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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:

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- Fee paid previously with preliminary materials.
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6. Amount Previously Paid:

7. Form, Schedule or Registration Statement No.:

8. Filing Party:

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

**NOTICE OF
2004 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2004 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Wednesday, May 26, 2004 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 OTHER 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 2004 ANNUAL MEETING OF STOCKHOLDERS

Date: Wednesday, May 26, 2004

Time: 2:00 P.M., Pacific Time

Place: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Stockholders,

At our 2004 Annual Meeting, we will ask you to:

- Elect three Directors to serve for a three-year term each;
- Amend and restate, as described in more detail in Proposal 2, the 1989 Stock Option Plan (the "1989 Plan") to increase the number of shares authorized for issuance under the 1989 Plan from 10,200,000 to 13,200,000 and to make other revisions;
- Ratify the selection by the Audit Committee of the Board of Directors of Ernst & Young LLP as independent auditors for our fiscal year ending December 31, 2004; 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 March 29, 2004 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 16, 2004

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 SHARES ARE HELD OF RECORD BY A BROKER, BANK OR OTHER NOMINEE AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN FROM THE RECORD HOLDER A PROXY ISSUED IN YOUR NAME.

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

PROXY STATEMENT

INFORMATION ABOUT THE 2004 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 2004 Annual Meeting of Stockholders to be held on Wednesday, May 26, 2004, at 2:00 P.M. local time, or at any adjournment or postponement of the meeting, for the purposes stated in this document. 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, Outstanding Shares and Quorum

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

A quorum of stockholders is necessary to hold a valid meeting. A quorum will be present if at least a majority of the outstanding shares are represented by stockholders present at the meeting or by proxy. Your shares will be counted towards the quorum only if you submit a valid proxy vote or vote at the meeting. Abstentions and broker non-votes will be counted towards the quorum requirement.

Each share of our Common Stock that you own entitles you to one vote. The proxy card indicates the number of shares of our Common Stock that you own. Votes will be counted by the inspector of election appointed for the meeting, who will separately count "For" and "Against" votes, abstentions and broker non-votes, except that with respect to the election of directors, stockholders do not affirmatively vote "Against" certain directors. Instead, if a stockholder does not want to elect a particular director, the stockholder may simply withhold their "For" vote. Abstentions will be counted towards the vote total for each proposal, and will have the same effect as "Against" votes. Broker non-votes have no effect and will not be counted towards the vote total for any proposal.

If your shares are held by your broker as your nominee (that is, in "street name"), you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. This year, Proposal 2 regarding the amendment and restatement of our 1989 Stock Option Plan is a non-discretionary item, which means that if you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares.

You may vote in one of the following ways:

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

We will announce preliminary voting results at the annual meeting and publish final voting results in our quarterly report on Form 10-Q for the second quarter of 2004.

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. Directors and employees will not be paid any additional compensation for soliciting proxies, but we have retained Georgeson Shareholder Communications, Inc. to assist with the solicitation of proxies for a fee of approximately \$12,000, plus reimbursement for out-of-pocket expenses.

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

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

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

For Shares Registered in Your Name

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

For Shares Registered in the Name of a Broker or Bank

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

A number of brokers and banks are participating in a program provided through ADP Investor Communication Services that allows proxies to vote shares by means of the telephone and Internet. If your shares are held in an account with a broker or bank participating in the ADP Investor Communication Services program, you may vote your shares online or via telephone (have the voting form in hand) and call the number or go to the website indicated on the form and follow the instructions.

Revocability of Proxies

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

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

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 2005 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 17, 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 January 26, 2005 and no later than the close of business on February 25, 2005. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

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 with two classes consisting of three directors and one class consisting of two directors. Each class serves a three-year term, and we hold elections each year at the Annual Meeting to elect the directors whose terms are expiring.

During 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 or the term of the class to which he or she was appointed.

Information about the 2004 Elections

The Board has nominated three directors for election at the 2004 Annual Meeting. Each of the nominees currently serves as one of our directors and, except for Dr. Reed, each was previously elected by the stockholders. If re-elected, each will serve until the 2007 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. Shares represented by executed proxies will be voted for the election of three nominees listed below, unless authority to vote in favor of the nominees is withheld. 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 authorized directors.

We provide below a short biography of each of the nominees and of each director whose term of office will continue after the Annual Meeting. All of our directors have been previously elected by the stockholders except Dr. Berthelsen who will be up for election at the 2005 Annual Meeting and Dr. Reed who is up for election at the 2004 Annual Meeting.

Biographies of Nominees for Election for a Three-year Term Expiring at the 2007 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 59, 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, EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents, Northern Arizona University Arts and Sciences Advisory council, Flagstaff, Arizona, and BIOCUM, San Diego, California. 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 45, 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

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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 55, has served as a director of Isis since January 1989. Mr. Skaletsky is currently the Chairman, Chief Executive Officer and President of Trine Pharmaceuticals, Inc., a biopharmaceutical company, formerly known as Essential Therapeutics. On May 1, 2003 Essential Therapeutics filed a voluntary petition for relief under Chapter 11 of the U.S. Bankruptcy Code. 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 DIRECTORS RECOMMENDS THAT YOU VOTE IN FAVOR OF THE ELECTION OF EACH OF THE ABOVE NOMINEES

Biographies of Board Members Continuing Until the 2006 Annual Meeting

Christopher F.O. Gabrieli, age 44, has served as a director of Isis since May 1994. Mr. Gabrieli also served as a director of Isis 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 50, 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.

Biographies of Board Members Continuing Until the 2005 Annual Meeting

Spencer R. Berthelsen, M.D., age 52, has served as a director of Isis since 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 of Baylor College of Medicine. Dr. Berthelsen has served on the Board of the Texas Academy of Internal Medicine in the past and the Caremark National Pharmacy and Therapeutics Committee since 1999.

B. Lynne Parshall, age 49, 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

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Licensing Executives Society and a member of the American, California and San Diego bar associations.

Joseph H. Wender, age 59, has served as a director of Isis since January 1994. Mr. Wender is currently an Advisory Director and 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.

Independence of the Board of Directors

As required under The Nasdaq Stock Market ("Nasdaq") listing standards, a majority of the members of a listed company's Board of Directors must qualify as "independent," as affirmatively determined by the Board of Directors. The Board consults with our counsel to ensure that the Board's determinations are consistent with all relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in pertinent Nasdaq listing standards, as in effect from time to time.

Consistent with these considerations, after review of all relevant transactions or relationships between each director, or any of his or her family members, and Isis, its senior management and its independent auditors, the Board affirmatively has determined that all of our directors are independent directors within the meaning of the applicable Nasdaq listing standards, except for Dr. Crooke and Ms. Parshall, the Chief Executive Officer and Executive Vice President of the Company, respectively. With respect to Mr. Muto who is a partner of Cooley Godward LLP, our outside counsel, he is independent for purposes other than serving on the Audit Committee of which he is not a member.

Information Regarding the Board of Directors and its Committees

As part of each Board meeting, our independent directors meet in executive session without the presence of our employee directors. The Chairpersons of the Audit Committee, the Compensation Committee and the Nominating, Governance and Review Committee will each preside over at least one executive session. Persons interested in communicating with the independent directors about their concerns or issues may address correspondence to a particular director, or to the independent directors generally, in care of Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, CA 92008. If no particular director is named, letters will be forwarded, depending on the subject matter, to the Chair of the Audit, Compensation, or Nominating, Governance and Review Committee.

The Board of Directors met five times in 2003, including four regularly scheduled meetings and one special meeting, and acted by unanimous written consent five times. During 2003, all directors attended at least 80% of the meetings of the Board and the committees on which they served.

The Board has three committees: an Audit Committee, a Compensation Committee, and a Nominating, Governance and Review Committee. The following table provides membership and meeting information for fiscal 2003 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X		X
Dr. Stanley T. Crooke			
Mr. Christopher F. O. Gabrieli			X*
Mr. Frederick T. Muto			
Ms. B. Lynne Parshall			
Dr. John C. Reed		X	
Mr. Mark B. Skaletsky	X	X*	
Mr. Joseph H. Wender	X*	X	
Total meetings in fiscal year 2003	7	3**	0

* Committee Chairperson

** 13 meetings were held by Written Consent

Below is a description of each committee of the Board of Directors. Each of the committees has authority to engage legal counsel or other experts or consultants, as it deems appropriate to carry out its responsibilities. The Board of Directors has determined that each member of each committee meets the applicable rules and regulations regarding "independence" and that each member is free of any relationship that would interfere with his or her individual exercise of independent judgment with regard to Isis.

Audit Committee

The Audit Committee of the Board of Directors oversees our corporate accounting and financial reporting process. For this purpose, the Audit Committee performs several functions.

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.

In addition to the responsibilities listed above, the Audit Committee charter codifies 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

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- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law.

In 2003, the Audit Committee met seven times and its members were Mr. Wender (Chairman), Dr. Berthelsen and Mr. Skaletsky. Our Audit Committee charter requires that 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 ("SEC") 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 met 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.

Compensation Committee

The Compensation Committee of the Board of Directors reviews, modifies (as needed) and approves the overall compensation strategy and policies of Isis. The Compensation Committee reviews and approves corporate performance goals and objectives relevant to the compensation of our executive officers and other senior management; reviews and approves the compensation and other terms of employment of our directors and executive officers, including our Chief Executive Officer; and administers our stock option and purchase plans. We also have a Non-Management Stock Option Committee that may award stock options to employees who are below director level which consists of one member, Dr. Crooke.

Three directors comprise the Compensation Committee: Messrs. Skaletsky (Chairman), Reed and Wender. All members of our Compensation Committee are independent (as independence is currently defined in Rule 4200(a)(15) of the Nasdaq listing standards). The committee met three times in 2003 and acted by unanimous written consent 13 times.

