directors. Each person nominated for election has agreed to serve if elected, and we have no reason to believe that any nominee will be unable to serve. However, if any nominee cannot serve, your proxy may vote for another nominee proposed by the Board, or the Board may reduce the number of directors.

We provide below a short biographical description of each of the nominees.

THE BOARD RECOMMENDS THAT YOU VOTE "IN FAVOR" OF THE ELECTION OF EACH OF THE FOLLOWING NOMINEES.

BIOGRAPHIES OF NOMINEES FOR ELECTION FOR A THREE-YEAR TERM EXPIRING AT THE 2002 ANNUAL MEETING

LARRY SOLL, Ph.D., age 56, has served as a director of Isis since July 1992. He was Chairman of the Board of Directors of Synergen, Inc., a biopharmaceutical company, from 1986 to December 1994 and CEO from April 1993 to May 1994. Dr. Soll is a trustee of INVESCO Global Health Sciences, a closed-end investment fund; a director of the INVESCO Family of Mutual Funds, an open-ended mutual fund; and was a director of ImmuLogic Pharmaceuticals Corporation, a biopharmaceutical company, until February 1997.

JOSEPH H. WENDER, age 54, has served as a director of Isis since January 1994. Mr. Wender is currently Senior Director of the Financial Institutions Group at Goldman, Sachs & Co., an investment banking firm. He joined Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982 and a Limited Partner in 1992. He is also a director of First Coastal Bancshares, a bank holding company.

BIOGRAPHIES OF CONTINUING BOARD MEMBERS UNTIL THE 2000 ANNUAL MEETING

ALAN C. MENDELSON, age 51, has served as a director of Isis since January 1989. He has been a partner of Cooley Godward LLP since January 1980. Mr. Mendelson served as Acting General Counsel at Cadence Design Systems, Inc., an electronic design automation software company, from November 1995 to June 1996. He is also a director of CoCensys, Inc., a biopharmaceutical company.

WILLIAM R. MILLER, age 70, has served as a director of Isis since March 1991. In January 1991, he retired as Vice Chairman of the Board of Directors of Bristol-Myers Squibb Company, a position he had held since 1985. He is Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory. Mr. Miller is also Chairman of the Board of SIBIA Neurosciences, Inc. and of Vion Pharmaceuticals, both biopharmaceutical companies. He is a director of ImClone Systems, Inc. and Transkaryotic Therapies, Inc., both biopharmaceutical companies, Westvaco Corporation, a paper/packaging/specialty chemical manufacturer, and Xomed Surgical Products, Inc., a medical device company.

CHRISTOPHER F.O. GABRIELI, age 39, has served as a director of Isis since May 1994. Mr. Gabrieli was a founder of Isis and served as a director from January 1989 to May 1992. He is currently a manager of the general partners of Bessemer Venture Partners II L.P., Bessemer Venture Partners III L.P., and Bessemer Venture Partners IV L.P., related venture capital partnerships, where he has worked since 1986. He is Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. He also serves on the Board of several privately held healthcare companies.

BIOGRAPHIES OF CONTINUING BOARD MEMBERS UNTIL THE 2001 ANNUAL MEETING

BURKHARD BLANK, M.D., age 44, has served as a director of Isis since June, 1997. Dr. Blank joined Boehringer Ingelheim GmbH in 1986 and has been head of its Project Management Division since 1993. Dr. Blank also serves on the Board of Directors at Cambridge Neuroscience, Inc., a biopharmaceutical company. We have an agreement with Boehringer Ingelheim International GmbH that entitles it to designate a representative reasonably satisfactory to Isis for election to our Board of Directors. Dr. Blank is Boehringer's representative.

STANLEY T. CROOKE, M.D., Ph.D., age 54, was a founder of Isis and has been its CEO and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke is Chairman of the Board of GeneMedicine, Inc., and a director of SIBIA Neurosciences, Inc., both pharmaceutical companies, and is a director of EPIX Medical, Inc. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

MARK B. SKALETSKY, age 50, has served as a director since January 1989. Since May 1993, Mr. Skaletsky has been President and CEO of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. Enzytech, Inc., a biopharmaceutical company, employed Mr. Skaletsky from April 1988 to February 1993 in a variety of positions, including Chairman of the Board and CEO. In February 1993, Enzytech merged into a wholly owned subsidiary of Alkermes, Inc. Mr. Skaletsky is a director of Microcide, Inc. and LeukoSite, Inc., both biopharmaceutical companies; the Biotechnology Industry Organization, an industry organization; and the Massachusetts Biotechnology Council.

