

[QuickLinks](#) -- Click here to rapidly navigate through this document

SCHEDULE 14A INFORMATION

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:

 - (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
2003 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2003 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Tuesday, June 10 at 2:00 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.

If you are a stockholder of record (that is, if your stock is registered with us in your own name), you may vote by telephone, or electronically through the Internet, by following the instructions included with your proxy card. If your shares are registered in the name of a broker or other nominee, your nominee may be participating in a program provided through ADP Investor Communication Services that allows you to vote by phone or the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions.

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 2003 ANNUAL MEETING OF STOCKHOLDERS

Date: Tuesday, June 10
Time: 2:00 P.M., Pacific Time
Place: Isis Pharmaceuticals
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Stockholders,

At our 2003 Annual Meeting, we will ask you to:

- Elect two Directors to each serve for a three-year term;
- Ratify the selection by the Audit Committee of the Board of Directors of Ernst & Young LLP as independent auditors for its fiscal year ending December 31, 2003; and
- Transact any other business that may properly be presented at the Annual Meeting.

The foregoing items of business are more fully described in the enclosed Proxy Statement.

If you were an Isis stockholder of record at the close of business on April 11, 2003 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
May 1, 2003

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. ALTERNATIVELY, YOU MAY VOTE BY PHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND WITH YOUR PROXY CARD. EVEN IF YOU HAVE GIVEN YOUR PROXY, YOU MAY STILL VOTE IN PERSON IF YOU ATTEND THE MEETING. PLEASE NOTE, HOWEVER, THAT IF YOUR

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

PROXY STATEMENT

INFORMATION ABOUT THE 2003 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, for use at the 2003 Annual Meeting of Stockholders to be held on Tuesday, June 10, 2003, at 2:00 P.M. local time, or at any adjournment or postponement thereof, for the purposes stated herein. The Annual Meeting will be held at 2292 Faraday Avenue, Carlsbad, California. 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 May 1, 2003 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on April 11, 2003 are entitled to vote at the Annual Meeting. On this record date, we had 55,381,331 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, with respect to proposals other than the election of directors, 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. Broker non-votes will not count towards whether the stockholders have approved a proposal.

You may vote in one of the following ways:

- Attend the 2003 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.

Solicitation

We 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 our Common Stock beneficially owned by others to forward to such beneficial owners. We 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 employees of Isis.

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 June 9, 2003. 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.

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. You will be required to provide the control number contained on your proxy card when you vote either by telephone or the Internet, so please have it 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 telephonically by calling the telephone number shown on the instruction form received from your broker or bank, or via the Internet at ADP Investor Communication Services' website at <http://www.proxyvote.com>.

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.

Stockholder Proposals

If you have a proposal or director nomination that you would like to be included in our proxy statement and form of proxy for, or to be presented at, the 2004 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than January 2, 2004. Stockholders wishing to submit proposals or director nominations that are not to be included in such proxy statement and proxy must do so no earlier than the close of business on February 11, 2004 and no later than the close of business on March 12, 2004. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

2

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 nine members with three classes consisting of three directors. Each class serves a three-year term, and we hold elections each year at the Annual Meeting to elect the directors whose terms have 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. Spencer R. Berthelsen, M.D., was elected by the Board in May 2002. Dr. Berthelsen is scheduled for election by the stockholders at the 2005 Annual Meeting.

Information about the 2003 Elections

The Board has nominated two directors for election at the 2003 Annual Meeting. Each of the nominees currently serves as one of our directors. If re-elected, each will serve until the 2006 Annual Meeting or until his or her successor is elected and has qualified.

Although Mr. William R. Miller is currently a member of our Board of Directors, he is not running for re-election at the Annual Meeting. As a result, he will continue to serve as a director through the date of the Annual Meeting. At that time, the number of members on the Board will be reduced to eight members.

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. Shares represented by executed proxies will be voted for the election of the nominees listed below, unless authority to vote in favor of the nominees is withheld, and cannot be voted for more than two nominees for director. Each person nominated for election has agreed to serve if elected, and we have no reason to believe that any of the nominees will be unable to serve. However, if any nominee cannot serve, your proxy may be voted 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 and of each director whose term of office will continue after the Annual Meeting.

Biographies of Nominees for Election for a Three-year Term Expiring at the 2006 Annual Meeting

Christopher F.O. Gabrieli, age 43, has served as a director of Isis since May 1994. Mr. Gabrieli served as a director from January 1989 to May 1992. He is the Chairman of Massachusetts 2020, a non-profit public policy organization. He is also a member of the general partners of Bessemer Venture Partners III L.P., Bessemer Venture Partners IV L.P. and related venture capital partnerships, where he worked from 1986 to 2000. He is also Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents.

Frederick T. Muto, age 49, has served as a director of Isis since March 2001. Mr. Muto joined the law firm of Cooley Godward LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is a founding partner of Cooley's San Diego office and serves as the partner in charge of that office. Mr. Muto also serves on Cooley's firmwide management committee.

The Board recommends that you vote IN FAVOR of the election of each of the above nominees

3

Biographies of Board Members Continuing Until the 2005 Annual Meeting

Spencer R. Berthelsen, M.D., age 51, was elected to the Isis Board of Directors in May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 280 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold including Chairman of the Department of Internal Medicine, Medical Director, and Chairman of the Board of Directors since October 2001. He is a Clinical Professor of Medicine at the University of Texas Health Science Center at Houston and a Clinical Associate Professor of Medicine

at Baylor College of Medicine. Dr. Berthelsen has served on the Board of the Texas Academy of Internal Medicine and the Caremark National Pharmacy and Therapeutics Committee since 1999.

B. Lynne Parshall, age 48, has served as a director of Isis since September 2000. She has served as our Executive Vice President since December 1995, our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is on the Board of Visitors at Stanford University Law School and the Board of Trustees of the Bishops School. Ms. Parshall is also a member of the Licensing Executives Society and a member of the American, California and San Diego bar associations.

Joseph H. Wender, age 58, 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, and Affinity Financial, an Internet financial institution.

Biographies of Board Members Continuing Until the 2004 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 58, was a founder of Isis and has been Chief Executive Officer 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. He serves as a director of Antisense Therapeutics Ltd., a biopharmaceutical company, Axon Instruments, Inc., a developer and manufacturer of novel high-technology devices and software for drug discovery, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. Dr. Crooke is also an adjunct professor of pharmacology at the University of California, San Diego, and San Diego State University.

John C. Reed, M.D., Ph.D., age 44, has served as a director of Isis since February 2002. Dr. Reed has been the President and Chief Executive Officer of The Burnham Institute, an independent, nonprofit, public benefit organization dedicated to basic biomedical research, since January 2002. Dr. Reed has been with The Burnham Institute for the past ten years, serving as Director, Oncogene and Tumor Suppressor Gene Program, as the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as adjunct professor in the University of California, San Diego's (UCSD) Department of Molecular Pathology and in San Diego State University's Biology department. In addition, Dr. Reed is an associate member of UCSD's Cancer Center. Prior to these positions, from 1989 to 1992, Dr. Reed worked as Assistant Director, Laboratory of Molecular Diagnosis at the hospital of the University of Pennsylvania and Assistant Professor, Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine.