Nominating, Governance and Review Committee

The Nominating, Governance and Review Committee of the Board of Directors is responsible for:

- interviewing, evaluating, nominating and recommending individuals for membership on Isis' Board of Directors. As part of this process, the Nominating, Governance and Review Committee will consider nominees recommended by Isis' stockholders;
- on an annual basis, reviewing 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;
- annually reviewing and assessing the adequacy of Isis' corporate governance guidelines and recommending any proposed changes to the Board for approval; and
- performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

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Two directors currently comprise the Nominating, Governance and Review Committee: Dr. Berthelsen and Mr. Gabrieli. Both members of the Nominating, Governance and Review Committee are independent (as independence is currently defined in Rule 4200(a)(15) of the Nasdaq listing standards). Our Nominating, Governance and Review Committee charter can be found on our corporate website at www.isispharm.com. Any information that is included on or linked to our website is not part of this proxy statement or any registration statement or report that incorporates this proxy statement by reference.

The Nominating, Governance and Review Committee did not have a formal meeting during 2003. Although the Nominating, Governance and Review Committee did not meet in 2003, because the Sarbanes-Oxley Act of 2002 rules are new and we have been diligently reviewing and revising our policies and

procedures, corporate compliance matters have been a topic at each of the Board Meetings held in 2003. Now that the procedures are in place, the Nominating, Governance and Review Committee will begin meeting in 2004 to discuss corporate governance issues. In addition, the Nominating, Governance and Review Committee met earlier this year informally to recommend to the Board the candidates for election at the 2004 meeting. The Nominating, Governance and Review Committee believes that candidates for director should have certain minimum qualifications, including the ability to read and understand basic financial statements, and having the highest personal integrity and ethics. The Committee also considers such factors as:

- possessing relevant expertise to offer advice and guidance to management;
- having sufficient time to devote to the affairs of Isis;
- demonstrating excellence in his or her field;
- having sound business judgment; and
- having the commitment to rigorously represent the long-term interests of our stockholders.

New candidates for director nominees are reviewed in the context of the current composition of the Board, the operating requirements of Isis and the long-term interests of our stockholders. In conducting this assessment, the Committee considers diversity, maturity, skills, and such other factors as it deems appropriate given the current needs of the Board and Isis, to maintain a balance of knowledge, experience and capability. In the case of incumbent directors whose terms of office are set to expire, the Nominating, Governance and Review Committee reviews such directors' overall service to Isis during their term, including the number of meetings attended, level of participation, quality of performance, and any other relationships and transactions that might impair such directors' independence. In the case of new director candidates, the Committee also determines whether the nominee is independent, which determination is based upon applicable Nasdaq listing standards, applicable SEC rules and regulations and the advice of counsel, if necessary. The Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a professional search firm. The Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of the Board.

The Committee meets to discuss and consider such candidates' qualifications and then selects a nominee for recommendation to the Board by majority vote. To date, the Nominating, Governance and Review Committee has not paid a fee to any third party to assist in the process of identifying or evaluating director candidates. To date, the Nominating, Governance and Review Committee has not received, and therefore has not rejected, a timely director nominee from a stockholder or stockholders holding more than 5% of our voting stock.

The Nominating, Governance and Review Committee will consider director candidates recommended by stockholders. The Committee does not intend to alter the manner in which it

evaluates candidates, including the minimum criteria set forth above, based on whether the candidate was recommended by a stockholder or not. Stockholders who wish to recommend individuals for consideration by the Nominating, Governance and Review Committee to become nominees for election to the Board may do so by delivering a written recommendation to the Nominating, Governance and Review Committee at the following address: 2292 Faraday Avenue, Carlsbad, CA 92008, by December 17, 2004. Submissions must include the full name of the proposed nominee, a description of the proposed nominee's business experience for at least the previous five years, complete biographical information, a description of the proposed nominee's qualifications as a director and a representation that the nominating stockholder is a beneficial or record owner of our stock. Any such submission must be accompanied by the written consent of the proposed nominee to be named as a nominee and to serve as a director if elected.

Stockholder Communications With The Board Of Directors

We make every effort to ensure that the views of stockholders are heard by the Board or individual directors, as applicable, and that appropriate responses are provided to stockholders in a timely manner. Stockholders who wish to communicate with the Board may do so by sending written communications addressed to the Secretary of Isis at 2292 Faraday Avenue, Carlsbad, CA 92008. All communications will be compiled by the Secretary and submitted to the Board or the individual Directors on a periodic basis. These communications will be reviewed by one or more employees of Isis designated by the Board, who will determine whether they should be presented to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications (such as advertisements, solicitations and hostile communications). All communications directed to the Audit Committee in accordance with our Code of Ethics policy that relate to questionable accounting or auditing matters involving Isis will be promptly and directly forwarded to the Audit Committee. Our Board has not adopted a formal process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent. During the upcoming year, the Nominating, Governance and Review Committee plans to draft a formal process for stockholder communications with the Board and, if adopted, will promptly publish the policy and post it to our website.

Code Of Ethics

Isis has adopted a Code of Ethics that applies to all officers, directors and employees. We filed the Code of Ethics as an exhibit to our Annual Report on Form 10-K for the fiscal year ended December 31, 2003, and posted the Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website at www.isispharm.com. Any information that is included on or linked to our website is not part of this proxy statement or any registration statement or report that incorporates this proxy statement by reference.

In June 1989, the Board of Directors adopted, and the stockholders subsequently approved, our 1989 Stock Option Plan (the "1989 Plan"). As of February 27, 2004, a total of 10,200,000 were reserved for issuance under the 1989 Plan. Of these, options to purchase an aggregate of 3,692,757 shares had been granted and were outstanding, options to purchase an aggregate of 4,788,672 shares had been exercised, and 1,718,571 shares remained available for grant thereunder.

Our management, Board and Compensation Committee believe that stock options are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists among many pharmaceutical and health care companies. The Board, upon the recommendation of the Compensation Committee, has approved an amendment and restatement of the 1989 Plan to increase the aggregate number of shares of Common Stock authorized for issuance under the 1989 Plan by 3,000,000 shares to an aggregate of 13,200,000 shares, in order to ensure that for a period of approximately two years, based on business plans, we are able to continue to grant stock options to employees and consultants at appropriate levels as determined by the Compensation Committee. If the stockholders do not approve Proposal 2, and as a consequence, we are unable to continue to grant options at competitive levels, we believe that it will negatively affect our ability to meet our needs for highly qualified personnel and our ability to manage future growth. Without these additional shares, management expects that the current shares available for grant under the 1989 Plan will not be sufficient to maintain our option grant practices for new employees or for promotions or merit awards for current employees after January 2005.

In addition to the proposed increase, the Board, upon the recommendation of the Compensation Committee, has approved additional amendments that will further strengthen the 1989 Plan's alignment with stockholder interests. As part of our best practices, we already follow several of the mandates listed below. However, our goal is to formalize these practices in the 1989 Plan to ensure stockholder interests come first. For example, the 1989 Plan will, among other things:

- Prohibit the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders;
- Limit the 1989 Plan to the grant of options and not authorize stock bonuses or restricted stock awards;
- Limit the term of each newly granted option to 7 years rather than the 10 years currently allowed;
- Require that each newly granted option not become fully vested until a date at least two years after the date of grant, except in the case of certain corporate events, although our past practice has been to fully vest four years after date of grant;
- Require all options outstanding under the 1989 Plan to have an exercise price of not less than 100% of the fair market value of our Common Stock on the date of grant, which is consistent with our current practices;
- Provide that our Compensation Committee, which is composed entirely of independent directors, will administer the 1989 Plan, which is consistent with our current practices;
- Require that the exercise price for options outstanding under the 1989 Plan can only be paid in cash, which is consistent with our current practices; and
- Extend the term of the 1989 Plan from January 31, 2008 to January 31, 2014.

Required Vote and Board of Directors Recommendation

The affirmative vote of a majority of the votes cast at the meeting, at which a quorum is present, either in person or by proxy, is required to approve the amendment and restatement of the 1989 Plan. If you hold your shares through a broker and you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares. Abstentions will be counted toward the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes. Broker non-votes are counted towards a quorum, but are not counted for any purpose in determining whether this matter has been approved.

Should we not obtain stockholder approval, then we will not implement the amendment and restatement of the 1989 Plan, including the amendments specified above, and no additional stock options will be granted on the basis of such increase or such proposed amended terms. However, the 1989 Plan will remain in effect, and we may continue to make stock option grants and other awards pursuant to the current provisions of the 1989 Plan until we deplete the share reserve.

The Board believes that the proposed amendment and restatement of the 1989 Plan is in the best interests of Isis and our stockholders for the reasons stated above. ***THEREFORE, THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF THE AMENDMENT AND RESTATEMENT OF THE 1989 PLAN.***

The essential features of the 1989 Plan, as amended, are outlined below.

Purpose

The 1989 Plan was adopted to provide a means by which we may give our employees (including officers), directors and consultants an opportunity to benefit from increases in value of our Common Stock through the granting of incentive and supplemental (or nonstatutory) stock options (collectively, the "Options"). Incentive stock options granted under the 1989 Plan are intended to qualify as "incentive stock options" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"). Supplemental stock options granted under the 1989 Plan are intended not to qualify as incentive stock options under the Code. See "Federal Income Tax Information" for a discussion of the tax treatment of incentive and supplemental stock options.

Before the proposed amendment, the 1989 Plan allowed us to grant stock bonuses and restricted stock awards. We have not granted these types of awards in the past. Subject to stockholder approval, the amended 1989 Plan would prevent us from granting stock bonuses and restricted stock awards under the 1989 Plan.