THE BOARD OF DIRECTOR COMMITTEES AND MEETINGS

The Board of Directors met five times in 1998. The Board of Directors also has Audit and Financing, Compensation, and Nominating committees.

The Audit and Financing Committee is comprised of Mr. Mendelson (Chairman), Mr. Wender and Mr. Skaletsky. The committee met six times in 1998. The Audit and Financing Committee:

- o Recommends engagement of our independent auditors;
- o Approves services performed by the auditors (including the review and evaluation of our accounting system and its system of internal controls) in connection with our annual audit;
- o Reviews our balance sheet and statement of operations and cash flows for each interim period;
- o Reviews any changes in accounting policy that have occurred during the interim period;
- o Reviews any changes in accounting systems and procedures as well as the system of internal controls;
- o Helps our management review financing opportunities, make recommendations to the Board, and implement financing projects as approved by the Board.

The Compensation Committee is comprised of Mr. Skaletsky (Chairman), Mr. Miller and Mr. Wender. Every member of the Compensation Committee is a non-employee director. The committee met three times in 1998. The Compensation Committee:

- o Makes recommendations concerning executive salaries and incentive compensation;
- o Awards stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan; o Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

The Nominating Committee is composed of two non-employee directors: Mr. Mendelson and Dr. Soll. The Committee did not meet in 1998. The Nominating Committee:

- o Interviews, evaluates, nominates and recommends individuals for membership on our Board of Directors and its committees;
- o Considers nominees our stockholders recommend.

During 1998, all of the directors attended at least 80% of the meetings of the Board and the committees on which they served except Mr. Gabrieli who missed two Board meetings during the year.

SECTION 16(a) BENEFICIAL OWNERSHIP REPORTING COMPLIANCE

Section 16(a) of the Securities Exchange Act of 1934 requires our directors, executive officers, and holders of more than 10% of our Common Stock to file with the Securities and Exchange Commission (the "SEC") initial reports of ownership and reports of changes in ownership of our Common Stock. We believe that during the fiscal year ended December 31, 1998, our officers and directors complied with all these filing requirements; however, David J. Ecker, one of our officers, inadvertently failed to report on his initial report that his son and daughter each owned a small amount of our Common Stock. Now he has reported all his transactions. In making this statement, we relied upon the written representations of our directors and executive officers. Based on stockholder filings, we do not believe the filing requirements of Section 16(a) apply to any other stockholders.

PROPOSAL 2

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "IN FAVOR" OF PROPOSAL #2

The Board of Directors has selected Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 1999, and has requested the management to ask for stockholder approval at the Annual Meeting. Ernst & Young LLP have audited our financial statements since we were founded in 1989. Representatives of Ernst & Young LLP will be at the 1999 Annual Meeting to answer any questions and make a statement should they choose to do so.

Although our Bylaws do not require stockholders to approve our independent auditors, the Board would like to hear the stockholders' opinion as a matter of good corporate practice. If the stockholders vote against Ernst & Young LLP, the Board will reconsider whether or not to keep the firm. However, even if the stockholders approve the selection, the Board may choose to appoint a different independent accounting firm at any time during the year if it feels that any change would be in the best interests of Isis and its stockholders.

To ratify the selection of Ernst & Young LLP, the holders of a majority of shares must vote in favor of Proposal #2 at the 1999 Annual Meeting.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our Common Stock as of February 28, 1999 by:

- o Each executive officer named in the Summary Compensation Table under "Executive Compensation--Compensation of Executive Officers";
- o All other directors and executive officers as a group; and
- o Every entity we know that beneficially owns more than five percent of our Common Stock.