Mark B. Skaletsky, age 54, has served as a director of Isis since January 1989. Mr. Skaletsky is currently the Chairman, Chief Executive Officer and President of Essential Therapeutics, a biopharmaceutical company. From May 1993 to January 2001, Mr. Skaletsky served as President and Chief Executive Officer of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. From 1989 to 1993, Mr. Skaletsky was Chairman of Enzytech, Inc., a biopharmaceutical company, and Chief Executive Officer of Enzytech from 1988 to 1993. Mr. Skaletsky is also a director of ImmunoGen, Inc., a biopharmaceutical company, and Paradigm Genetics, Inc., an integrated life science company. He is a director and past Chairman of the Biotechnology Industry Organization. In addition, Mr. Skaletsky is a member of the Board of Trustees of Bentley College located in Waltham, Massachusetts.

The Board of Director Committees and Meetings

The Board of Directors met five times in 2002, including four regularly scheduled meetings and one special telephone meeting, and acted by unanimous written consent five times. As part of each Board meeting, our non-employee directors meet in executive session without the presence of our employee directors. The Board of Directors also has Audit, Compensation and Nominating committees. During 2002, all directors attended at least 70% of the meetings of the Board and the committees on which they served except for Mr. Gabrieli who attended 40% of the Board meetings due to his leave of absence while he ran for public office in Massachusetts. Mr. Gabrieli attended 100% of the Board meetings that occurred when he was not on his leave of absence.

In 2002, the Audit Committee met five times and its members were Mr. Wender (Chairman), Mr. Miller and Mr. Muto. In response to the Sarbanes-Oxley Act of 2002, we revised the Audit Committee charter to specify membership criteria. Under the revised Audit Committee charter, each member must be independent. We consider the members as independent as long as they:

- do not accept any consulting, advisory or other compensatory fee from us, except in connection with their service as a director,
- are not an affiliate of Isis or one of its subsidiaries; and
- meet the Nasdaq independence requirements.

In addition, all Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by Securities and Exchange Commission regulations. Currently, Mr. Skaletsky serves as the financial expert. We provide the Audit Committee with the funding it needs to perform its duties.

In 2003, the members consist of Mr. Wender (Chairman), Mr. Skaletsky and Dr. Berthelsen. Each of these members meet the membership criteria set forth in the Audit Committee charter. None of the members of our Audit Committee are officers or employees of Isis and all are independent directors under currently applicable rules.

The Audit Committee:

- Reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes;
- Selects and hires our independent auditors;

- Oversees the independence of our independent auditors;
- Evaluates our independent auditors' performance; and
- Has the authority to hire its own outside consultants and advisors if necessary.

5

In December 2002, the Audit Committee amended its formal written Audit Committee charter, which is filed as Appendix A to this Proxy Statement. In addition to the responsibilities listed above, the new charter codified the following Audit Committee functions:

- Reviewing our annual budget with management and, if acceptable, recommending the budget to the Board for approval;
- Receiving and considering our independent auditors' comments as to internal controls, adequacy of staff and management performance and procedures in connection with internal controls;
- Reviewing and, if appropriate, approving related party transactions;
- Establishing and enforcing procedures for the receipt, retention and treatment of complaints regarding accounting or auditing improprieties; and
- Pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law.

In 2002, the members of the Compensation Committee were Mr. Skaletsky (Chairman), Mr. Miller and Mr. Wender, and in 2003, the members consist of Mr. Wender (Chairman), Mr. Skaletsky and Dr. Reed, all of whom are non-employee directors of Isis. The committee met two times in 2002 and acted by unanimous written consent sixteen times. The Compensation Committee:

- Makes recommendations concerning Board and executive salaries and incentive compensation;
- Awards stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan (the "1989 Plan") and 2000 Broad-Based Equity Incentive Plan (the "2000 Plan");
- Administers our 1989 Plan, 2000 Plan and 2000 Employee Stock Purchase Plan; and
- Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

In 2002, the Nominating Committee consisted of two non-employee directors, Mr. Gabrieli (Chairman) and Mr. Muto. In 2003, the members are Mr. Gabrieli (Chairman) and Dr. Berthelsen. Each current member of the Nominating Committee is not an officer or employee of Isis and is an independent director under currently applicable rules. The committee informally discussed Board composition on a number of occasions but did not conduct any formal meetings in 2002. The Nominating Committee:

- Interviews, evaluates, nominates and recommends individuals for membership on our Board of Directors;
- Considers nominees whom our stockholders may recommend; and
- On an annual basis, reviews the performance of the Board and its committees, including evaluating the Board's ability to function as a group and the integrity and competency of the individual Board members.

The Nominating Committee also reviews items related to corporate governance.

6

PROPOSAL 2

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee of the Board of Directors has selected Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2003, and has requested management to ask for stockholder ratification at the Annual Meeting. Ernst & Young LLP has audited our financial statements since we were founded in 1989. Representatives of Ernst & Young LLP will be at the 2003 Annual Meeting to answer any questions and make a statement should they be asked to do so.

Although our Bylaws do not require stockholders to approve our independent auditors, the Audit Committee of the Board would like the stockholders' opinion as a matter of good corporate practice. If the stockholders vote against Ernst & Young LLP, the Audit Committee of the Board will reconsider whether to keep the firm. However, even if the stockholders ratify the selection, the Audit Committee of the Board may choose to appoint a different independent accounting firm at any time during the year if it believes that a 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 present in person or represented by proxy and entitled to vote at the 2003 Annual Meeting must vote in favor of Proposal 2.

As of December 31, 2002, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past six years.

Audit Fees:

For the fiscal year ended December 31, 2002, the aggregate fees paid to or due to Ernst & Young LLP related to the audit of our financial statements for such fiscal year and for the reviews of our interim financial statements was \$114,101.

Audit-Related Fees:

During the fiscal year ended December 31, 2002, the aggregate fees billed by Ernst & Young LLP for assurance and related services that were reasonably related to the performance of the audit or review of our financial statements that are not included under "Audit Fees" above were \$100,105. These fees were for services related to Ernst & Young LLP's issuance of a comfort letter and related review of the offering memorandum in connection with our offering of \$125 million in 5¹/₂% convertible promissory notes, review of the registration statements we filed in 2002 and consultations related to accounting for a number of our collaborations.

Tax Fees:

During the fiscal year ended December 31, 2002, the aggregate fees billed by Ernst & Young LLP for professional services rendered for tax compliance, tax advice and tax planning were \$27,820. These fees were for services related to our preparation of our tax returns and other filings we made with the Internal Revenue Service and consultations regarding the application of various provisions of the Code.