Administration

The 1989 Plan authorizes the Compensation Committee to administer the 1989 Plan. The Compensation Committee has delegated administration of the 1989 Plan to the Non-Management Stock Option Committee with respect to certain option grants to certain employees, none of whom is subject to Section 16 of the Exchange Act. Each person serving on the Compensation Committee is a "non-employee director" within the meaning of Rule 16b-3 of the Exchange Act, an "outside director" within the meaning of Section 162(m) of the Code and an "independent director" within the meaning of applicable Nasdaq listing standards. As used herein with respect to the 1989 Plan, the "Committee" refers to the Compensation Committee and the Non-Management Stock Option Committee.

The Committee has the power to construe and interpret the 1989 Plan and, subject to the provisions of the 1989 Plan, to select the persons to whom Options are to be made, to designate the number of shares to be covered by each Option, to determine whether an Option is an incentive stock option or a supplemental stock option, to establish vesting schedules, to specify the exercise price and, subject to certain restrictions, to specify any other terms.

Before the proposed amendment, the 1989 Plan allowed administration by our Board, who, in turn delegated administration to the Compensation Committee. We believe limiting administration to the Compensation Committee is important because the Compensation Committee must be composed entirely of independent directors.

Eligibility

Incentive stock options may be granted under the 1989 Plan only to our key employees (including officers). In addition, key employees (including officers), directors and consultants are eligible to receive supplemental (or nonstatutory options). As of February 27, 2004, we had approximately 450 employees and eight directors who were eligible to receive options under the 1989 Plan.

No incentive stock option may be granted under the 1989 Plan to any person who, at the time of the grant, owns (or is deemed to own) stock possessing more than 10% of the total combined voting power of all classes of our stock, unless the option exercise price is at least 110% of the fair market value of the stock subject to the option on the date of grant, and the term of the option does not exceed five years from the date of grant. In addition, the aggregate fair market value, determined at the time of grant, of the shares of Common Stock with respect to which such options are exercisable for the first time by an optionee during any calendar year may not exceed \$100,000. Further, the 1989 Plan contains a per-employee, per-calendar year limitation equal to 294,873 shares.

Stock Subject to the 1989 Plan

Subject to stockholder approval of this Proposal 2, 13,200,000 shares are reserved for issuance under the 1989 Plan. If Options granted under the 1989 Plan expire or otherwise terminate without being exercised, the Common Stock not purchased pursuant to such Options again becomes available for issuance under the 1989 Plan.

Terms of Options

The following is a description of the permissible terms of Options under the 1989 Plan. Individual option grants may be more restrictive as to any or all of the permissible terms described below.

Exercise Price; Payment. The exercise price of Options under the 1989 Plan may not be less than the fair market value of the Common Stock subject to the Option on the date of the option grant, and in some cases may not be less than 110% of such fair market value (see "Eligibility" above). Prior to the proposed amendment, the 1989 Plan allowed supplemental stock options priced as low as 85% of the fair market value. However, we have routinely granted options at 100% of the fair market value. At February 27, 2004, the closing price of our Common Stock as reported on The Nasdaq National Market was \$7.95 per share.

Subject to stockholder approval of this Proposal 2, an optionholder must pay the exercise price of Options granted under the 1989 Plan either: in cash at the time of exercise or pursuant to a "same-day sale" program developed pursuant to Regulation T of the Federal Reserve Board. Again, we have always required cash payments to exercise options, but without the proposed amendments, the 1989 Plan would have allowed other forms of consideration, including deferred payment arrangements.

Transferability. Under the 1989 Plan, an optionee may not transfer an incentive stock option other than by will or by the laws of descent and distribution. Optionees may transfer supplemental stock options for limited estate planning purposes or by will or the laws of descent and distribution.

Option Exercise. Options granted under the 1989 Plan may become exercisable in cumulative increments ("vest") as determined by the Compensation Committee. Shares covered by currently outstanding options under the 1989 Plan typically vest at the rate of 25% per year after year one and

2.08% per month thereafter during the optionee's employment or service as a consultant or director. Shares covered by options granted in the future under the 1989 Plan may be subject to different vesting terms. However, subject to stockholder approval of this Proposal 2, no Option granted to an employee will, unless otherwise provided by the 1989 Plan in very limited circumstances (see Effect of Certain Corporate Events below), become fully vested in a period of less than two years after the grant of such Option. Subject to the two-year limitation, the Compensation Committee has the power to accelerate the time during which an option may be exercised. Before the proposed amendment and restatement of the 1989 Plan, there was no minimum vesting requirement.

Term. Subject to stockholder approval of this Proposal 2, the maximum term of options under the 1989 Plan is seven years, except that in certain cases the maximum term is five years (see "Eligibility"). With certain exceptions, options under the 1989 Plan terminate three months after the optionee ceases to render services to us. Before this proposed amendment and restatement of the 1989 Plan, the maximum term of options under the 1989 Plan was ten years. We propose reducing the maximum term of options to seven years to further align employee and stockholder interests.

Prohibition of Option Repricing

Subject to stockholder approval of this Proposal 2, the 1989 Plan has been amended so as to expressly provide that, without the approval of a majority of votes cast in person or by proxy at a meeting of stockholders, we may not provide for either the cancellation of outstanding options in exchange for the grant of new options at a lower exercise price or the amendment of outstanding options to reduce the exercise price. Without the approval of the proposed amendment, the 1989 Plan would allow us to reprice or exchange options without stockholder approval.

Adjustment Provisions

If there is any change in the stock subject to the 1989 Plan or subject to any Option granted under the 1989 Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or otherwise), the 1989 Plan and the Options outstanding thereunder will be appropriately adjusted as to the class and the maximum number of shares, the maximum number of shares which may be granted to an employee during a calendar year and price per share of stock subject to the 1989 Plan and such Options.

Effect of Certain Corporate Events

The 1989 Plan provides that, in the event of our dissolution or liquidation, or of a specified type of merger or other corporate reorganization, to the extent permitted by law, any surviving corporation will be required to either assume any Options outstanding under the 1989 Plan or substitute similar Options for those outstanding under the 1989 Plan, or such outstanding Options will continue in full force and effect. In the event that any surviving corporation declines to assume or continue the Options outstanding under the 1989 Plan, or to substitute similar Options, then, with respect to Options held by persons then performing services as employees or as consultants or directors for us, the time during which such Options may be exercised will be accelerated and the Options terminated if not exercised during such time.

Duration, Amendment and Termination

The Committee may suspend or terminate the 1989 Plan without stockholder approval or ratification at any time or from time to time. Subject to stockholder approval of this Proposal 2, unless sooner terminated, the 1989 Plan will terminate on January 31, 2014 (instead of January 31, 2008).

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The Committee may also amend the 1989 Plan at any time or from time to time. However, no amendment will be effective unless approved by our stockholders within 12 months before or after its adoption by the Committee if such amendment (i) increases the maximum aggregate number of shares of our Common Stock that may be issued pursuant to Options granted under the 1989 Plan, or (ii) requires stockholder approval in order to comply with Rule 16b-3, Section 422(b) of the Code or any Nasdaq or securities exchange requirements.

Option Budget and Potential Dilution

Each year the Compensation Committee approves a budget that sets the number of stock options we can grant to our employees for that year. We do not grant options that exceed the budget without the Compensation Committee's approval. The options we grant in any year primarily represent options for new hires and annual merit grants for our existing employees. Over the past three years, the average option budget set by the Compensation Committee has been approximately 2.55% of our outstanding Common Stock on an as-issued basis. The option budget is a "net" budget, which means that if options expire or otherwise terminate without being exercised, the Common Stock not purchased pursuant to such options is added to the budget. Since cancelled or terminated options already counted against the budget for the year in which such options were granted, it makes sense to add them to the current budget to avoid double counting. We believe the option budget is an important tool to balance our equity compensation objectives with stockholder interests.

Since the option budget has historically been below 3% of our outstanding Common Stock on an as-issued basis, we believe we have administered our stock option plans in a way that minimizes the potential dilution to our stockholders. However, the above-average potential dilution attributable to our stock option plans merits explanation. We have historically low employee turnover, particularly in our management team and our employees typically hold their options for a long period of time before exercise (approximately 6.2 years). The low turnover is indicative of our employees' commitment to Isis and its technology. Similarly, we believe the fact that our employees are not exercising their options as soon as they become vested represents our employees' positive expectations of improved stockholder value over the long term. As a result, we believe most of the potential dilution attributable to our stock option plans is the product of these two factors, rather than excessive stock option grants.

No Evergreen

The 1989 Plan does not include any automatic share reserve increase provision (i.e. an evergreen provision).

Federal Income Tax Information

Incentive Stock Options. Incentive stock options under the 1989 Plan are intended to be eligible for the favorable federal income tax treatment accorded "incentive stock options" under the Code.

There generally are no federal income tax consequences to the participant or Isis by reason of the grant or exercise of an incentive stock option. However, the exercise of an incentive stock option may increase the participant's alternative minimum tax liability, if any.

If a participant holds stock acquired through exercise of an incentive stock option for more than two years from the date on which the option is granted and more than one year from the date on which the shares are transferred to the participant upon exercise of the option, any gain or loss on a disposition of such stock will be a long-term capital gain or loss if the participant held the stock for more than one year.

Generally, if the participant disposes of the stock before the expiration of either of these holding periods (a "disqualifying disposition"), then at the time of disposition the participant will realize taxable

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ordinary income equal to the lesser of (i) the excess of the stock's fair market value on the date of exercise over the exercise price, or (ii) the participant's actual gain, if any, on the purchase and sale. The participant's additional gain or any loss upon the disqualifying disposition will be a capital gain or loss, which will be long-term or short-term depending on whether the stock was held for more than one year.

To the extent the participant recognizes ordinary income by reason of a disqualifying disposition, we will generally be entitled (subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code and the satisfaction of a tax reporting obligation) to a corresponding business expense deduction in the tax year in which the disqualifying disposition occurs.

Slightly different rules may apply to optionees who acquire stock subject to certain repurchase options or whose stock is subject to forfeiture under Section 16(b) of the Exchange Act.