| BENEFICIAL OWNER ----- | BENEFICIAL OWNERSHIP(1) | |
|--|---------------------------|------------------------------|
| | NUMBER OF SHARES ----- | PERCENT OF TOTAL(2) ----- |
| Boehringer Ingelheim International GmbH Binger Strasse 173 D-55216 Ingelheim Am Rhein GERMANY | 2,412,607 | 8.9 |
| Novartis AG(3) Lichtstrasse 35 CH-4002, Basel SWITZERLAND | 2,354,150 | 8.7 |
| Christopher F. O. Gabrieli(4) 83 Walnut Street Wellesley Hills, MA 02181 | 1,694,334 | 6.1 |
| Reliance Financial Services Corporation(5) Park Avenue Plaza 55 East 52nd Street New York, NY 10055 | 1,607,500 | 5.7 |
| Bessemer Venture Partners(6) 1400 Old Country Road, Suite 407 Westbury, NY 11590 | 1,536,465 | 5.6 |
| Burkhard Blank(7) | 5,500 | * |
| Stanley T. Crooke(8) | 1,332,527 | 4.9 |
| Daniel L. Kisner(9) | 429,667 | 1.6 |
| Alan C. Mendelson(10) | 32,157 | * |
| William R. Miller(11) | 50,750 | * |
| Mark B. Skaletsky(12) | 37,750 | * |
| Larry Soll(13) | 50,750 | * |
| Joseph H. Wender(14) | 61,750 | * |
| C. Frank Bennett(15) | 62,069 | * |
| David J. Ecker(16) | 166,197 | * |
| B. Lynne Parshall(17) | 302,063 | 1.1 |
| All directors and executive officers as a group (13 persons)(18) ... | 4,348,730 | 15.0 |

* Less than one percent

- (1) We based this table upon information our directors, executive officers and principal stockholders supplied us and filed with the Securities and Exchange Commission on Schedules 13D and 13G. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, each of the stockholders we name in this table has sole voting and investment power for the shares we indicate as beneficially owned. Unless otherwise indicated, the address of each stockholder listed above is in the care of Isis at 2292 Faraday Avenue, Carlsbad, California 92008.
- (2) Applicable percentage ownership is based on 27,169,623 shares of Common Stock outstanding on February 28, 1999.
- (3) Includes 2,219,000 shares currently registered to Novartis Pharma AG, 38,053 shares registered to Novartis Pharmaceuticals Corporation, and 97,097 shares registered to Genetic Therapy Inc. Novartis Pharma AG, Novartis Pharmaceuticals Corporation and Genetic Therapy Inc. are all directly or indirectly wholly owned subsidiaries of Novartis AG, a corporation registered in Switzerland. Novartis Pharmaceuticals Corporation and Genetic Therapy, Inc. are Delaware corporations.
- (4) Includes 759,566 shares held of record by Bessemer Venture Partners II L.P. ("BVP II"), 335,485 shares held of record by Bessemer Venture Partners III L.P. ("BVP III") and 350 shares held of record by the Gabrieli Family Foundation ("GFF"). Also includes 434,639 shares issuable upon exercise of Class A Warrants held of record by BVP III and 1,123 shares issuable upon exercise of Class A Warrants held of record by GFF. Mr. Gabrieli is a Manager of Deer II & Co. LLC, the general partner of BVP II, and of Deer III & Co. LLC, the general partner of BVP III, and disclaims beneficial ownership of the shares 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 held of record by or issuable to GFF. Does not include an aggregate of 1,610 shares and an aggregate of 5,165 shares issuable upon exercise of Class A Warrants held of record by seven stockholders who have agreed to vote the shares as directed by BVP III; Mr. Gabrieli also disclaims beneficial ownership of the shares. Also includes 2,246 shares issuable upon exercise of Class A Warrants held by Mr. Gabrieli and 40,916 shares issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 29, 1999.
- (5) Includes 800,000 common stock purchase warrants exercisable at a price of \$25.00 per share.
- (6) Includes 759,566 shares held of record by BVP II, 335,485 shares held of record by BVP III and 434,639 shares issuable upon exercise of Class A Warrants held of record by BVP III. Also includes an aggregate of 1,610 shares and an aggregate of 5,165 shares issuable upon exercise of Class A Warrants held of record by seven stockholders who have agreed to vote the shares as directed by BVP III; BVP III disclaims beneficial ownership of the shares.
- (7) Excludes shares beneficially owned by Boehringer Ingelheim International AG as Dr. Blank does not, directly or indirectly, have or share voting power or investment power over these shares.
- (8) Includes 211,173 shares issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 29, 1999 and 11,854 shares issuable upon exercise of options held by his wife that are exercisable on or before April 29, 1999. Dr. Crooke disclaims beneficial ownership of the shares issuable upon exercise of options held by his wife.
- (9) Includes 429,667 shares issuable upon exercise of options held by Dr. Kisner that are exercisable on or before April 29, 1999 and an aggregate of 4,000 shares issuable upon exercise of options which Dr. Kisner transferred to his son and daughter that are exercisable on or before April 29, 1999.
- (10) Includes an aggregate of 620 shares held in trust by Mr. Mendelson's wife for his sons and 26,250 shares issuable upon exercise of options held by Mr. Mendelson that are exercisable on or before April 29, 1999. Mr. Mendelson disclaims beneficial ownership of the shares held in trust by his wife for his sons.