Financial Information Systems Design and Implementation Fees:

During the fiscal year ended December 31, 2002, there were no fees generated by Ernst & Young LLP for information technology consulting.

7

All Other Fees:

During the fiscal year ended December 31, 2002, all other fees billed by Ernst & Young LLP were \$6,035. These fees were for consultations regarding our deferred compensation plans and a subscription to an online accounting and tax information service.

The Audit Committee has determined that the rendering of all other non-audit services by Ernst & Young LLP is compatible with maintaining the auditor's independence.

During the fiscal year ended December 31, 2002, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's full-time permanent employees.

The Board of Directors recommends a vote IN FAVOR of Proposal 2

8

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our Common Stock as of February 28, 2003 by:

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

Beneficial Owner	Beneficial Ownership (1)	
	Number of Shares	Percent of Total (2)
Citigroup Inc. (3) 399 Park Avenue New York, NY 10043	6,900,955	12.3
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285	4,166,167	7.5
Mazama Capital Management, Inc. (4) One S. W. Columbia, Suite 1500 Portland, Oregon 97258	4,627,150	8.4
Deutsche Bank AG (5) Taufhausanlage 12, D-60325	3,133,418	5.7

Frankfurt am Main
Federal Republic of Germany

Spencer R. Berthelsen (6)	29,370	*
Stanley T. Crooke (7)	1,565,356	2.8
Christopher F. O. Gabrieli (8)	541,150	1.0
William R. Miller (9)	75,500	*
Frederick T. Muto (10)	11,500	*
B. Lynne Parshall (11)	366,145	*
John C. Reed (12)	15,000	*
Mark B. Skaletsky (13)	62,500	*
Joseph H. Wender (14)	86,500	*
Richard K. Brown (15)	47,348	*
F. Andrew Dorr (16)	98,325	*
David J. Ecker (17)	250,546	*
All directors and executive officers as a group (19 persons)(18)	3,953,169	6.9

* Less than one percent.

(1) This table is based upon information supplied by officers, directors, principal stockholders and Schedules 13D and 13G filed with the Securities and Exchange Commission (the "SEC"). Unless

9

otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe 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 55,381,331 shares of Common Stock outstanding on February 28, 2003, adjusted as required by rules promulgated by the SEC.
- (3) Includes 601,504 shares issuable upon the conversion of 5¹/₂% convertible notes, 6,235,681 shares held by Salomon Smith Barney Holdings Inc. ("SSB Holdings") and 4,727,731 shares held by Salomon Brothers Holding Company Inc. ("SBHC") and Salomon Smith Barney Inc. ("SSB"), all wholly-owned subsidiaries of Citigroup Inc. SBHC is the sole stockholder of SSB, SSB Holdings is the sole stockholder of SBHC, and Citigroup Inc. is the sole stockholder of SSB Holdings. These holdings are as of February 28, 2003.
- (4) Mazama Capital Management, Inc. has sole voting authority over 2,479,700 shares and sole dispositive power over 4,217,350 shares. These holdings are as of February 28, 2003.
- (5) Includes 1,362,400 shares held by Deutsche Asset Management Europe GmbH, Investment Co., 1,319,518 shares held by Deutsche Bank Trust Company Americas, 271,700 shares held by Deutsche Investment Management Americas Inc. and 179,800 shares held by Deutsche Asset Management Group Ltd, London, all directly or indirectly wholly-owned subsidiaries of Deutsche Bank AG. This information is based solely on a Schedule 13G filed on February 13, 2003 with the SEC.
- (6) Includes 70 shares owned by Dr. Berthelsen's daughter of which he disclaims beneficial ownership.
- (7) Includes 567,812 shares of Common Stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 29, 2003. It also includes 24,253 shares of Common Stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before April 29, 2003, and 1,050 shares owned by her. Dr. Crooke disclaims beneficial ownership of the shares of Common Stock owned and issuable upon exercise of options held by his wife.
- (8) Includes 329,479 shares of Common Stock held of record by Bessemer Venture Partners III L.P. ("BVP III") and 740 shares of Common Stock held of record by the Gabrieli Family Foundation ("GFF"). Mr. Gabrieli is a Manager of Deer III & Co. LLC, the General Partners of BVP III, and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to 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 55,500 shares of Common Stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 29, 2003.
- (9) Includes 13,000 shares of Common Stock issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 29, 2003.
- (10) Includes 1,500 shares of Common Stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 10,000 shares of Common Stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 29, 2003.

- (11) Includes 329,597 shares of Common Stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 29, 2003, and an aggregate of 30,090 shares of Common Stock issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before April 29, 2003.
- (12) Includes 15,000 shares of Common Stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before April 29, 2003, granted to him under a previous consulting agreement.

10

- (13) Includes 40,500 shares of Common Stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 29, 2003.
- (14) Includes 55,500 shares of Common Stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 29, 2003.
- (15) Includes 45,000 shares of Common Stock issuable upon exercise of options held by Dr. Brown that are exercisable on or before April 29, 2003.
- (16) Includes 98,287 shares of Common Stock issuable upon exercise of options held by Dr. Dorr that are exercisable on or before April 29, 2003.
- (17) Includes 42,723 shares of Common Stock held by the Ecker Family Revocable Trust in which Dr. Ecker is a trustee, and an aggregate of 7,882 shares of Common Stock held by Dr. Ecker's son and daughter. Also includes 199,941 shares of Common Stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 29, 2003.
- (18) Includes an aggregate of 2,274,526 shares issuable upon exercise of options held by all current directors and executive officers as a group that are exercisable on or before April 29, 2003.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") requires Isis' directors, executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of Common Stock and other equity securities of Isis. Officers, directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2002, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with except Dr. Berthelsen timely reported his initial holdings but inadvertently did not include in that report indirect shareholdings of his daughter. This omission was corrected by reporting these shares on an amended report.

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, 2002, we paid total fees of \$93,750 to our non-employee directors. Dr. Berthelsen joined the Board in May 2002 and, therefore, only received \$7,500. Dr. Reed joined the Board in February 2002 and, therefore, only received \$11,250.

In 2002, each non-employee director also received automatic stock option grants under our 2002 Non-Employee Directors' Stock Option Plan. On July 1, 2002, under the 2002 Non-Employee Directors' Stock Option Plan, each of our non-employee directors at that time received an option to purchase 10,000 shares of our Common Stock, at an exercise price of \$8.15 per share. In addition, Dr. Reed and Dr. Berthelsen, upon their election to the Board on February 22 and May 31, 2002, respectively, were each granted an option to purchase 20,000 shares of Common Stock under our 2002 Non-Employee Directors' Stock Option Plan at an exercise price of \$17.95 and \$9.40, respectively, the fair market value on the date of grant. The exercise price of each of the stock option grants mentioned above was equal to 100% of the fair market value of the Common Stock on the date of the grant (based on the closing sales price reported on the Nasdaq National Market). The options vest over a four-year period in equal annual installments.