Supplemental Stock Options. Supplemental stock options granted under the 1989 Plan generally have the following federal income tax consequences:

There are no tax consequences to the optionee or Isis by reason of the grant of a supplemental stock option. Upon exercise of a supplemental stock option, the optionee normally will recognize taxable ordinary income equal to the excess of the stock's fair market value on the date of exercise over the option exercise price. Generally, with respect to employees, we are required to withhold from regular wages or supplemental wage payments an amount based on the ordinary income recognized. Subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code, and the satisfaction of a tax-reporting obligation, we will generally be entitled to a business expense deduction equal to the taxable ordinary income realized by the optionee. Upon disposition of the stock, the optionee will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option. Such gain or loss will be long-term, mid-term or short-term depending on how long the stock was held. Slightly different rules apply to optionees who acquire stock subject to certain repurchase options or who are subject to Section 16(b) of the Exchange Act.

Potential Limitation on Company Deductions. Section 162(m) of the Code denies a deduction to any publicly held corporation for compensation paid to certain employees in a taxable year to the extent that compensation exceeds \$1 million for such employee. It is possible that compensation attributable to stock options, when combined with all other types of compensation received by a covered employee from Isis, may cause this limitation to be exceeded in any particular year.

Certain kinds of compensation, including qualified "performance-based compensation," are disregarded for purposes of the deduction limitation. In accordance with Treasury Regulations issued under Section 162(m), compensation attributable to stock options will qualify as performance-based compensation if the award is granted by a compensation committee comprised solely of "outside directors" and either (i) the plan contains a per-employee limitation on the number of shares for which such awards may be granted during a specified period, the per-employee limitation is approved by the stockholders, and the exercise price of the award is no less than the fair market value of the stock on the date of grant, or (ii) the award is granted (or exercisable) only upon the achievement (as certified in writing by the compensation committee) of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain, and the award is approved by stockholders.

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New Plan Benefits

The following table presents certain information with respect to merit-based options granted during the fiscal year ended December 31, 2003 to (i) our Chief Executive Officer and our other four most highly compensated executive officers, (ii) all executive officers as a group, (iii) all non-employee directors as a group and (iv) all non-executive officer employees as a group. This information regarding grants for the fiscal year ended December 31, 2003 is for illustration only and may not be indicative of grants that are made in the future under the 1989 Plan.

NEW PLAN BENEFITS 1989 STOCK OPTION PLAN

Name and Position	Number of Shares Underlying Options
Stanley T. Crooke Chairman, CEO and President	50,000
B. Lynne Parshall Director, Executive VP & Chief Financial Officer	25,000
C. Frank Bennett Vice President, Antisense Research	11,500
Richard K. Brown Vice President, Business Development	16,500
David J. Ecker President, Ibis Therapeutics	12,500
All Executive Officers as a Group	212,396
All Non-Employee Directors as a Group	60,000
All Non-Executive Officer Employees as a Group	1,413,530

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PROPOSAL 3

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, 2004, 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 2004 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 our 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 our stockholders and us.

To ratify the selection of Ernst & Young LLP, the affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote at the annual meeting will be required to ratify the selection of Ernst & Young LLP. Abstentions will be counted toward the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes. Broker non-votes are counted towards a quorum, but are not counted for any purpose in determining whether this matter has been approved.

As of December 31, 2003, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past six years.

Independent Auditors' Fees

The Audit Committee has adopted a policy and procedures for the pre-approval of audit and permissible non-audit services rendered by our independent auditor, Ernst & Young LLP. The policy generally pre-approves specific services in the defined categories of audit services, audit-related services, and tax services up to pre-determined amounts. Pre-approval may also be given as part of the Audit Committee's approval of the scope of the engagement of the independent auditor or on an individual explicit case-by-case basis before the independent auditor is engaged to provide each service. All fees described below were pre-approved by the Audit Committee.

Audit Fees

For the fiscal years ended December 31, 2003 and 2002, the aggregate fees billed by Ernst & Young LLP related to the audit of our financial statements for such fiscal years and for the reviews of our interim financial statements was \$123,000 and \$110,950, respectively.

Audit Related Fees

During the fiscal years ended December 31, 2003 and 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 \$17,140 and \$105,630, respectively. The fees billed during fiscal 2003 were primarily for services related to Ernst & Young LLP's consultations related to accounting for a number of our collaborations. The fees billed in fiscal 2002 were primarily 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 registration statements we filed in 2002 and consultations related to accounting for a number of our collaborations.

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Tax Fees:

During the fiscal years ended December 31, 2003 and 2002, the aggregate fees billed by Ernst & Young LLP for professional services rendered for tax compliance, tax advice and tax planning were \$20,905 and \$30,885, respectively. 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 years ended December 31, 2003 and 2002, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees:

During the fiscal years ended December 31, 2003 and 2002, all other fees billed by Ernst & Young LLP were \$1,616 and \$3,000, respectively. These fees were for a subscription to an online accounting and tax information service.

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

During the fiscal year ended December 31, 2003, 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 3

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SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our Common Stock as of February 27, 2004 by:

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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	6,017,275	10.8
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	3,870,302	6.9
Spencer R. Berthelsen(5)	36,870	*
Stanley T. Crooke(6)	1,433,367	2.5
Christopher F. O. Gabrieli(7)	219,671	*
Frederick T. Muto(8)	19,500	*
B. Lynne Parshall(9)	302,016	*
John C. Reed(10)	22,500	*
Mark B. Skaletsky(11)	65,500	*
Joseph H. Wender(12)	74,500	*
C. Frank Bennett(13)	131,568	*
Richard K. Brown(14)	27,921	*
David J. Ecker(15)	152,524	*
All directors and executive officers as a group (15 persons)(16)	2,835,727	4.9

* 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 SEC. Unless 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 55,882,937 shares of Common Stock outstanding on February 27, 2004, adjusted as required by rules promulgated by the SEC.
- (3) Includes 4,046,673 shares held by Citigroup Global Markets Inc. ("CGM") and Citigroup Financial Products Inc. ("CFP"), 5,964,530 shares held by Citigroup Global Markets Holdings Inc. ("CGM Holdings") and 6,017,275 shares held by Citigroup Inc. CFP is the sole stockholder of CGM. CGM Holdings is the sole stockholder of CFP. Citigroup Inc. is the sole stockholder of CGM Holdings. As a result, the holdings reported for CGM Holdings and Citigroup Inc. include the shares held by their respective wholly-owned subsidiaries.

- (4) Mazama Capital Management, Inc. has sole voting authority over 1,987,950 shares and sole dispositive power over 3,870,302 shares. These holdings are as of January 31, 2004.
- (5) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 7,500 shares of Common Stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 27, 2004.
- (6) Includes 489,306 shares of Common Stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 27, 2004. Also includes 20,770 shares of Common Stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before April 27, 2004, 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.
- (7) Includes 740 shares of Common Stock held of record by the Gabrieli Family Foundation ("GFF"). 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 63,500 shares of Common Stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 27, 2004.
- (8) Includes 1,500 shares of Common Stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 18,000 shares of Common Stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 27, 2004.
- (9) Includes 263,999 shares of Common Stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 27, 2004, 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 27, 2004.

- (10) Includes 22,500 shares of Common Stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before April 27, 2004.
- (11) Includes 43,500 shares of Common Stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 27, 2004.
- (12) Includes 43,500 shares of Common Stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 27, 2004.
- (13) Includes 131,005 shares of Common Stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 27, 2004.
- (14) Includes 25,573 shares of Common Stock issuable upon exercise of options held by Dr. Brown that are exercisable on or before April 27, 2004.
- (15) Includes 37,009 shares of Common Stock held by the Ecker Family Revocable Trust in which Dr. Ecker is a trustee, and an aggregate of 3,498 shares of Common Stock held by Dr. Ecker's son. Also includes 112,017 shares of Common Stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 27, 2004.
- (16) Includes an aggregate of 1,618,044 shares issuable upon exercise of options held by all current directors and executive officers as a group that are exercisable on or before April 27, 2004.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") requires our 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, 2003, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with except Mr. Gabrieli was five days late reporting shares sold by Bessemer Venture Partners III L. P. ("BVP III") because BVP III failed to timely notify Mr. Gabrieli regarding such sale. Mr. Gabrieli is a General Partner of Deer III & Co., the sole General Partner of BVP III and disclaims beneficial ownership except to the extent of his partnership interest.

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, 2003, we paid total fees of \$97,500 to our non-employee directors. For 2004, the fee has been increased to \$25,000 per year.

In 2003, each non-employee director also received automatic stock option grants under our 2002 Non-Employee Directors' Stock Option Plan. On July 1, 2003, 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 \$5.17 per share. 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.

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, 2003, 2002, and 2001.