- (11) Includes 8,750 shares issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 29, 1999.
- (12) Includes 15,750 shares issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 29, 1999.
- (13) Includes 50,750 shares issuable upon exercise of options held by Dr. Soll that are exercisable on or before April 29, 1999.
- (14) Includes 30,750 shares issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 29, 1999.
- (15) Includes 61,994 shares issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 29, 1999.
- (16) Includes 54,874 shares held in the Ecker Family Revocable Trust in which Dr. Ecker is a trustee, 967 shares owned by his daughter, and 1,367 shares owned by his son. Also includes 108,989 shares issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 29, 1999.
- (17) Includes 277,437 shares issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 29, 1999, and an aggregate of 4,000 shares issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before April 29, 1999.
- (18) Includes shares described in the notes above, as applicable.

EXECUTIVE COMPENSATION

COMPENSATION OF DIRECTORS

We pay our non-employee directors a fee of \$15,000 per year. We do not pay additional compensation for attending Board or Board Committee meetings, but we do reimburse Board members for the expenses they incur to attend the meetings. For the fiscal year ending December 31, 1998, we paid a total of \$105,000 to our non-employee directors.

We also grant each non-employee director a stock option under the 1992 Non-Employee Directors' Stock Option Plan (the "Directors' Plan"). The options are non-discretionary and only non-employee directors may receive options under this plan. On July 1 of each year (or the next business day should this date fall on a weekend or holiday), we automatically grant each non-employee director an option to purchase 4,000 shares of our Common Stock. On July 1, 1998, we granted options to purchase an aggregate of 28,000 shares of stock. The fair market value of the Common Stock (and the exercise price of the options) was \$13.25 per share (based on the closing sales price reported in the Nasdaq National Market on the date of grant).

In addition, upon initial election to the Board, we grant each new Non-Employee Director an option to purchase 18,000 shares of our Common Stock. The exercise price of all the stock options we grant is equal to 100% of the fair market value of the Common Stock on the date of the grant.

As of February 28, 1999, none of the options granted in 1998 under the Directors' Plan had vested.

COMPENSATION OF EXECUTIVE OFFICERS AND OTHER EMPLOYEES

The following table outlines the compensation paid by Isis to the Chief Executive Officer and each of the four other highest paid executive officers whose total annual salary and bonus exceeded \$100,000. The table shows compensation information for the fiscal years ending December 31, 1998, 1997, and 1996.