11

Compensation of Executive Officers

The following table outlines the compensation paid to or earned by our Chief Executive Officer and each of our four other highest paid executive officers whose total annual salary and bonus exceeded \$100,000, for the fiscal years ending December 31, 2002, 2001, and 2000.

Summary Compensation Table

Name and Principal Position	Year	Annual Compensation			Long-Term Compensation Awards Securities Underlying Options (#)	All Other Compensation (\$)
		Salary (\$)	Bonus (\$)(1)	Other Annual Compensation (\$)(2)		
Stanley T. Crooke Chairman, CEO and President	2002	486,000	205,286	—	55,000	—
	2001	450,009	432,000	—	50,000	—
	2000	400,008	257,605	—	250,000(3)	—

B. Lynne Parshall	2002	385,799	136,650	—	35,000	—
Director, Executive VP & Chief Financial Officer	2001	358,883	282,620	—	28,000	—
	2000	330,168	172,760	—	170,000(3)	—
Richard K. Brown	2002	290,943	49,926	—	12,000	—
President, GeneTrove	2001	162,436	95,004	—	90,000(4)	—
Vice President	2000	—	—	—	—	—
F. Andrew Dorr	2002	308,983	48,943	—	23,000(5)	—
Former Vice President, Chief Medical Officer (7)	2001	290,125	163,195	—	14,400	—
	2000	261,372	109,106	—	118,749(6)	—
David J. Ecker	2002	257,597	81,607	—	23,200(8)	—
President, Ibis Therapeutics	2001	241,125	150,964	—	18,000	—
	2000	209,249	93,150	—	70,000	—

- (1) Bonuses are included here in the years they were earned. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2002 were paid in January 2003.
- (2) As permitted by rules promulgated by the SEC, no amounts are shown for any executive officers where the amounts constitute perquisites and do not exceed the lesser of 10% of the sum of the aggregate amount in the Salary and Bonus columns or \$50,000.
- (3) Options were to fully vest on January 2, 2006; provided, however, that the options would fully vest on January 2, 2002 if certain performance objectives were met prior to that date. As of January 2, 2002, all of the objectives had been met and therefore the options fully vested.
- (4) Dr. Brown joined Isis in June 2001. The 90,000 stock options granted in 2001 represent options Dr. Brown received in connection with his initial hire.
- (5) Includes 10,000 options granted to Dr. Dorr in January 2002 in association with his promotion.
- (6) Includes 10,000 options granted to Dr. Dorr in August 2000 in association with his promotion and 48,749 options issued in a 2 for 1 stock exchange offered to all non-executive officer employees. At the time of the exchange, Dr. Dorr was not an executive officer.
- (7) Dr. Dorr's employment with us terminated on March 31, 2003.
- (8) Includes 10,000 options granted to Dr. Ecker in January 2002 in association with his promotion.

Stock Option Grants and Exercises

Executive officers are granted stock options under our 2000 Plan and our 1989 Plan. During 2002, options to purchase a total of 2,086,977 shares of our Common Stock had been granted under the 2000 Plan, including 20,000 options granted to two consultants. In 2002, no options to purchase shares of our Common Stock had been granted under the 1989 Plan.

We implemented a stock trading program for our Board of Directors, corporate executive officers and other insiders, under Rule 10b5-1 of the Exchange Act. When there is no material non-public information available, Rule 10b5-1 allows corporate insiders to establish plans that permit prearranged future sales of his or her securities. With respect to our insiders who participate in our 10b5-1 trading program, we do not allow them to buy or sell our stock outside of the 10b5-1 trading program. All of our executive officers who have vested stock options and/or own shares of our stock currently participate in our 10b5-1 trading program.

The following tables show certain information regarding options granted to, exercised by, and held at year end December 31, 2002 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)	Exercise Price (\$/Sh)	Expiration Date	5% (\$)	10% (\$)
Stanley T. Crooke	55,000	2.7	21.05	01-01-12	727,851	1,844,371
B. Lynne Parshall	35,000	1.7	21.05	01-01-12	463,178	1,173,691
Richard K. Brown	12,000	0.6	21.05	01-01-12	158,804	402,408
F. Andrew Dorr (4)	23,000	1.1	21.05	01-01-12	304,374	771,283
David J. Ecker	23,200	1.1	21.05	01-01-12	307,021	777,989

- (1) Options granted in 2002 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 2,066,977 shares granted in 2002 to employees only under our 2000 Plan. This is not necessarily indicative of the number of options that will be granted in the future.
- (3) The potential realizable value is calculated based on the term of the option at its time of grant, based on the assumption that the market value of the underlying stock increases at the stated values, compounded annually. Actual gains, if any, on stock option exercises are dependent on the future performance of the Common Stock, overall market conditions and the option holders continued employment through the vesting periods. The amounts reflected in this table may not necessarily be achieved.
- (4) Dr. Dorr's employment with us terminated on March 31, 2003.

13

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 Fiscal Year End	Value of Unexercised In Options at Fiscal Year End (2)	Number of Securities Underlying Options That Expired Out-of-Money During Fiscal Year
			Exercisable/Unexercisable	Exercisable/Unexercisable	
Stanley T. Crooke	—	—	575,728/81,772	\$ 132,750/—	16,642
B. Lynne Parshall	52,128	\$ 226,144	(3)345,895/50,105	—/—	61,500
Richard K. Brown	—	—	33,750/68,250	—/—	—
F. Andrew Dorr (4)	43,749	\$ 172,233	83,650/51,334	—/—	—
David J. Ecker	2,975	\$ 1,877	185,045/53,305	\$ 54,719/—	9,000

- (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, 2002 (\$6.59) multiplied by the applicable number of shares minus the aggregate exercise price of the options for the number of shares.
- (3) Includes an aggregate of 10,090 options transferred to Ms. Parshall's two daughters.
- (4) Dr. Dorr's employment with us terminated on March 31, 2003.

14

EQUITY COMPENSATION PLAN INFORMATION

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2002.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders	5,241,000(a)	\$ 10.82	1,383,000(c)
Equity compensation plans not approved by stockholders	4,014,000(b)	\$ 12.02	1,723,000
Total	9,255,000	\$ 11.34	3,106,000

- (a) Consists of two Isis plans: 1989 Plan and the 2002 Non-Employee Directors' Stock Option Plan.
- (b) Consists of the 2000 Plan only.
- (c) Of these shares, 307,208 remain available for purchase under the 2000 Employee Stock Purchase Plan. The 2000 Employee Stock Purchase Plan incorporates an evergreen formula, which was approved by our stockholders, pursuant to which on each January 6 for the first 9 anniversaries, the aggregate number of shares reserved for issuance under the plan will be increased automatically by the lesser of (i) 1% of the total number of shares of Common Stock outstanding on such anniversary date or (ii) 200,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Plan to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of nonstatutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. We intend to request stockholder approval for future share increases to the 2000 Plan. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2002, there were 5,737,000 shares reserved for issuance under the 2000 Plan, options to purchase an aggregate of 4,014,000 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 253,000 shares had been exercised under the 2000 Plan, and 1,723,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the optionee's employment or service as a consultant or an affiliate.