Summary Compensation Table

Name and Principal Position	Year	Annual Compensation			Long-Term Compensation Awards	All Other Compensation (\$)
		Salary (\$)	Bonus (\$)(1)	Other Annual Compensation (\$)(2)	Securities Underlying Options (#)	
Stanley T. Croke Chairman, CEO and President	2003	510,300	191,363	—	117,333(3)	—
	2002	486,000	205,286	—	55,000	—
	2001	450,009	432,000	—	50,000	—
B. Lynne Parshall Director, Executive VP & Chief Financial Officer	2003	405,089	127,603	—	81,466(4)	—
	2002	385,799	136,650	—	35,000	—
C. Frank Bennett Vice President, Antisense	2001	358,883	282,620	—	28,000	—
	2003	274,939	77,327	—	46,099(5)	—
	2002	261,847	76,040	—	19,000	—

Research	2001	244,260	153,884	—	20,000	—
Richard K. Brown	2003	305,490	72,172	—	65,500(6)	—
Vice President, Business Development	2002	290,943	49,926	—	12,000	—
David J. Ecker	2001	162,436	95,004	—	90,000(7)	—
President, Ibis Therapeutics	2003	271,765	79,491	—	92,865(8)	—
	2002	257,597	81,607	—	23,200(9)	—
	2001	241,125	150,964	—	18,000	—

- (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 2003 were paid in January 2004.
- (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) Includes 67,333 options issued in a stock exchange offered to all employees in which 147,500 options previously granted to Dr. Crooke were cancelled.
- (4) Includes 56,466 options issued in a stock exchange offered to all employees in which 128,000 options previously granted to Ms. Parshall were cancelled.
- (5) Includes 34,599 options issued in a stock exchange offered to all employees in which 71,000 options previously granted to Dr. Bennett were cancelled.
- (6) Includes 49,000 options issued in a stock exchange offered to all employees in which 102,000 options previously granted to Dr. Brown were cancelled.
- (7) 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.
- (8) Includes 80,365 options issued in a stock exchange offered to all employees in which 148,200 options previously granted to Dr. Ecker were cancelled.
- (9) 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 Broad-Based Equity Incentive Plan (the "2000 Plan") and our 1989 Plan. During 2003, options to purchase a total of 2,664,331 shares of our Common Stock had been granted under the 2000 Plan which included 1,038,405 shares issued in the option exchange offered to all employees. In 2003, no options to purchase shares of our Common Stock were 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. Ten of our twelve 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, 2003 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	50,000	1.88	6.84	1/1/13	\$ 194,721	\$ 512,638
	67,333(4)	2.53	5.15	12/31/08	109,102	246,048
B. Lynne Parshall	25,000	.94	6.84	1/1/13	\$ 97,360	\$ 256,319
	56,466(4)	2.12	5.15	12/31/08	91,494	206,338
C. Frank Bennett	11,500	.43	6.84	1/1/13	\$ 44,786	\$ 117,907
	34,599(4)	1.30	5.15	12/31/08	56,062	126,432
Richard K. Brown	16,500	.62	6.84	1/1/13	\$ 64,258	\$ 169,171
	49,000(4)	1.84	5.15	12/31/08	79,396	179,056
David J. Ecker	12,500	.47	6.84	1/1/13	\$ 48,680	\$ 128,160
	80,365(4)	3.02	5.15	12/31/08	130,218	293,670

- (1) The replacement options issued in our option exchange were nonqualified stock options and have a three-year vesting period; 33.34% vested on January 1, 2004 and then at the rate of 2.78% per month thereafter. The replacement options expire on December 31, 2008. All other options granted in 2003 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 2,664,331 shares granted in 2003 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

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continued employment through the vesting periods. The amounts reflected in this table may not necessarily be achieved.

- (4) Options issued through a stock exchange offered to all employees. In order to receive their respective option grant, Dr. Crooke cancelled options to purchase 147,500 shares; Ms. Parshall cancelled options to purchase 128,000 shares; Dr. Bennett cancelled options to purchase 71,000 shares; Dr. Brown cancelled options to purchase 102,000 shares and Dr. Ecker cancelled options to purchase 148,200 shares.

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-the-Money 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	—	—	441,458/130,875	\$125,000/\$90,900	55,000
B. Lynne Parshall	—	—	260,416/89,050(3)	—/\$76,229	35,457
C. Frank Bennett	—	—	108,079/63,079	\$4,793/\$46,813	491
Richard K. Brown	—	—	—/65,500	—/\$66,150	—
David J. Ecker	—	—	84,025/98,990	\$30,375/\$108,493	—

- (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, 2003 (\$6.50) 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 30,090 options transferred to Ms. Parshall's two daughters.

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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, 2003.

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	3,013,000(a) \$	9.90	3,251,000(c)
Equity compensation plans not approved by stockholders	5,198,000(b) \$	7.94	539,000
Total	8,211,000 \$	8.66	3,790,000

- (a) Consists of two Isis plans: the 1989 Plan and the 2002 Non-Employee Directors' Stock Option Plan.
- (b) Consists of the 2000 Plan only.
- (c) Of these shares, 200,138 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 1 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 will 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 Compensation Committee 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 February 27, 2004, there were 5,683,630 shares reserved for issuance under the 2000 Plan, options to purchase an aggregate of 5,289,266 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 306,370 shares had been exercised under the 2000 Plan, and 394,364 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. Options granted pursuant to the April 2003 stock option exchange program vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month thereafter for 24 months during the optionee's employment or service.

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,

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recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, 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 stockholders 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.

In addition, as of December 31, 2003, approximately 5,198,000 stock awards granted under the 2000 Plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

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 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.

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Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2003, our Compensation Committee was composed of Messrs. Skaletsky, Reed and Wender. 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.

Option Exchange Information

Due to the disappointing results of our Phase III clinical trial of Affinitak in non-small cell lung cancer which were announced in March 2003, the share price of our Common Stock declined significantly from its levels prior to the announcement, leaving many employees with stock options that were "underwater;" that is, with exercise prices that were significantly higher than the market price of our stock. Our Compensation Committee believed that many of those options no longer provided an effective incentive to motivate and retain employees. In addition, because of the drop in the stock price, historically low employee turnover and the longevity of our senior management team, the number of unexercised options had grown to an undesirable level. Sensitive to stockholder concerns

regarding the dilutive effect of stock options, rather than granting additional options to compensate for the underwater options, our Compensation Committee determined that a reduction in such potential dilution was more in line with building stockholder value and presented an opportunity to decrease the fully diluted shares outstanding. Accordingly, in April 2003, our Board authorized a stock option exchange program. The Board structured the exchange program such that:

- eligible employees had to cancel a larger number of options to receive a smaller number of new stock options;
- vesting for the replacement options restarted on January 1, 2003 (ensuring that the options would provide long term retention value); and
- new options carried a shorter expiration term of approximately five years (minimizing long term dilution and overhang).

Proposal 2, if approved by our stockholders, would prohibit the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders.

The following table shows certain information concerning the exchange of options received by Executive Officers during the last ten years. These shares were issued in connection with a stock option exchange program offered to all employees. The options were exchanged at a ratio of existing option shares (option shares rounded down and each grant calculated individually) as follows for options granted prior to January 5, 2002:

Option Exercise Price	Exchange Ratio (new for old)
> \$5 < \$10	1-1.5
> \$10 < \$15	1-2
> \$15 < \$20	1-2.5
> \$20	1-3

Ten Year Option Repricings

Name	Date	Number of Securities Underlying Options Canceled in Exchange (#)	Market Price of Stock at Time of Exchange (\$)	Exercise Price at Time of Exchange (\$)	Number of Securities Issued in the Exchange (#)	New Exercise Price (\$)	Length (in Years) of Original Option Term Remaining at Date of Exchange
Stanley T. Crooke	5/9/03	55,000	\$ 5.15	\$ 21.0500	18,333	\$ 5.15	8.65
		30,000		\$ 6.7500	20,000		0.65
		40,000		\$ 13.1250	20,000		2.65
		22,500		\$ 18.0000	9,000		3.65
		<u>147,500</u>			<u>67,333</u>		
B. Lynne Parshall	5/9/03	35,000	\$ 5.15	\$ 21.0500	11,666	\$ 5.15	8.65
		60,000		\$ 12.6250	30,000		2.60
		16,000		\$ 13.1250	8,000		2.65
		17,000		\$ 18.0000	6,800		3.65
		<u>128,000</u>			<u>56,466</u>		
C. Frank Bennett	5/9/03	50,000	\$ 5.15	\$ 12.2500	24,999	\$ 5.15	2.10
		12,000		\$ 13.1250	6,000		2.65
		9,000		\$ 18.0000	3,600		3.65
		<u>71,000</u>			<u>34,599</u>		
Richard K. Brown	5/9/03	90,000	\$ 5.15	\$ 12.0400	45,000	\$ 5.15	8.07
		12,000		\$ 21.0500	4,000		8.65
		<u>102,000</u>			<u>49,000</u>		
David J Ecker	5/9/03	23,200	\$ 5.15	\$ 21.0500	7,733	\$ 5.15	8.65
		50,000		\$ 6.1250	33,333		0.18
		15,000		\$ 6.7500	9,999		0.65
		18,000		\$ 13.1250	9,000		2.65
		7,000		\$ 18.0000	2,800		3.65
		10,000		\$ 12.3125	5,000		4.65
		15,000		\$ 12.9375	7,500		5.65
		10,000		\$ 12.1875	5,000		7.27
		<u>148,200</u>			<u>80,365</u>		
Arthur A. Levin	1/1/00	6,000	\$ 6.25	\$ 13.1250	4,000	\$ 6.81	6.00
		15,000		\$ 13.8800	9,999		6.61
		5,453		\$ 18.0000	2,726		7.00
	5/9/03	14,000	\$ 5.15	\$ 9.6250	9,333	\$ 5.15	7.65
		10,000		\$ 21.0500	3,333		8.65
		12,550		\$ 12.3125	6,275		4.65
		8,850		\$ 12.9375	4,425		
<u>71,853</u>		<u>40,091</u>					
Patricia Lowenstam	5/9/03	21,000	\$ 5.15	\$ 21.0500	6,999	\$ 5.15	8.65
		12,000		\$ 6.7500	8,000		.65
		16,000		\$ 13.1250	8,000		2.65
		8,500		\$ 18.0000	3,400		3.65

12,000	\$	12.3125	6,000	4.65
15,000	\$	12.9375	7,500	5.65
<hr/>			<hr/>	
84,500			39,899	

Compensation Committee Report(1)

In 2003, the Compensation Committee of the Board of Directors consisted of Mark B. Skaletsky, Chairman, John Reed and Joseph H. Wender, none of whom has ever been an officer or employee of Isis. The Compensation Committee's responsibilities include:

- Overall Compensation Strategy;
- Reviewing and approving corporate performance goals and objectives relevant to the compensation of the Company's Executive Officers;
- Evaluating and recommending to the Board the compensation plans and programs advisable for the Company, as well as modification or termination of existing plans and programs;
- Establishing policies with respect to equity compensation arrangements;
- Reviewing and approving compensation arrangements for the Company's executive officers, including its Chief Executive Officer;
- Reviewing and approving compensation arrangements for the Company's Directors;
- Administering the Company's benefit plans, including stock option and employee stock purchase plans;
- Performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- Reporting to the Board of Directors from time to time, or whenever it shall be called upon to do so.