SUMMARY COMPENSATION TABLE

| Name and Principal Position | Year | Annual Compensation | | | Long-Term Compensation Awards | All Other Compensation (\$)(3) |
|--|------|---------------------|---------------|---|--|--------------------------------------|
| | | Salary (\$) | Bonus (\$) | Other Annual Compensation (\$)(1)(2) | Securities Underlying Options (#) | |
| Stanley T. Crooke Chairman and Chief Executive Officer 1996 | 1998 | 361,992 | 253,400 | 0 | 70,000 | 0 |
| | 1997 | 310,008 | 169,531 | 0 | 22,500 | 0 |
| | 1996 | 280,344 | 98,119 | 0 | 40,000 | 0 |
| Daniel L. Kisner President and Chief Operating Officer | 1998 | 294,000 | 167,213 | 0 | 50,000 | 0 |
| | 1997 | 272,712 | 122,724 | 0 | 18,000 | 0 |
| | 1996 | 257,280 | 77,185 | 0 | 25,000 | 0 |
| B. Lynne Parshall Executive Vice President & Chief Financial Officer | 1998 | 265,368 | 139,315 | 0 | 45,000 | 0 |
| | 1997 | 250,344 | 112,653 | 0 | 17,000 | 0 |
| | 1996 | 236,171 | 70,851 | 0 | 16,000 | 0 |
| David J. Ecker Vice President, Managing Director, Ibis Therapeutics(TM) | 1998 | 175,331 | 65,749 | 0 | 10,000 | 0 |
| | 1997 | 166,981 | 57,400 | 0 | 7,000 | 0 |
| | 1996 | 159,030 | 41,745 | 0 | 18,000 | 0 |
| C. Frank Bennett Vice President, Biology | 1998 | 160,206 | 57,574 | 0 | 14,000 | 0 |
| | 1997 | 151,138 | 59,038 | 0 | 9,000 | 0 |
| | 1996 | 141,250 | 42,375 | 0 | 12,000 | 0 |

- (1) As permitted by rules promulgated by the SEC, no amounts are shown where the amounts constitute perquisites and do not exceed the higher of 10% of the sum of the amount in the Salary and Bonus column and \$50,000.
- (2) None of the persons listed in the table held restricted stock as of December 31, 1998.
- (3) Does not include excess group term life insurance premiums which do not exceed, for any individual, \$3,000 and which were paid on the same basis as was offered to all salaried employees.

STOCK OPTION GRANTS AND EXERCISES

Executive officers are granted options under the 1989 Stock Option Plan. As of February 28, 1999, options to purchase a total of 7,411,417 shares had been granted and were outstanding under the 1989 Stock Option Plan.

The following tables show certain information regarding options granted to, exercised by and held at year end (for the fiscal year ended December 31, 1998) by each of the executive officers named in the Summary Compensation Table:

OPTION GRANTS IN LAST FISCAL YEAR

| Name | Individual Grants | | | | | Potential Realizable Value at Assumed Annual Rates of Stock Price Appreciation for Option Term (3) | |
|--|--|---|--------------------|----------------------------|-----------------|--|-----------|
| | Number of Securities Underlying Options Granted (#)(1) | % of Total Options Granted to Employees in Fiscal Year(2) | Base Price (\$/Sh) | Aggregate Dollar Value(\$) | Expiration Date | ----- | |
| | | | | | | 5%(\$) | 10%(\$) |
| Stanley T. Crooke | 70,000 | 6.19 | \$ 12.3125 | 861,875 | 12-31-07 | 541,841 | 1,373,023 |
| Daniel L. Kisner | 50,000 | 4.42 | \$ 12.3125 | 615,625 | 12-31-07 | 387,029 | 980,731 |
| C. Frank Bennett | 14,000 | 1.24 | \$ 12.3125 | 172,375 | 12-31-07 | 108,368 | 274,605 |
| David J. Ecker | 10,000 | .88 | \$ 12.3125 | 123,125 | 12-31-07 | 77,406 | 196,146 |
| B. Lynne Parshall | 45,000 | 3.98 | \$ 12.3125 | 554,063 | 12-31-07 | 348,326 | 882,658 |
| All Executive Officers as a Group | 201,000 | | | 2,474,813 | | | |
| All Non-Executive Officer Directors as a Group (4) | 28,000 | | | 371,000 | | | |
| All Non-Executive Officer Employees as a Group (5) | 929,863 | | | 11,378,055 | | | |

- (1) Options granted in 1998 vest over a four-year period: 25% after the first year and 2.08% per month thereafter.
- (2) Based on options to purchase an aggregate of 1,130,863 shares granted in 1998. Represents the number of options granted under the 1989 Stock Option Plan in 1998 and is not necessarily indicative of the number of options that will be granted in the future. Does not include 5,000 options granted in December 1998 to a consultant.
- (3) The potential realizable value is calculated based on the term of the option at its time of grant.
- (4) All the options were granted under the Directors' Plan.
- (5) Does not include 5,000 options granted in December 1998 to a consultant.