If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split,

15

liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), the 2000 Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the 2000 Plan, and the outstanding stock awards will be appropriately adjusted in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. The conversion of any of our convertible securities will not be treated as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, then all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- a reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, the vesting of such stock awards (and, if applicable, the time during which such stock awards may be exercised) will be accelerated in full, and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event.

Employment, Severance and Change of Control Agreements

To continue the employee retention program we started in 2000, in April 2003, we entered into agreements with certain key employees, including each of our named executive officers then employed by Isis, pursuant to which we agreed to provide the covered employees with severance benefits under the following conditions:

- In the event that a covered employee's employment is terminated without "cause," as defined in the agreement, by Isis on or before December 31, 2005 (the "Severance Period"), the employee will be eligible to receive a severance payment equal to a minimum of 9 months and up to a maximum of 24 months of his or her then current base salary depending on his or her position with Isis, less payroll deductions and withholdings.
- In the event that the covered employee's employment is terminated by Isis as a result of a change in control as defined in the agreement, the employee's severance payment will be increased so that he or she will receive a minimum of 13.5 months and up to a maximum of 36 months of his or her then current base salary depending on his or her position with Isis, less payroll deductions and withholdings.

In connection with Dr. Dorr's termination from Isis in March 2003, we paid him a lump sum payment equal to \$315,163, subject to standard payroll deductions and withholdings. The lump sum payment represented twelve months of Dr. Dorr's salary at the time of his termination.

16

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2002, our Compensation Committee was composed of Messrs. Skaletsky, Miller and Wender. Dr. Reed replaced Mr. Miller as a member of the Compensation Committee effective January 1, 2003. None of the members of the Committee has ever been an employee or officer of Isis. None of our executive officers serves as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving as a member of our Board of Directors or Compensation Committee.

COMPENSATION COMMITTEE REPORT(1)

In 2002, the Compensation Committee of the Board of Directors consisted of Mark B. Skaletsky, Chairman, William R. Miller(2) and Joseph H. Wender, none of whom has ever been an officer or employee of Isis. The Compensation Committee's responsibilities include:

-
- 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 Isis under the Securities Act of 1933, as amended (the "1933 Act"), or the Exchange Act.
 - 2 Mr. Miller will retire from the Board of Directors effective June 10, 2003. He was replaced on the Compensation Committee by John C. Reed effective January 1, 2003.
 - Making recommendations concerning Board and executive salaries and incentive compensation;
 - Awarding stock options, bonus stock and rights to purchase restricted stock under our 1989 Plan and 2000 Plan;
 - Administering our 1989 Plan, 2000 Plan and 2000 Employee Stock Purchase Plan; and
 - Determining executive compensation levels and performing other functions regarding compensation as the Board of Directors 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 help us meet our 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 in this Proxy Statement. 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 our Chief Executive Officer, at levels comparable to competitive companies of comparable size in similar industries. We structure our management bonus program around both the individual's and the Company's performance. We base the total size of the cash bonus pool on our success in meeting performance goals for the year, accounting for changes the Compensation Committee discusses and agrees to during the course of the year.

We use our 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 individual annual option grants is related to the executive's position and performance in the previous year. The Compensation Committee does consider the number of options held by executive officers when awarding new grants.

Taxes

Under Section 162(m) of the Code, 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 Plan and the 2000 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.

Assessment of 2002

We set very challenging objectives for 2002. In achieving the majority of those objectives, we made significant progress in the areas discussed below. However, there were also objectives set for our GeneTrove division which were not achieved. At the end of 2002, we did not yet know the results of the Phase III Affinitak trial.

Strengthened Financial Position

In 2002, Isis successfully strengthened its financial position through the preservation of a significant cash balance and the prudent management of its debt. Isis ended the year with \$289 million in cash, even as it continued the aggressive development of its pipeline of 13 products. Isis reduced future cash outflows by

retiring nearly \$95 million in expensive debt with proceeds from the issuance of 5.5% convertible notes. As a result, Isis has a net savings of approximately \$40 million in total future interest payments.

Advanced Antisense Drug Discovery

In 2002 we continued to make progress in advancing our core technology platform and in identifying antisense drug candidates and in moving these candidates toward clinical trials both for ourselves and for our partners. Specifically, we:

- Advanced the broad antisense drug discovery program with Eli Lilly and Company ("Lilly"). To date, Isis has delivered antisense inhibitors to Lilly to more than 225 different gene targets. Several genes have been validated as drug targets by the partnership. These genes, which span multiple therapeutic areas, have advanced into antisense drug discovery together with other gene targets in the therapeutic areas of focus.
- Expanded the Lilly research collaboration to include select targets in cancer.
- Expanded therapeutic potential of antisense technology to cardiovascular disease as demonstrated by data presented on the lipid-regulating target ApoB-100.
- Achieved a milestone in the Amgen antisense drug discovery collaboration.

Advanced Antisense Drug Development

We made significant progress in moving forward drugs in development. At the end of 2002, we did not yet know the results of the Phase III Affinitak trial.

In 2002, Isis:

- Completed enrollment of the 600-patient Phase III Affinitak trial.
 - Announced positive clinical data from five Phase II programs:
 - In pancreatic cancer, with ISIS 2503
 - In hepatitis C, with ISIS 14803
-
- In Crohn's disease with alicaforsen (ISIS 2302)
 - In psoriasis with alicaforsen (ISIS 2302)
 - In non-small cell lung cancer with Affinitak
- Initiated five new clinical trials:
 - Phase III European study of alicaforsen (ISIS 2302) in Crohn's disease
 - Phase II, pivotal-quality study of alicaforsen (ISIS 2302) in ulcerative colitis (UC)
 - Phase II trial of ISIS 104838 in rheumatoid arthritis
 - Phase II trial of ISIS 14803 in hepatitis C
 - Phase I trial of OGX-011 in prostate cancer
 - Announced positive data of a capsule form of ISIS 104838, which demonstrates that antisense drugs can be administered in oral solid form for the first time in human clinical trials
 - Progressed in multiple partnerships:
 - Expanded Lilly antisense alliance to include new Affinitak manufacturing agreement and collaboration to discover cancer treatments
 - Achieved a \$3.75 million development milestone in HepaSense joint venture with Elan
 - Extended hepatitis C drug discovery collaboration with Merck & Co., Inc. for a second time

- Reacquired rights to ISIS 14803 for hepatitis C as a result of the conclusion of the HepaSense collaboration with Elan.