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

- (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 "1934 Act"), or the Exchange Act.

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 the Company's 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 our executives an economic interest in the long-term appreciation of our Common Stock. We grant existing executives 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.

Stock Option Exchange Program

Due to the disappointing results of Isis' Phase III clinical trial of Affinitak in non-small cell lung cancer which were announced in March 2003, the share price of the Company's Common Stock declined significantly from its levels prior to the announcement, leaving many employees with stock options that were "underwater;" that is, with exercise prices that were significantly higher than the market price of the Company's stock. The Committee believed that many of those options no longer provided an effective incentive to motivate and retain employees. In addition, because of the drop in the stock price, historically low employee turnover and the longevity of Isis' senior management team, the number of unexercised options had grown to an undesirable level. Sensitive to stockholder concerns regarding the dilutive effect of stock options, rather than granting additional options to compensate for the underwater options, the Committee determined that a reduction in such potential dilution was more in line with building stockholder value and presented an opportunity to decrease the fully diluted shares outstanding. Accordingly, in April 2003, the Board authorized a stock option exchange program whereby eligible employees had an opportunity to exchange outstanding options with exercise prices at or above \$5.00 per share granted prior to January 5, 2002 for a predetermined smaller number

of new stock options. Vesting for the replacement options restarted on January 1, 2003 (ensuring that the options would provide long term retention value) and the new options carried a shorter expiration term of approximately five years (minimizing long term dilution and overhang). As a matter of good practice, we recommended an amendment to the 1989 Plan, subject to stockholder approval of Proposal 2, that would prohibit the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders.

In accordance with the terms of the stock option exchange program, approximately 2,236,206 options having a weighted average exercise price of \$14.89 per share and an average remaining life of six years were cancelled in exchange for new options totaling approximately 1,038,405 shares at an exercise price of \$5.15 per share, which was equal to the closing price of the Company's stock on May 8, 2003.

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 2003

We set very challenging objectives for 2003. In achieving the majority of those objectives, we made significant progress in the areas discussed below. However, in March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single study new drug application.

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Strengthened Financial Position

In 2003, 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 \$216.0 million in cash, even as it continued the aggressive development of its pipeline of 11 products. In June 2003, we renegotiated our manufacturing relationship with Lilly which waived repayment of the \$21.2 million manufacturing loan it provided us to build our new manufacturing facility. In December 2003, we also retired higher interest rate debt with a term loan from Silicon Valley Bank at the prime rate, which on December 31, 2003 was 4%.

Advanced Antisense Drug Discovery

In 2003, we made significant progress in advancing our core technology platform, in identifying antisense drug candidates and in moving these candidates toward clinical trials both for ourselves and for our partners.

Specifically we:

- Earned a \$1.5 million milestone from Lilly in the development of LY2181308 as part of the research collaboration oncology expansion;
- Achieved a second milestone in our antisense drug discovery collaboration with Amgen Inc;
- Expanded the cancer research component of our antisense drug discovery collaboration with Lilly to include multiple antisense mechanisms, such as RNAi and alternative splicing, as well as alternative chemistries, such as Peptide Nucleic Acid, or PNA;
- Initiated a multi-year collaboration with Ercole Biotech, Inc. to discover antisense drugs that regulate alternative RNA splicing;
- In June 2003, initiated a collaboration with Industrial and Technology Research Institute of Taiwan (ITRI) to identify antisense candidates targeting the coronavirus associated with SARS. In addition to an upfront payment of \$1.0 million, we achieved two milestones for which we received a total of \$1.0 million related to the identification of second-generation antisense drugs that inhibit SARS virus replication; and
- In November 2003, received a grant of up to \$8.0 million over three years from the Singapore Economic Development Board which will fund, in part, the broadening of two of our RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS.

Advanced Antisense Drug Development

The progress of our drug development in 2003 was mixed. We announced the results of our Phase III clinical trial of Affinitak in combination with traditional cancer chemotherapy drugs to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in a primary log-rank analysis of overall survival, the primary endpoint of the trial, of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone.

The following describes the substantial progress we made during 2003 with our other drugs in development:

Alicaforsen (ISIS 2302)—Ulcerative Colitis, Pouchitis

- In April 2003, we initiated a Phase II trial in 100 ulcerative colitis patients throughout the U.S. and Europe.

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- In May 2003, we reported interim data from a Phase II trial of patients with pouchitis. The first eight patients experienced an improvement in clinical disease symptoms after receiving treatment of an enema formulation of Alicaforsen. In October 2003, we reported additional data that

demonstrated sustained improvement of patients with pouchitis that lasted up to nine months.

ISIS 104838—Rheumatoid Arthritis

- We reported in early January 2004, data from a Phase II clinical trial which demonstrated that ISIS 104838 produced a disease response in patients with rheumatoid arthritis compared to placebo-treated patients. Results from an earlier Phase II trial demonstrated that ISIS 104838 reduced TNF-alpha mRNA levels in synovial tissue and stabilized levels of TNF-alpha in the blood.

ISIS 14803—HCV

- In a four-week Phase I/II clinical trial, ISIS 14803 demonstrated dose-dependent antiviral activity, decreasing the level of virus in the blood in patients with drug resistant chronic HCV. All but one patient had failed previous interferon-based therapy. In October 2003, we reported the final results of a twelve-week, single agent study of ISIS 14803 in drug-resistant genotype 1 patients. ISIS 14803 produced up to 3.8 log dose-dependent reductions in plasma virus levels in five of 17 patients with HCV.
- In May 2003, we initiated a 30-patient Phase II clinical trial to assess the benefits of adding ISIS 14803 to standard treatments for HCV in patients who do not achieve an early response to the current standard therapy.

ISIS 113715—Diabetes

- In September 2003, we reported the results of a Phase I clinical trial begun in May 2003 to assess the safety and pharmacokinetic profile of several doses of ISIS 113715 in 20 healthy volunteers. The trial demonstrated improved glucose tolerance and increased insulin sensitivity in all patients who received ISIS 113715.

ISIS 301012—Cardiovascular Disease

- In late 2003, we initiated a double-blind placebo-controlled, dose escalation Phase I clinical study of ISIS 301012, our first drug for the treatment of cardiovascular disease. The goal of this trial is to assess the safety of ISIS 301012 and its ability to reduce several components of cholesterol that are important in the management and prevention of cardiovascular disease.

Partnerships Progressed

Eli Lilly & Co.

- Lilly is continuing to follow patients currently enrolled in a second Phase III study of Affinitak. Lilly and we will make a decision about the future development of Affinitak pending review upon completion of this trial.
- We expect Lilly to initiate Phase I trials of LY2181308 targeting survivin for cancer during 2004.

OncoGenex

- In April 2003, OncoGenex and we initiated a second Phase I/II trial to evaluate OGX-011 in combination with TAXOTERE® in various solid tumors.

Antisense Technologies, Limited (ATL)

- In August 2003, ATL initiated a Phase I clinical trial of ATL 1102 (ISIS 107248) for the treatment of multiple sclerosis.

Expanded Ibis' TIGER Program

In 2003, Isis:

- successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples;
- received a three-year grant from the CDC for up to \$6.0 million to develop and apply our diagnostic technology to the surveillance of human infectious disease in the U.S; and
- to date, we have received grants and contracts representing potential funding of up to \$55 million from agencies of the U.S. Government for the development of our TIGER biosensor technology.

Out-Licensing Arrangements

Eyetech Pharmaceuticals, Inc.

- In 2003, Pfizer and Eyetech reported encouraging Phase III data for Macugen, a non-antisense compound intended for the treatment of ophthalmic diseases, which incorporates proprietary technology licensed from Isis. Eyetech says these data will serve as the basis for an NDA, with commercialization of the drug expected in 2005. Assuming successful commercialization of Macugen, we have the opportunity to earn future milestone payments and royalties that could be substantial to us.

Patents and Proprietary Rights

We own or have exclusively licensed more than 1,300 issued patents worldwide. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. To date, we have generated more than \$40 million in license and royalty fees related to our patent portfolio.

As a result, based on a combination of the accomplishment of major research and drug development objectives and the failure to achieve statistical significance in our single-study Phase III trial of Affinitak, the Compensation Committee recommended, and the Board approved, a corporate bonus guideline of 75% which, together with individual performance, formed the basis for bonus awards for 2003. 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 4.5% to \$533,264 for 2004. Dr. Crooke received a salary increase in 2003 of 5% and an increase of 8% in 2002. In January 2004, Dr. Crooke received a bonus of \$191,363 for accomplishments in 2003, likewise based on the assessment of objectives achieved and not achieved. In January 2003, the Committee also approved an option grant of 50,000 shares of Common Stock for performance in 2002 for Dr. Crooke, pursuant to our 2000 Plan, at an exercise price of \$6.84 per share, the fair market value on the date of grant. On January 2, 2004 the

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Committee also approved an option grant of 80,000 shares of Common Stock for performance in 2003 for Dr. Crooke, pursuant to our 1989 Plan, at an exercise price of \$6.81 per share, the fair market value on the date of grant.

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

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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, 2003 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.

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, 2003 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of our independent auditors.