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 AGGREGATED OPTION EXERCISES IN LAST FISCAL YEAR AND FY-END OPTION VALUES

| Name | Shares Acquired on Exercise(#) | Value Realized (\$)(1) | Number of Securities Underlying Unexercised Options at FY-End(#) Exercisable/ Unexercisable | Value of Unexercised In-the-Money Options at FY-End (\$)(2) Exercisable/ Unexercisable |
|-------------------|--------------------------------|------------------------|--|---|
| Stanley T. Crooke | 0 | 0 | 15,000/0 1,642/0 30,000/0 25,000/0 30,000/0 19,583/5,417 19,583/5,417 29,166/10,834 10,781/11,719 0/70,000 | \$66,188/\$0 \$7,245/\$0 \$115,725/\$0 \$161,938/\$0 \$185,625/\$0 \$175,023/\$48,414 \$175,023/\$48,414 \$0/\$0 \$0/\$0 \$0/\$43,750 |
| Daniel L. Kisner | 80,000 | \$797,095 | 90,000/0 4,167/0 50,000/0 22,500/0 25,000/0 25,000/0 81,000/9,000 11,750/3,250 11,750/3,250 14,229/6,771 (3) 8,625/9,375 0/50,000 | \$1,100,089/\$0 \$21,616/\$0 \$184,375/\$0 \$105,469/\$0 \$176,563/\$0 \$154,688/\$0 \$470,813/\$52,313 \$105,016/\$29,047 \$105,016/\$29,047 \$0/\$0 \$0/\$0 \$0/\$31,250 |
| C. Frank Bennett | 5,200 | \$46,250 | 1,750/0 525/0 1,500/0 2,291/0 1,834/2,925 35,000/15,000 8,750/3,250 4,312/4,688 0/14,000 | \$5,359/\$0 \$3,905/\$0 \$4,781/\$0 \$14,176/\$0 \$16,391/\$26,142 \$24,063/\$10,313 \$0/\$0 \$0/\$0 \$0/\$8,750 |
| David J. Ecker | 0 | 0 | 2,975/0 9,000/0 50,000/0 15,000/0 9,517/2,633 13,124/4,876 3,354/3,646 0/10,000 | \$15,433/\$0 \$28,688/\$0 \$340,625/\$0 \$92,813/\$0 \$85,058/\$23,532 \$0/\$0 \$0/\$0 \$0/\$6,250 |

| Name | Shares Acquired on Exercise(#) | Value Realized (\$)(1) | Number of Securities Underlying Unexercised Options at FY-End(#) Exercisable/ Unexercisable | Value of Unexercised In-the-Money Options at FY-End (\$)(2) Exercisable/ Unexercisable |
|-------------------|--------------------------------------|------------------------------|--|---|
| B. Lynne Parshall | 0 | 0 | 20,000/0 | \$88,750/\$0 |
| | | | 59,728/0 | \$429,295/\$0 |
| | | | 47,500/0 (4) | \$175,156/\$0 |
| | | | 18,000/0 | \$84,375/\$0 |
| | | | 25,000/0 | \$176,563/\$0 |
| | | | 20,000/0 | \$123,750/\$0 |
| | | | 7,751/3,250 | \$69,275/\$29,047 |
| | | | 5,167/2,167 | \$46,180/\$19,368 |
| | | | 36,000/24,000 | \$11,250/\$7,500 |
| | | | 11,666/4,334 | \$0/\$0 |
| | | | 8,145/8,855 | \$0/\$0 |
| | | | 0/45,000 | \$0/\$28,125 |

- (1) Fair market value of our Common Stock on the date of exercise minus the exercise price.
- (2) Fair market value of our Common Stock at December 31, 1998 (\$12.9375) multiplied by the applicable number of shares minus the aggregate exercise price of the options for the number of shares.
- (3) Includes options to purchase an aggregate of 4,000 shares transferred to Dr. Kisner's son and daughter.
- (4) Includes options to purchase an aggregate of 4,000 shares transferred to Ms. Parshall's daughters.