Established New Partnerships for Divisions: GeneTrove and Ibis Therapeutics

In 2002, Isis:

- Initiated GeneTrove collaborations with GlaxoSmithKline, Merck, Pharmacia Corporation, and Amgen.
- Awarded \$2.4 million three-year contract from U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) to advance Ibis Therapeutics' antibacterial drug discovery program.

However, we did not achieve our revenue objectives from our GeneTrove division, nor was the database business successful which resulted in a restructuring of the GeneTrove division and a reduction in force in October 2002. As a result, we discontinued the database portion of our GeneTrove offering in November 2002.

Strengthened Intellectual Property Estate

In 2002, Isis:

- Received grant of 1000th U.S. patent, affirming Isis' position as the leader in antisense technology.
- Expanded gene-related intellectual property estate to 200 patents.
- Received grant of a key U.S. patent covering second-generation antisense.
- Settled, on favorable terms to Isis, patent infringement lawsuits against Sequitur, Inc.

As a result based on a combination of the accomplishment of major research and drug development objectives and the failure to accomplish revenue and database objectives, the Compensation Committee recommended, and the Board approved, a corporate bonus guideline of 88% which, together with individual performance, formed the basis for bonus awards for 2002. Individual executive officer base salary increases were based on individual executive officer performance.

Compensation for Our CEO

Dr. Crooke's compensation is determined in accordance with the criteria described above for all executive officers. The Compensation Committee reviewed published salary survey data for CEO's in comparable biotech companies and assessed Dr. Crooke's performance in light of the Company objectives achieved and not achieved, as discussed above. As a result, the Compensation Committee recommended that Dr. Crooke receive a salary increase of 5%, to \$510,300 for 2003. Dr. Crooke received a salary increase in 2002 of 8% and an increase of 12.5% in 2001. In January 2003, Dr. Crooke received a bonus of \$205,286 for accomplishments in 2002 likewise based on the assessment of objectives achieved and not achieved. In January 2002, the Committee also approved an option grant of 55,000 shares of Common Stock for performance in 2001 for Dr. Crooke, pursuant to our 2000 Plan, at an exercise price of \$21.05 per share, the fair market value on the date of grant.

Mark B. Skaletsky, Chairman
John C. Reed
Joseph H. Wender

AUDIT COMMITTEE REPORT(4)

The Audit Committee oversees our financial reporting process on behalf of the Board of Directors. Management has the primary responsibility for the financial statements and the reporting process, including the systems of internal controls. In fulfilling its oversight responsibilities, the Audit Committee reviewed the audited financial statements in our Annual Report on Form 10-K for the fiscal year ended December 31, 2002 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

⁴ 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 Isis under the 1933 Act or the Exchange Act.

The Audit Committee reviewed with our independent auditors, who are responsible for expressing an opinion on the conformity of our audited financial statements with generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under generally accepted auditing standards. In addition, the Audit Committee has discussed with the independent auditors the auditors' independence from management and Isis, including the matters in the written disclosures required by the Independence Standards Board. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by Independence Standards Board Standard No. 1. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 61.

The Audit Committee discussed with our independent auditors the overall scope and plans for their audit. The Audit Committee met with the independent auditors, with and without management present, to discuss the results of their examinations, their evaluations of our internal controls, and the overall quality of our financial reporting.

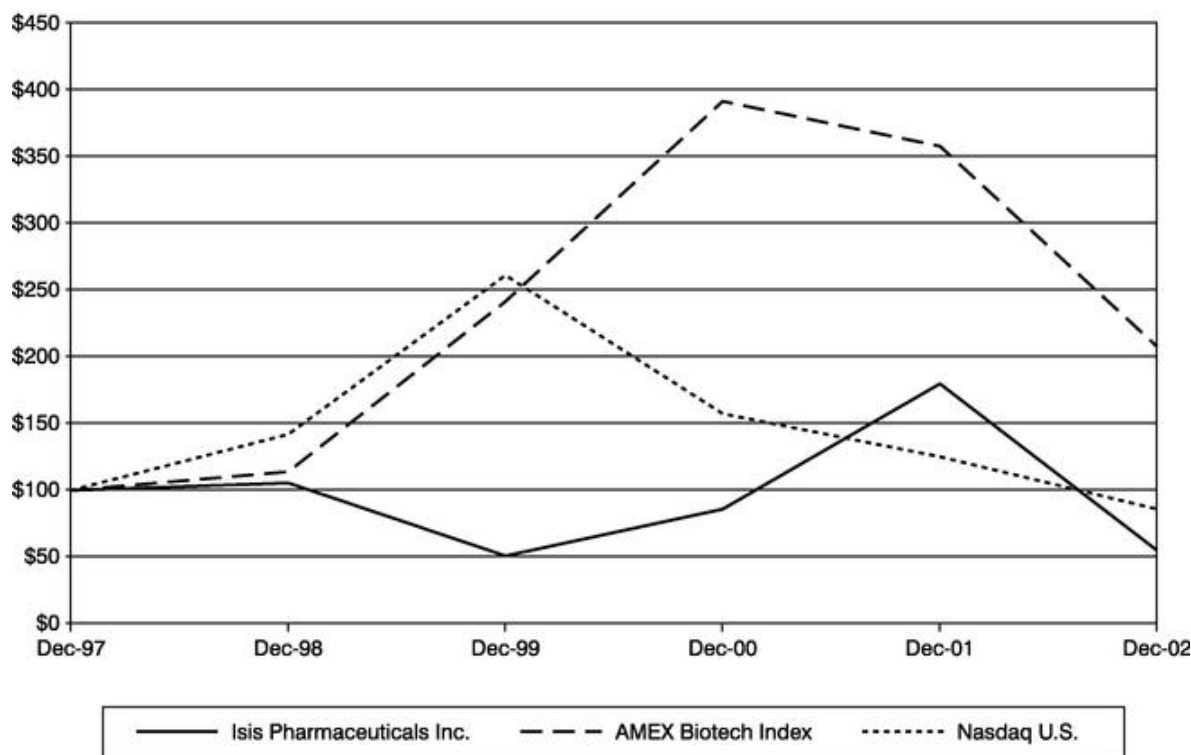
In reliance on the reviews and discussions referred to above, the Audit Committee recommended to the Board of Directors, and the Board has approved, that the audited financial statements be included in the Annual Report on Form 10-K for the fiscal year ended December 31, 2002 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of our independent auditors.

Joseph H. Wender, Audit Committee Chairman
 Mark B. Skaletsky, Audit Committee Member
 Spencer R. Berthelsen, Audit Committee Member

Performance Measurement Comparison(1)

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN AMONG ISIS PHARMACEUTICALS, INC.,
 THE NASDAQ COMPOSITE INDEX (TOTAL RETURN) AND
 THE AMEX BIOTECH INDEX

CUMULATIVE TOTAL RETURN
 Based upon an initial investment of \$100 on December 31, 1997
 with dividends reinvested



SOURCE: GEORGESON SHAREHOLDER COMMUNICATIONS INC.