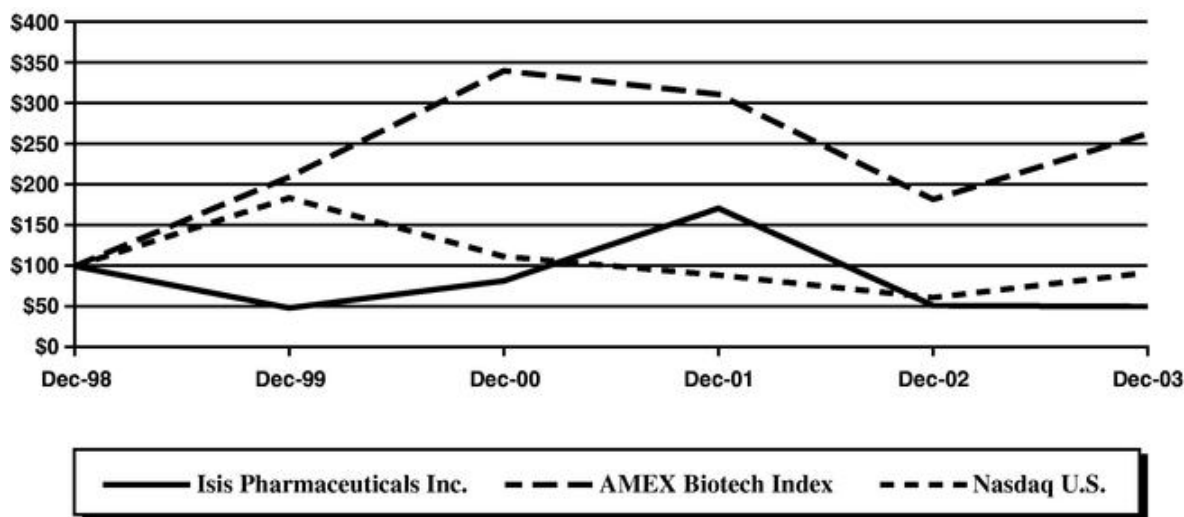
Joseph H. Wender, Chairman
Mark B. Skaletsky
Spencer R. Berthelsen

(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.

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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



	Dec-98	Dec-99	Dec-00	Dec-01	Dec-02	Dec-03
Isis Pharmaceuticals Inc.	\$ 100	\$ 48	\$ 82	\$ 172	\$ 51	\$ 50
AMEX Biotech Index	\$ 100	\$ 211	\$ 343	\$ 314	\$ 183	\$ 265
Nasdaq U.S.	\$ 100	\$ 185	\$ 112	\$ 89	\$ 61	\$ 92

The above table and chart assume \$100 invested on December 31, 1998 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 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 new suite. In June 2003, we reached a mutually beneficial renegotiation of our manufacturing relationship with Lilly. Lilly waived repayment of the \$21.2 million manufacturing loan it provided us to build the new manufacturing facility. Lilly agreed to allow us to use the facility to manufacture other drugs. In exchange, we released Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from us and the obligation to pay for the costs of maintaining an idle manufacturing suite. At December 31, 2003, Lilly owned approximately 7.5% of our outstanding Common Stock.

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 2003 fiscal year.

In 2003, we entered into the transactions described in this 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.

Our policies and procedures 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 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 includes our Form 10-K for the year ended December 31, 2003 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

April 16, 2004

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ISIS PHARMACEUTICALS, INC. 1989 STOCK OPTION PLAN

As Amended September 5, 1991
As Amended September 4, 1992
As Amended January 4, 1993
As Amended December 2, 1993 and January 20, 1994
As Amended December 7, 1994
As Amended February 27, 1995 and December 14, 1995
As Amended September 6, 1996
As Amended February 27, 1998
As Amended March 29, 2004

1. PURPOSE.

(a) The purpose of the Plan is to provide a means by which selected employees and directors (if declared eligible under paragraph 4) of and consultants to Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), and its Affiliates, as defined in subparagraph 1(b), may be given an opportunity to benefit from increases in value of the stock of the Company through the granting of (i) incentive stock options and (ii) supplemental stock options, all as defined below.

(b) The word "Affiliate" as used in the Plan means any parent corporation or subsidiary corporation of the Company, as those terms are defined in Sections 424(e) and (f), respectively, of the Internal Revenue Code of 1986, as amended (the "Code").

(c) The Company, by means of the Plan, seeks to retain the services of persons now employed by or serving as consultants or directors to the Company, to secure and retain the services of new employees/persons capable of filling such positions, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the rights issued under the Plan will, in the discretion of the Compensation Committee of the Board of Directors of the Company (the "Committee"), be stock options granted pursuant to paragraph 5 hereof, including incentive stock options as that term is used in Section 422 of the Code ("Incentive Stock Options"), or options which do not qualify as Incentive Stock Options ("Supplemental Stock Options") (together hereinafter referred to as "Options"). All Options will be separately designated Incentive Stock Options or Supplemental Stock Options at the time of grant, and in such form as issued pursuant to paragraph 5, and a separate certificate or certificates will be issued for shares purchased on exercise of each type of Option. An Option designated as a Supplemental Stock Option will not be treated as an Incentive Stock Option.

2. ADMINISTRATION.

(a) The Plan will be administered by the Committee.

(b) The Committee will have the power, subject to, and within the limitations of, the express provisions of the Plan:

(1) To determine from time to time which of the persons eligible under the Plan will be granted Options; when and how Options will be granted; whether an Option will be an Incentive Stock Option or a Supplemental Stock Option; the provisions of Option granted (which need not be identical), including the time or times when a person will be permitted to purchase or receive stock pursuant to an Option; and the number of shares with respect to which Options will be granted to each such person.

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(2) To construe and interpret the Plan and Options granted under it, and to establish, amend and revoke rules and regulations for its administration. The Committee, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Option, in a manner and to the extent it will deem necessary or expedient to make the Plan fully effective.

(3) To amend the Plan as provided in paragraph 11.

(4) Generally, to exercise such powers and to perform such acts as the Committee deems necessary or expedient to promote the best interests of the Company.

(c) The Committee may delegate to a single member of the Board of Directors the authority to grant one or more Options, without further approval of the Committee, to any person eligible pursuant to Section 4 (other than a person who, at the time of such grant, is an executive officer or member of the Board of Directors); provided, however, that each such Option will be subject to the terms and conditions of the appropriate standard form of Option Agreement approved by the Committee and will conform to the provisions of the Plan and such other guidelines as the Committee may establish from time to time.

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 10 relating to adjustments upon changes in stock, the stock that may be issued pursuant to Options granted under the Plan will not exceed in the aggregate 13,200,000 shares of the Company's common stock. If any Option granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such Option will again become available for the Plan.

(b) The stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

(c) An Incentive Stock Option may be granted to an eligible person under the Plan only if the aggregate fair market value (determined at the time the Option is granted) of the stock with respect to which incentive stock options (as defined in the Code) granted after 1986 are exercisable for the first time by such optionee during any calendar year under all Incentive Stock Option plans of the Company and its Affiliates does not exceed \$100,000. If it is determined that an entire Option or any portion thereof does not qualify for treatment as an Incentive Stock Option by reason of exceeding such maximum, such Option or the applicable portion will be considered a Supplemental Stock Option.

4. ELIGIBILITY.

(a) Incentive Stock Options may be granted only to employees (including officers) of the Company or its Affiliates. A director of the Company will not be eligible to receive Incentive Stock Options unless such director is also an employee (including an officer) of the Company or any Affiliate. Options other than Incentive Stock Options may be granted only to employees (including officers) of, directors of or consultants to the Company or its Affiliates.

(b) No person will be eligible for the grant of an Incentive Stock Option under the Plan if, at the time of grant, such person owns (or is deemed to own pursuant to Section 424(d) of the Code) stock possessing more than 10% of the total combined voting power of all classes of stock of the Company or of any of its Affiliates unless the exercise price of such Option is at least 110% of the fair market value of such stock at the date of grant and the term of the Option does not exceed 5 years from the date of grant.

(c) No person will be eligible to be granted Options covering more than 294,873 shares of the Company's common stock in any 12 month period.

5. OPTION PROVISIONS.

Each Option will be in such form and will contain such terms and conditions as the Committee will deem appropriate. The provisions of separate Options need not be identical, but each Option will include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) No Option will be exercisable after the expiration of 7 years from the date it was granted.

(b) The exercise price of each Option (whether an Incentive Stock Option or Supplemental Stock Option) will be not less than 100% of the fair market value of the stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option (whether an Incentive Stock Option or Supplemental Stock Option) may be granted with an exercise price lower than set forth in the preceding sentences if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) The purchase price of stock acquired pursuant to an Option will be paid in cash at the time the Option is exercised.

(d) An Incentive Option will not be transferable except by will or by the laws of descent and distribution, and will be exercisable during the lifetime of the person to whom the Option is granted only by such person. A Supplemental Stock Option may be transferable at the discretion of the Committee.

(e) The total number of shares of stock subject to an Option may, but need not, be allotted in periodic installments (which may, but need not, be equal). From time to time during each of such installment periods, the Option may become exercisable ("vest") with respect to some or all of the shares allotted to that period, and may be exercised with respect to some or all of the shares allotted to such period and/or any prior period as to which the Option was not fully exercised; *provided, however*, that no Option granted to an employee or member of the Company's Board of Director will become 100% vested in a period of less than 2 years after the grant of such Option (except as provided in Section 10(b)). During the remainder of the term of the Option (if its term extends beyond the end of the installment periods), the Option may be exercised from time to time with respect to any shares then remaining subject to the Option. The provisions of this subparagraph 5(e) are subject to any Option provisions governing the minimum number of shares as to which an Option may be exercised.

(f) The Company may require any optionee, or any person to whom an Option is transferred under subparagraph 5(d), as a condition of exercising any such Option, (1) to give written assurances satisfactory to the Company as to the optionee's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters, and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (2) to give written assurances satisfactory to the Company stating that such person is acquiring the stock subject to the Option for such

person's own account and not with any present intention of selling or otherwise distributing the stock. These requirements, and any assurances given pursuant to such requirements, will be inoperative as to any particular requirement, if a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws.