COMPENSATION COMMITTEE REPORT1

The Compensation Committee of the Board of Directors consists of Mark B. Skaletsky (Chairman), William R. Miller and Joseph H. Wender, none of whom have ever been officers or employees of Isis. The Compensation Committee's responsibilities include:

- o Makes recommendations concerning executive salaries and incentive compensation;
- o Awards stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan;
- o Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

The full Board of Directors reviews the Compensation Committee's recommendations regarding the compensation of executive officers.

EXECUTIVE COMPENSATION

We design our executive compensation programs to attract and retain executives who can lead Isis to meet its business objectives and to motivate them to enhance long-term stockholder value. The executive officers' annual compensation consists of three elements: cash salary, a cash incentive bonus and stock option grants.

To determine fair compensation, the Compensation Committee reviews historical and current salary, bonus and stock award information for other comparable companies in similar geographic areas and at similar stages of growth and development. The group of comparable companies is not necessarily the same as the companies included in the market indices included in the performance graph on page 18. The Compensation Committee also reviews a variety of industry surveys throughout the year, which provide additional information about short and long-term executive compensation. Based in part on this information, the Compensation Committee generally sets salaries, including that of the Chief Executive Officer, at levels comparable to competitive companies of comparable size in similar industries. We structure our management by objective bonus program around both individual and Company performance. We base the total size of the bonus pool on our success in meeting performance goals for the year, accounting for changes the Compensation Committee discussed and agreed to during the course of the year.

We use the stock option program to give management employees a substantial economic interest in the long-term appreciation of our Common Stock. We grant existing members of management new options on an annual basis to provide a continuing financial incentive. The size of the option grant is related to the executive's position and performance in the previous year.

TAXES

Under Section 162(m) of the Internal Revenue Code of 1986, as amended, we can only deduct up to \$1 million of compensation we pay to certain executive officers each taxable year. However, we may deduct compensation above \$1 million if it is "performance based compensation" within the meaning of the Internal Revenue Code. The Compensation Committee has determined that stock options granted under the 1989 Stock Option Plan with an exercise price at least equal to the fair market value of our Common Stock on the date of grant will be treated as performance-based compensation.

1 The material in this report is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of the Company under the Securities Act of 1933, as amended (the "1933 Act"), or the Exchange Act.

KEY ACCOMPLISHMENTS FOR 1998

We made the following advancements this year in developing our drug candidates:

- o The Food and Drug Administration (the "FDA") approved Vitravene(TM) (fomivirsen), a compound to treat cytomegalovirus-induced retinitis in AIDS patients. Ciba-Vision launched the product in November 1998. We received \$7.5 million in milestone payments;
- o We conducted an interim evaluation of ISIS 2302 for Crohn's disease that supported the decision to continue development of the drug in that indication. The Phase IIa trial for renal transplantation continues and the Phase IIa trial for rheumatoid arthritis has been completed. Progress continues with a topical formulation ISIS 2302 for psoriasis, an aerosol formulation for asthma and an enema formulation for ulcerative colitis;
- o We completed Phase I trials for ISIS 2503, an anticancer compound, and expect to initiate Phase II trials in early 1999. We also continued Phase II trials for both ISIS 3521 and ISIS 5132.

ADDITIONAL ACHIEVEMENTS

- o In accordance with our patenting strategy, we were issued 38 additional patents in 1998.
- o We completed deals with Merck & Co. Inc., CpG ImmunoPharmaceuticals, Inc., Zeneca Limited, Pantheco ApS and Abbott Laboratories, Inc.
- o We also completed a \$15 million tranche of a total \$40 million debt financing.
- o We continued to strengthen our position in antisense chemistry with the purchase of Gilead's patent assets.

COMPENSATION FOR OUR CEO

The Compensation Committee approved a 10.5% salary increase for Dr. Crooke for 1999. This salary increase resulted from an industry-wide analysis of Dr. Crooke's cash compensation and stock option position. In 1998, we met or exceeded most of our performance objectives. The Compensation Committee believes that rewarding performance with a significant cash bonus program is an appropriate method of executive compensation. The Compensation Committee approved a bonus of \$253,400 for Dr. Crooke, which was 140% of the 40% bonus guideline for the CEO under our Management By Objective program. The Compensation Committee based this bonus on Isis meeting 125% of its goals, and Dr. Crooke meeting 125% of his personal goals. In January 1999, the Committee also approved an option for 35,000 shares of stock for Dr. Crooke, which is within the guidelines for the CEO under our annual stock option grant program.