	Dec-97	Dec-98	Dec-99	Dec-00	Dec-01	Dec-02
Isis Pharmaceuticals Inc.	\$ 100	\$ 105	\$ 51	\$ 86	\$ 180	\$ 54
AMEX Biotech Index	\$ 100	\$ 114	\$ 241	\$ 391	\$ 357	\$ 208
Nasdaq U.S.	\$ 100	\$ 141	\$ 261	\$ 157	\$ 125	\$ 86

The above table and chart assume \$100 invested on December 31, 1997 in our 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 Isis under the 1933 Act or the Exchange Act.

Certain Transactions

In June 2002, we expanded our antisense drug discovery collaboration with Lilly beyond the original areas of inflammatory and metabolic diseases to include the discovery of antisense drugs to inhibit specific gene targets associated with cancer. At December 31, 2002, Lilly owned approximately 7.5% of our

outstanding Common Stock.

In September 2002, we entered a manufacturing agreement with Lilly in which we agreed to manufacture Affinitak during the product launch period for Lilly. Through this agreement we upgraded and expanded our manufacturing facility. We added a new state-of-the-art manufacturing suite dedicated to Affinitak. Lilly provided us with funding in the form of a loan of up to \$21 million, to build the Affinitak suite. We will repay the loan from Affinitak success milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan.

In December 2002, we purchased 10,333,333 shares of the common stock of Antisense Therapeutics Limited or ATL for an aggregate purchase price of US\$441,130. Dr. Crooke, our Chairman, Chief Executive Officer and President is a member of ATL's board of directors and one of its stockholders.

One of our directors, Mr. Frederick T. Muto, who was elected by the Board in March 2001, is a partner at Cooley Godward LLP, our outside counsel. However, the fees we paid to Cooley Godward did not exceed five percent of its gross revenues for its 2002 fiscal year.

In 2003, we entered into the transactions described in the Proxy Statement under "Employment, Severance and Change of Control Arrangements."

We have entered into indemnity agreements with certain officers and directors which provide, among other things, that we will indemnify such officer or director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a director, officer or other agent of Isis, and otherwise to the fullest extent permitted under Delaware law and our bylaws. Our bylaws provide that we will indemnify our directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a director or executive officer in connection with any proceeding initiated by such director or executive officer.

In 2002, we updated our policies and procedures to specifically prohibit personal loans to our executive officers and any officer with a title of Vice President or higher.

HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g. brokers) to satisfy the delivery requirements for proxy statements and annual reports with respect to two or more stockholders sharing the same address by delivering a single proxy statement addressed to those stockholders. This process, which is commonly referred to as "householding," potentially means extra convenience for stockholders and cost savings for companies.

This year, a number of brokers with account holders who are Isis Pharmaceuticals, Inc. stockholders will be "householding" our proxy materials. A single proxy statement will be delivered to multiple stockholders sharing an address unless contrary instructions have been received from the affected stockholders. Once you have received notice from your broker that they will be "householding" communications to your address, "householding" will continue until you are notified otherwise or until you revoke your consent. If, at any time, you no longer wish to participate in "householding" and would prefer to receive a separate proxy statement and annual report, please notify

23

your broker, direct your written request to Isis Pharmaceuticals, Inc., Attn: Linda Powell, Assistant Corporate Secretary, 2292 Faraday Avenue, Carlsbad, California 92008 or contact Linda Powell at (760) 603-2471. Stockholders who currently receive multiple copies of the proxy statement at their address and would like to request "householding" of their communications should contact their broker.

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 proxy holders 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 Form 10-K for the year ended December 31, 2002 that we filed with the SEC, 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

May 1, 2003

24

Appendix A

BOARD OF DIRECTORS AUDIT COMMITTEE CHARTER

The general purpose of the Audit Committee is to assist the Board of Directors in the exercise of its fiduciary responsibility to provide oversight of the Company's financial statements and the financial reporting processes, internal accounting and financial controls, the annual independent audit of the Company's financial statements, and other aspects of the financial management of the Company.

The Audit Committee will be appointed by the Board of Directors and will comprise at least three directors, each of whom are independent of management and the Company. Members of the committee will be considered independent as long as they do not accept any consulting, advisory, or other compensatory fee from the Company (except in connection with their service as a director) and are not an affiliated person of the Company or its subsidiaries and meet Nasdaq independence requirements. All committee members must be financially literate, and at least one member must be a "financial expert," as defined by SEC regulations.

The powers and duties of the Audit Committee include the following:

1. The Audit Committee will oversee the annual and quarterly financial reporting processes.
2. The Audit Committee will select the independent auditor for the Company. The selection shall be proposed by management, confirmed by the Audit Committee and ratified by the stockholders. The Audit Committee will have a clear understanding with management and the independent auditors that the independent auditors are ultimately accountable to the Board and the Audit Committee, as representatives of the Company's stockholders. The Audit Committee shall have the ultimate authority and responsibility to engage, evaluate and, where appropriate, replace the independent auditors.
3. The Audit Committee will pre-approve all audit and non-audit services provided by the independent auditors and will not engage the independent auditors to perform the non-audit services prohibited by law or regulation.
4. The Audit Committee will discuss with the auditors their independence from management and the Company and the matters included in the written disclosures required by the Independence Standards Board.
5. The Audit Committee will meet with management, the independent auditors, and the internal auditors (when the Company has such a function) prior to their audits to review and discuss the planned scope and objectives of the audits.
6. The Audit Committee will meet with the independent auditors and the internal auditors, with and without management present, after their audits to review and discuss the results of their examinations and appropriate analyses of the financial statements.
7. The Audit Committee will review management's assertion on its assessment of the effectiveness of internal controls as of the end of the most recent fiscal year and the independent auditors' report on management's assertion as well as recommendations for improving internal accounting controls.
8. The Audit Committee will review and discuss the reports of the independent auditors, with and without management present, as to the state of the Company's financial reporting systems and procedures, the adequacy of internal accounting and financial controls, the integrity and competency of the financial and accounting staff, and other aspects of the financial management of the Company.