(g) An Option will terminate 3 months after termination of the optionee's employment or relationship as a consultant or director with the Company or an Affiliate, unless (i) such termination is due to such person's permanent and total disability, within the meaning of Section 422(c)(6) of the Code, in which case the Option may, but need not, provide that it may be

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exercised at any time within 1 year following such termination of employment or relationship as a consultant or director; or (ii) the optionee dies while in the employ of or while serving as a consultant or director to the Company or an Affiliate, or within not more than 3 months after termination of such relationship, in which case the Option may, but need not, provide that it may be exercised at any time within 18 months following the death of the optionee by the person or persons to whom the optionee's rights under such Option pass by will or by the laws of descent and distribution; or (iii) the Option by its terms specifies either (a) that it will terminate sooner than 3 months after termination of the optionee's employment or relationship as a consultant or director or (b) that it may be exercised more than 3 months after termination of the relationship with the Company or an Affiliate. This subparagraph 5(g) will not be construed to extend the term of any Option or to permit anyone to exercise the Option after expiration of its term, nor will it be construed to increase the number of shares as to which any Option is exercisable from the amount exercisable on the date of termination of the optionee's employment or relationship as a consultant or director.

(h) To the extent provided by the terms of an Option, the optionee may satisfy any federal, state or local tax withholding obligation relating to the exercise of such Option by any of the following means or by a combination of such means: (1) tendering a cash payment; (2) authorizing the Company to withhold from the shares of the common stock otherwise issuable to the participant as a result of the exercise of the Option a number of shares having a fair market value less than or equal to the amount of the withholding tax obligation; or (3) delivering to the Company owned and unencumbered shares of the common stock having a fair market value less than or equal to the amount of the withholding tax obligation.

6. COVENANTS OF THE COMPANY.

(a) During the terms of the Options granted under the Plan, the Company will keep available at all times the number of shares of stock required to satisfy such Options.

(b) The Company will seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock under the Options granted under the Plan; provided, however, that this undertaking will not require the Company to register under the Securities Act either the Plan, any Option granted under the Plan or any stock issued or issuable pursuant to any such Option. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company will be relieved from any liability for failure to issue and sell stock upon exercise of such Options unless and until such authority is obtained.

7. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to Options granted under the Plan will constitute general funds of the Company.

8. MISCELLANEOUS.

(a) Subject to the limitation set forth in Section 5(e), the Committee will have the power to accelerate the time during which an Option may be exercised or the time during which an Option or any part thereof will vest, notwithstanding the provisions in the Option stating the time during which it may be exercised or the time during which it will vest.

(b) Neither an optionee nor any person to whom an Option is transferred under subparagraph 5(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to such Option unless and until such person has satisfied all requirements for exercise of the Option pursuant to its terms.

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(c) Throughout the term of any Option granted pursuant to the Plan, the Company will make available to the holder of such Option, not later than 120 days after the close of each of the Company's fiscal years during the Option term, upon request, such financial and other information regarding the Company as comprises the annual report to the stockholders of the Company provided for in the bylaws of the Company.

(d) Nothing in the Plan or any instrument executed or Option granted pursuant thereto will confer upon any eligible employee, consultant, director or holder of Options under the Plan any right to continue in the employ of the Company or any Affiliate (or to continue acting as a consultant or director) or will affect the right of the Company or any Affiliate to terminate the employment or consulting relationship or directorship of any eligible employee, consultant, director or holder of Options under the Plan with or without cause. In the event that a holder of Options is permitted or otherwise entitled to take a leave of absence, the Company will have the unilateral right to (i) determine whether such leave of absence will be treated as a termination of employment or relationship as consultant or director for purposes of paragraph 5(g) hereof and corresponding provisions of any outstanding Options, and (ii) suspend or otherwise delay the time or times at which exercisability or vesting would otherwise occur with respect to any outstanding Options under the Plan.

9. OPTION REPRICING PROHIBITED.

The Board will not have the authority, at any time, without obtaining the approval of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, to (1) reduce the exercise price of any Options under the Plan that are currently outstanding; or (2) cancel any outstanding Options under the Plan and grant in substitution therefore new Options under the Plan at a lower exercise price (including entering into any "6 month and 1 day" cancellation and re-grant scheme), regardless of whether or not the cancelled Options revert to and again become available for issuance under the Plan This Section 10 may not be amended without the affirmative vote of the holders of a majority of the shares present or represented and entitled to vote at a duly convened meeting of the stockholders of the Company. Notwithstanding the foregoing, this paragraph will not be construed to apply to "issuing or assuming a stock option in a transaction to which section 424(a) applies," within the meaning of Section 424 of the Code.

10. *ADJUSTMENTS UPON CHANGES IN STOCK.*

(a) If any change is made in the stock subject to the Plan, or subject to any Option granted under the Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or otherwise), the Plan and outstanding Options will be appropriately adjusted in the class(es) and maximum number of shares subject to the Plan or an Option under paragraph 4(c) and the class(es) and number of shares and price per share of stock subject to outstanding Options.

(b) In the event of: (1) a dissolution or liquidation of the Company; (2) a merger or consolidation in which the Company is not the surviving corporation; or (3) a reverse merger in which the Company is the surviving corporation but the shares of the Company's 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 to the extent permitted by applicable law: (i) any surviving corporation will assume any Options outstanding under the Plan or will substitute similar Options for those outstanding under the Plan, or (ii) such Options will continue in full force and effect. In the event any surviving corporation refuses to assume or continue such Options, or to substitute similar Options for those outstanding under the Plan, then, with respect to Options held by persons then performing services as employees or as consultants or directors for the Company, as the case may be, the time during which such Options become vested

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or may be exercised will be accelerated and the Options terminated if not exercised prior to such event.

11. *AMENDMENT OF THE PLAN.*

(a) The Committee at any time, and from time to time, may amend the Plan. However, except as provided in paragraph 10 relating to adjustments upon changes in stock, no amendment will be effective unless approved by the stockholders of the Company within 12 months before or after the adoption of the amendment, where such amendment (i) increases the maximum aggregate number of shares of the Company's common stock that may be issued pursuant to Options granted under the Plan, (ii) requires stockholder approval in order for the Plan to satisfy the requirements of Section 422 of the Code, Rule 16(b)(3) promulgated under the Securities Exchange Act of 1934, as amended or (iii) requires stockholder approval in order for the Plan to satisfy any applicable Nasdaq or securities exchange requirements.

(b) It is expressly contemplated that the Committee may amend the Plan in any respect the Committee deems necessary or advisable to provide optionees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder relating to employee Incentive Stock Options and/or to bring the Plan and/or Incentive Stock Options granted under it into compliance therewith.

(c) Rights and obligations under any Option granted before amendment of the Plan will not be altered or impaired by any amendment of the Plan unless (i) the Company requests the consent of the person to whom the Option was granted and (ii) such person consents in writing.

12. *TERMINATION OR SUSPENSION OF THE PLAN.*

(a) The Committee may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan will terminate on January 31, 2014. No Options may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any Option granted while the Plan is in effect will not be altered or impaired by suspension or termination of the Plan, except with the consent of the person to whom the Option was granted.

13. *EFFECTIVE DATE OF PLAN.*

The Plan is effective April 19, 1991.

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

May 26, 2004

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

∨ Please detach along perforated line and mail in the envelope provided. ∨

THE BOARD OF DIRECTORS RECOMMENDS AVOTE "FOR" THE ELECTION OF DIRECTORS AND "FOR" PROPOSALS 2 AND 3. PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE. PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE

1. To elect three directors to hold office until the 2007 Annual Meeting of Stockholders

NOMINEES:

- FOR ALL NOMINEES Stanley T. Crooke
- WITHHOLD AUTHORITY FOR ALL NOMINEES John C. Reed
- FOR ALL EXCEPT (See instructions below) Mark B. Skaletsky

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: •

	FOR	AGAINST	ABSTAIN
2. To amend and restate, as described in more detail in the Proxy Statement, the 1989 Stock Option Plan	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2004	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please vote, date and promptly return this proxy in the enclosed return envelope which is postage prepaid if mailed in the United States.

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: Please sign exactly as your name or names appear on this Proxy. 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.

THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON MAY 26, 2004

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 Wednesday, May 26, 2004 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, 2 AND 3 AS MORE SPECIFICALLY DESCRIBED IN THE PROXY STATEMENT. IF SPECIFIC INSTRUCTIONS ARE INDICATED, THIS PROXY WILL BE VOTED IN ACCORDANCE THEREWITH.

(Continued and to be signed on the reverse side)

ANNUAL MEETING OF STOCKHOLDERS OF

ISIS PHARMACEUTICALS, INC.

May 26, 2004

PROXY VOTING INSTRUCTIONS

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

COMPANY NUMBER

-OR-

TELEPHONE—Call toll-free **1-800-PROXIES** (1-800-776-9437) from any touch-tone telephone and follow the instructions. Have your proxy card available when you call.

ACCOUNT NUMBER

-OR-

INTERNET—Access "**www.voteproxy.com**" and follow the on-screen instructions. Have your proxy card available when you access the web page.

∨ Please detach along perforated line 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 ELECTION OF DIRECTORS AND "FOR" PROPOSALS 2 AND 3. PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE. PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE

1. To elect three directors to hold office until the 2007 Annual Meeting of Stockholders

NOMINEES:

- FOR ALL NOMINEES Stanley T. Crooke
 WITHHOLD AUTHORITY John C. Reed
FOR ALL NOMINEES Mark B. Skaletsky
- 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: •

	FOR	AGAINST	ABSTAIN
2. To amend and restate, as described in more detail in the Proxy Statement, the 1989 Stock Option Plan	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2004	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please vote, date and promptly return this proxy in the enclosed return envelope which is postage prepaid if mailed in the United States.

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: Please sign exactly as your name or names appear on this Proxy. 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.

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