Mark B. Skaletsky, Chairman
William R. Miller
Joseph H. Wender

PERFORMANCE MEASUREMENT COMPARISON(1)

COMPARISON OF CUMULATIVE TOTAL RETURN AMONG ISIS PHARMACEUTICALS
THE NASDAQ COMPOSITE INDEX (TOTAL RETURN)
THE AMEX BIOTECH INDEX

[PERFORMANCE GRAPH]

| MARKET CLOSE PRICE (IN WHOLE DOLLARS) | Dec. 1993 ---- | | | Dec. 1994 ---- | | | Dec. 1995 ---- | | | | | |
|--|----------------------|-----|-----|----------------------|----|-----|----------------------|-----|-----|-----|-----|-----|
| Isis | 100 | 106 | 100 | 74 | 59 | 98 | 187 | 172 | 194 | 172 | 278 | 239 |
| NASDAQ Composite Index | 100 | 96 | 91 | 99 | 97 | 106 | 121 | 135 | 136 | 143 | 154 | 159 |
| Amex Biotech Index | 100 | 80 | 69 | 79 | 71 | 67 | 78 | 99 | 116 | 116 | 122 | 121 |

| MARKET CLOSE PRICE (IN WHOLE DOLLARS) | Dec. 1996 ---- | | | Dec. 1997 ---- | | | Dec. 1998 ---- | | |
|--|----------------------|-----|-----|----------------------|-----|-----|----------------------|-----|-----|
| Isis | 267 | 222 | 216 | 264 | 182 | 226 | 203 | 169 | 192 |
| NASDAQ Composite Index | 167 | 158 | 187 | 219 | 204 | 239 | 245 | 219 | 282 |
| Amex Biotech Index | 125 | 121 | 123 | 153 | 140 | 151 | 127 | 120 | 160 |

The above table and chart assume \$100 invested on December 31, 1993 in the Company's Common Stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

1 This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of the Company under the 1933 Act or the Exchange Act.

CERTAIN TRANSACTIONS

In 1998, we paid \$1.9 million in interest on a \$22.6 million loan from Boehringer Ingelheim International GmbH under a \$40 million line of credit made available in conjunction with a collaborative agreement with Boehringer. Dr. Burkhard Blank represents Boehringer on our Board of Directors.

OTHER MATTERS

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other issues are properly brought before the meeting, we will ask our stockholders to vote on the matters using their best judgment.

For further information about Isis Pharmaceuticals, please request a copy of our Annual Report. The report is the same Form 10-K that we filed with the Securities and Exchange Commission, and is available free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

By Order of the Board of Directors

B. Lynne Parshall
Secretary

ISIS PHARMACEUTICALS, INC.

PROXY SOLICITED BY THE BOARD OF DIRECTORS
FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON MAY 21, 1999

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 Annual Meeting of Stockholders of the Company to be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008 on Friday, May 21, 1999 at 2:00 p.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 ALL NOMINEES LISTED IN PROPOSAL 1 AND FOR PROPOSAL 2 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)

SEE REVERSE SIDE

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

ANNUAL MEETING OF STOCKHOLDERS
ISIS PHARMACEUTICALS, INC.

MAY 21, 1999

- Please Detach and Mail in the Envelope Provided -

Please mark
[X] votes as in this
example.

FOR all nominees
listed at right (except
as marked to the
contrary below).

WITHHOLD
AUTHORITY
to vote for all
nominees listed at right

THE BOARD OF DIRECTORS RECOM-
MENDS A VOTE FOR THE NOMINEES
FOR DIRECTOR LISTED BELOW

PROPOSAL 1: To elect two directors []
to hold office until the
2002 Annual Meeting of Stockholders.

[]

NOMINEES: Larry Soll
Joseph H. Wender

To withhold authority to vote for any nominee(s)
write such nominee(s) name(s) below.

- - - - -
- - - - -
- - - - -

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSAL 2.

Proposal 2: To ratify the selection of Ernst & Young LLP
as independent auditors of the Company for its fiscal
year ending December 31, 1999.

FOR AGAINST ABSTAIN
[] [] []

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.