-
9. The Audit Committee will review and discuss earnings press releases, as well as financial information and earnings guidance provided to the public.
 10. The Audit Committee will review the interim financial statements with management and the independent auditors prior to the filing of the Company's Quarterly Reports on Form 10-Q. The Audit Committee will also discuss the results of the quarterly reviews and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards. The Chair of the Audit Committee may represent the entire committee for the purposes of this review.
 11. The Audit Committee will review with management and the independent auditors the financial statements to be included in the Company's Annual Report on Form 10-K (or the annual report to stockholders if distributed prior to the filing of Form 10-K), including their judgment about the quality, not just acceptability, of accounting principles, the reasonableness of significant judgments, and the clarity of the disclosures in the financial statements. Also, the Audit Committee will discuss the results of the annual audit and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards.
 12. The Audit Committee will review and, if appropriate, approve, transactions that would qualify as a related party transaction under the Securities Act of 1933.
 13. The Audit Committee will review the Company's annual budget with management and, if acceptable, recommend such budget to the Board for approval.
 14. The Audit Committee will establish procedures for the receipt, retention, and treatment of complaints received by the Company regarding accounting, internal accounting controls, or auditing matters, and the confidential, anonymous submission by employees of the Company of concerns regarding questionable accounting or auditing matters.
 15. The Audit Committee will maintain free and open communication between the Audit Committee, directors who are not members of the Audit Committee, the Company's management, the internal auditors, and the independent auditors.
 16. The Audit Committee shall have adequate resources and authority to discharge its responsibilities and duties including the following:
 - a. The Audit Committee will have full authority at its own discretion to institute investigations of any matter brought to its attention, with full access to all books, records, facilities and personnel of the Company, and the authority to engage independent counsel and other advisors it

deems necessary to conduct its duties.

- b. The Audit Committee will have the authority to review all aspects of the Company's financial operations on a planned basis.
- c. The Audit Committee will have the authority to review the Company's policies and procedures and the actual implementation of such policies and procedures with respect to officers' expenses and perquisites.

- 17. The Audit Committee will report annually to the Board of Directors, outlining the Audit Committee's activities for the past year and its plans for the coming year. In addition, the Audit Committee shall report to the Board of Directors any significant matters as they occur during the year.

**ANNUAL MEETING OF STOCKHOLDERS OF
ISIS PHARMACEUTICALS, INC.**

June 10, 2003

Please date, sign and mail
your proxy card in the
envelope provided as soon
as possible.

Please detach and mail in the envelope provided.

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE NOMINEES FOR DIRECTOR
LISTED BELOW AND A VOTE FOR PROPOSAL 2.
PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE.
PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE**

Proposal 1: to elect two directors to hold office until the 2006 Annual Meeting of Stockholders

- | | | |
|-----------------------|--|---|
| <input type="radio"/> | FOR ALL NOMINEES | NOMINEES:
<input type="checkbox"/> Christopher F. O. Gabrieli
<input type="checkbox"/> Frederick T. Muto |
| <input type="radio"/> | WITHHOLD AUTHORITY
FOR ALL NOMINEES | |
| <input type="radio"/> | FOR ALL EXCEPT
(See instructions below) | |

INSTRUCTION: To withhold authority to vote for any individual nominee(s), mark "FOR ALL EXCEPT" and fill in the circle next to each nominee you wish to withhold, as shown here:

Proposal 2: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2003

FOR	AGAINST	ABSTAIN
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

To change the address on your account, please check the box at right and indicate your new address in the address space above. Please note that changes to the registered name(s) on the account may not be submitted via this method.

Signature of Stockholder _____ Date: _____ Signature of Stockholder _____ Date: _____

Note: This proxy must be signed exactly as the name appears hereon. When shares are held jointly, each holder should sign. When signing as executor, administrator, attorney, trustee or guardian, please give full title as such. If the signer is a corporation, please sign full corporate name by duly authorized officer, giving full title as such. If signer is a partnership, please sign in partnership name by authorized person.

ISIS PHARMACEUTICALS, INC.

**PROXY SOLICITED BY THE BOARD OF DIRECTORS
FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON JUNE 10, 2003**

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 Tuesday, June 10, 2003 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 PROPOSALS 1 AND 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)

**ANNUAL MEETING OF STOCKHOLDERS OF
ISIS PHARMACEUTICALS, INC.**

June 10, 2003

PROXY VOTING INSTRUCTIONS

MAIL - Date, sign and mail your proxy card in the envelope provided as soon as possible.

-OR-

TELEPHONE - Call toll-free **1-800-PROXIES** from any touch-tone telephone and follow the instructions. Have your control number and proxy card available when you call.

-OR-

INTERNET - Access "www.voteproxy.com" and follow the on-screen instructions. Have your control number available when you access the web page.

COMPANY NUMBER

ACCOUNT NUMBER

CONTROL NUMBER

Please detach and mail in the envelope provided *IF* you are not voting via telephone or the Internet.

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE NOMINEES FOR DIRECTOR LISTED BELOW AND A VOTE FOR PROPOSAL 2.
PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE.
PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE ☒**

Proposal 1: to elect two directors to hold office until the 2006 Annual Meeting of Stockholders

- FOR ALL NOMINEES**
- WITHHOLD AUTHORITY FOR ALL NOMINEES**
- FOR ALL EXCEPT**
(See instructions below)
- NOMINEES:**
- Christopher F. O. Gabrieli
- Frederick T. Muto

INSTRUCTION: To withhold authority to vote for any individual nominee(s), mark "FOR ALL EXCEPT" and fill in the circle next to each nominee you wish to withhold, as shown here: ●

Proposal 2: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2003

FOR	AGAINST	ABSTAIN
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

To change the address on your account, please check the box at right and indicate your new address in the address space above. Please note that changes to the registered name(s) on the account may not be submitted via this method.

Signature of Stockholder _____ Date: _____ Signature of Stockholder _____ Date: _____

Note: This proxy must be signed exactly as the name appears hereon. When shares are held jointly, each holder should sign. When signing as executor, administrator, attorney, trustee or guardian, please give full title as such. If the signer is a corporation, please sign full corporate name by duly authorized officer, giving full title as such. If signer is a partnership, please sign in partnership name by authorized person.

[ISIS PHARMACEUTICALS, INC. 2292 Faraday Avenue Carlsbad, CA 92008](#)

[NOTICE OF 2003 ANNUAL MEETING OF STOCKHOLDERS AND PROXY STATEMENT](#)

[ISIS PHARMACEUTICALS, INC. 2292 Faraday Avenue Carlsbad, CA 92008](#)

[NOTICE OF 2003 ANNUAL MEETING OF STOCKHOLDERS](#)

[ISIS PHARMACEUTICALS, INC. 2292 Faraday Avenue Carlsbad, CA 92008 PROXY STATEMENT INFORMATION ABOUT THE 2003 ANNUAL MEETING AND VOTING](#)

[PROPOSAL 1 ELECTION OF DIRECTORS](#)

[PROPOSAL 2 RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS](#)

[SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT](#)

[EXECUTIVE COMPENSATION](#)

[Summary Compensation Table](#)

[Option Grants in Last Fiscal Year](#)

[Aggregated Option Exercises in Last Fiscal Year and FY-End Option Values](#)

[EQUITY COMPENSATION PLAN INFORMATION](#)

[COMPENSATION COMMITTEE REPORT \(1\)](#)

[AUDIT COMMITTEE REPORT \(4\)](#)

[HOUSEHOLDING OF PROXY MATERIALS](#)

[Appendix A BOARD OF DIRECTORS AUDIT COMMITTEE CHARTER](#)